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alliance nationale
pour les sciences de la vie et de la santé

Directory

Institute Pathophysiology Metabolism & Nutrition

Circulatory system,
Hemostasis,
Pneumology,
Dermatology,
Diabetes,
Metabolism/Nutrition,
Endocrinology/Reproduction
Gastroenterology,
Hepatology,
Uro-Nephrology,
Osteoarticular system

- March 2023 -

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Introduction

1 – Fields covered

The life science Institute *Pathophysiology, Metabolism & Nutrition* (PMN) covers a wide spectrum of research in physiology, experimental medicine and human diseases. The fields covered include heart and vessels, lungs, endocrine organs, liver, kidney, skin, joints and bones, and organs involved in nutrient processing, from all aspects of nutrition, from the control of food intake and nutritional behavior to digestive processing, control of substrate use and storage. The diseases in question frequently show common biological mechanisms and often lack of suitable treatments designed on a pathophysiological basis.

2 – Major scientific challenges in biology and medicine

- **Public health care challenges**

Among diseases within the PMN scope, cardiovascular, respiratory, metabolic and nutritional diseases with their devastating complications represent a major public health care challenge. Diabetes, hyperlipidemia, obesity, renal insufficiency lead to cardiovascular disease, the major cause of mortality in industrialized countries and usually develop in relation with atherosclerosis.

Coronary artery disease, stroke and chronic heart failure are responsible for 75% of cardiovascular-related deaths. They represent 29% of deaths in France, almost equaling deaths due to cancer. Thrombotic diseases are very prevalent, arterial thrombosis (ischaemic diseases) and venous thrombosis (thrombo-embolic disease) are the world's leading cause of death. The prevalence of constitutional haemorrhagic diseases is limited, but their social and economic impact is significant, as in the case of haemophilia.

Respiratory diseases (asthma, chronic obstructive pulmonary disease, COPD; pulmonary fibroses) affect millions of people in France and their incidence is increasing. COPD alone already represents the third-largest cause of death in Europe (sixth in the world).

The prevalence of diabetes is 7.4% in France in the age range 20 to 79 (IDF 2015). The increasing prevalence of diabetes parallels that of obesity, which raised to 15.8% among men and 15.6% among women in France (age range 30 to 69, INVS 2013). Regarding the visceral obesity the prevalence reaches 41.6% and 48.5% respectively. Diabetes is among the leading causes of blindness, end stage renal disease, non-traumatic limb amputation in adults and coronary heart disease. Type 2 diabetes is a multifactorial disease that shows heterogeneity in many respects and is often a manifestation of a much broader underlying disorder often referred to as the metabolic syndrome, an operational paradigm that includes hyperinsulinaemia, dyslipidaemia, hypertension, visceral obesity, hypercoagulability and microalbuminuria. Metabolic syndrome also leads to various non-vascular complications, including steatohepatis, cirrhosis or arthrosis. The metabolic epidemics and its cardiovascular complications although world-wide have been most pronounced in non-European populations, as shown by studies from Native American and Canadian communities, Pacific and Indian Ocean island populations or populations throughout Asia.

Paradoxically, malnutrition is also a major threat to global human health and survival. Recent estimates indicate that nutritional deficiencies account for 3 million child deaths each year in less-developed countries while progress toward designing effective life-saving interventions is currently hampered by serious gaps in our understanding of nutrient metabolism in the human. Denutrition is further observed in 40% of patients suffering from chronic diseases, in 30 to 50% of hospitalized patients of all pathologies and is an independent factor for morbidity/mortality. Overall, there is a need for an increased research effort focusing on nutrition and its disorders, including the interrelationship with the environment, the human microbiome, digestive physiology, nutritional behaviors or food security.

Diseases of the bones and joints are also a concern for the French, particularly due to ageing of the population. On their own they represent half of chronic diseases in people over 65 and are a major cause of invalidity (arthrosis is the second largest handicap factor in men, the fourth in women).

Among the over 50s, one women in four and one man in eight will be affected by osteoporosis during their lives.

Skin diseases include a proportion of allergic complaints (atopic dermatitis, contact eczema, occupational dermatoses, photo-allergies, urticaria and skin accidents due to oral administration of a drug (toxicodermatitis)) and a proportion of chronic inflammatory disorders (psoriasis, atopic dermatitis, pelada, etc.). Among this latter group, psoriasis, affects between two and three million people in France and is associated with a significant change in the quality of life, often leading to a severe social handicap. The impact of this dermatosis on the quality of life is as significant as that caused by asthma, diabetes or chronic cardiac ischaemic diseases. The social cost of psoriasis is therefore considerable. Ageing of the population is increasingly frequently accompanied by chronic vascular complaints of the lower limbs. Their treatment is complex and should be multi-disciplinary, ideally as part of a care network led by dermatologists specialised in the field of cicatrisation.

Other diseases that are in the scope of the Institute are frequent and/or carry high morbidity/mortality rates. Basic and clinical research is required to progress in our understanding of the mechanisms involved in cardiac, vascular, respiratory, renal, endocrine, digestive, dermatologic and osteoarticular disorders.

- **Scientific challenges**

Diseases implicating heart and vessels, lungs, endocrine tissues, kidney, liver, skin, bone and joints and the digestive tract, although organ-specific, cannot be considered independently of the numerous interactions with the whole organism and the environment. Transversal aspects of physiology and pathology will be emphasized within the scope of the PMN Institute. Underlying fundamental research and biological issues that need to be addressed correspondingly cover a large field of disciplines requiring strong links between institutional partners, as well as with industrial partners. All these diseases share: 1- an incomplete knowledge of the genes involved in their etiology, a situation which is rapidly changing thanks in particular to the new genomic approaches, 2- an insufficient basic knowledge of gene and protein functions in target organs as well as their interaction with the environment; 3- incomplete understanding of pathophysiological mechanisms of diseases expressed within corresponding tissues, i.e. of mechanisms of initiation and progression of disease processes; 4- the general insufficiency of available treatments and preventive strategies based on a better understanding of the mechanisms of common diseases; 5- the understudied strategies of cell therapy, which could benefit to many of these diseases; 6- the importance of discovering new biomarkers that would be useful for diagnostic, prognostic and treatment guidance.

1) Gene/protein-function studies in physiology and interactions with environment

The availability of gene sequences encoding for molecules of unknown functions emphasizes the need for extensive gene-function studies and for the characterization of tissue distribution of newly identified genes. As part of this task, the development of new models to empower these studies is required. Other emphasis is required on development biology, on studies of ageing mechanisms, on comparative genomics with the goal of better understanding of human gene and protein functions, on integrative physiology to decipher signalling and metabolic pathways and interactions at the whole organism level, on the understanding of gene interactions and gene networks that impact on individual cell and tissue functions, on epigenetics and metagenomics to study gene interactions with the environment. The sequence of an increasing number of individual human genomes also paves the path toward in depth understanding of human gene and post-transcriptional diversity in cell, tissue and organ physiology. With few exceptions, the miRNA target genes and the mechanism of target suppression are currently unknown because reliable experimental methods for comprehensively identifying the miRNA targets have yet to be developed.

2) Disease-initiating mechanisms and mechanisms of disease progression in common diseases.

Mechanisms that trigger destructive processes within target tissues are seldom identified. Other than certain rare monogenic diseases involving key genes in cell function, common diseases usually develop on a multigenic susceptibility background associating “normal” gene variants, often affecting quantitative traits (intermediate phenotypes) that contribute to the clinical phenotype observed, most often interacting with environmental factors as part of a multifactorial process. As triggering factors remain elusive in most cases, new hypotheses in disease initiation should be tested, possibly stochastic events in initiation process or early external factors within perinatal or prenatal development. Genetic and molecular epidemiology can help to isolate specific risk factors, especially to identify subjects at risk of sudden death, a major problem in industrially developed countries. Furthermore, striking changes in the incidence of major multifactorial diseases will need to be addressed. Delineating initiation and progression events in common diseases is a challenge that applies at three levels: genetic susceptibility, cell pathways involved in disease and the role of environmental factors. Within a given genetic background, some genes concur at initiating the disease process while others control disease progression that directly impact on the age at disease onset following a preclinical phase. Seemingly, some environmental factors trigger the disease process while other modulate disease progression.

3) Treatments based on mechanisms of diseases

In many diseases within the PMN scope, current treatments remain insufficient for different reasons, depending of the field covered. Some treatments remain symptomatic or palliative (e.g. treatments of chronic heart disease, substitutive therapies in endocrine diseases, dialysis in end stage renal diseases, organ transplantation in renal, heart, lung, liver or gut failures). In other examples, pathophysiological treatment that remain non-specific (e.g. immunosuppressive treatments in immune/inflammatory diseases) induces severe side effects. Novel strategies aimed at controlling the immune/inflammatory response should be developed (small molecules targeting inflammatory pathways, monoclonal antibodies vaccination). In a third set of diseases, preventive strategies are available but only target biomarkers that relate with a risk factor associated with the disease process (e.g. treatment of obesity to prevent metabolic and cardiovascular diseases) but in most cases the risk factor that is amenable to treatment is only part of the susceptibility that underlies the pathological process (e.g. atherosclerosis in case of cardiovascular diseases). Finally, major ischemic diseases (heart, brain, limbs, kidney) suffer from the lack of treatments able to protect tissues for ischemic sequelae.

4) Strategies for cell replacement

Among the aforementioned palliative therapeutic strategies, organ transplantation have developed since the mid fifties. They have now been generalized in many field of medicine (e.g. renal transplantation imply a favorable risk to benefit ratio as compared to dialysis, heart or liver transplantation are the only feasible strategies in corresponding organ failures). However, transplantation still face the lack of organ donors, significant side effects relating with long term immunosuppression and the complexity of surgical procedures. Evolution of organ replacement strategies faces the need for new strategies to provide cells or organs amenable to transplantation in human diseases. An underlying emphasis will be in study of organ development and molecular mechanisms involved, the study of stem cell biology and strategies to develop artificial or in vitro-engineered tissues and organs. Embryonic and adult stem cell transplantation as a potential means of regenerating injured tissues is currently receiving a great deal of interest. To exploit this as a viable therapy, methods need to be developed for harvesting and expansion of stem cells in sufficient quantities. This in turn implies greater knowledge of the pathways controlling replication and maturation of stem cells. Genomic and proteomic methods are ideally suited to provide these new

insights. Standardised experimental animal models that reproduce human disease are required for translational research. Furthermore information regarding the safety of cells based therapy in patients is needed.

- **Technological challenges**

To achieve insight into physiology and pathophysiological processes in the fields covered by the PMN institute, technological challenges are multifold. The human genome opens the need for better understanding of gene regulation and interaction with the environment, both in physiology and in pathology. Beyond high-throughput DNA sequencing and transcriptomics, epigenetics and metagenomics will need to be developed to get insight into both organ development and physiology and into mechanisms of common diseases. A parallel challenge is, at the other extreme of the spectrum from fundamental research to applied medicine, the need for setting up clinical phenotyping platforms including sensory platform in an effort towards an improved classification of common diseases that, as aforementioned, lack identified aetiologies on which medical classifications may rely on.

Specific challenges:

1) Development of improved models to apply the advances of genetics, genomics transcriptomics and proteomics to the study of gene and protein functions, and creation of tools (platforms) enabling genomic analysis of epigenetic programs and changes in individual or small groups of cells in integrated contexts

2) Development of appropriate facilities for study of both large animals models and small model organisms where teams of researchers and clinicians can address molecular, physiological and pathological questions by studying underlying mechanisms in integrated contexts. This includes the development of advanced imageing techniques (e.g. cell imageing, high-resolution imageing, multiphoton microscopy, small animal imageing).

3) Development of translational research networks at the crossroad of research institutes and hospitals with the aim of developing biomarkers and innovative therapeutic strategies.

4) Optimize the use of the important human bioresources (blood, plasma, DNA, tissue samples) available and currently being constituted in the fields covered by the PMN Institute, and facilitate their exploitation using advanced technology.

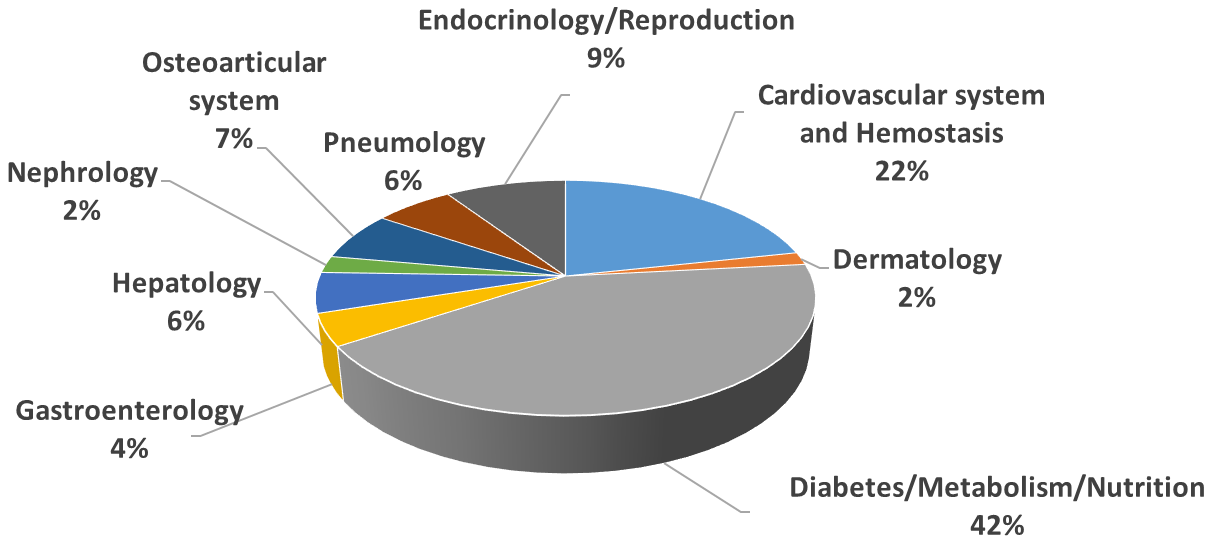
5) Establishment of resource centres centralising interactive data sets such as that (Standards based Infrastructure with Distributed Resources, SIDR) set up by the CNRS/INIST to better collect, annotate, exploit and harness qualitative and quantitative data sets from different sources to be used in modelling and systems biology approaches for understanding basic biological mechanisms and pathophysiological regulations.

3 – ITMO PMN in numbers

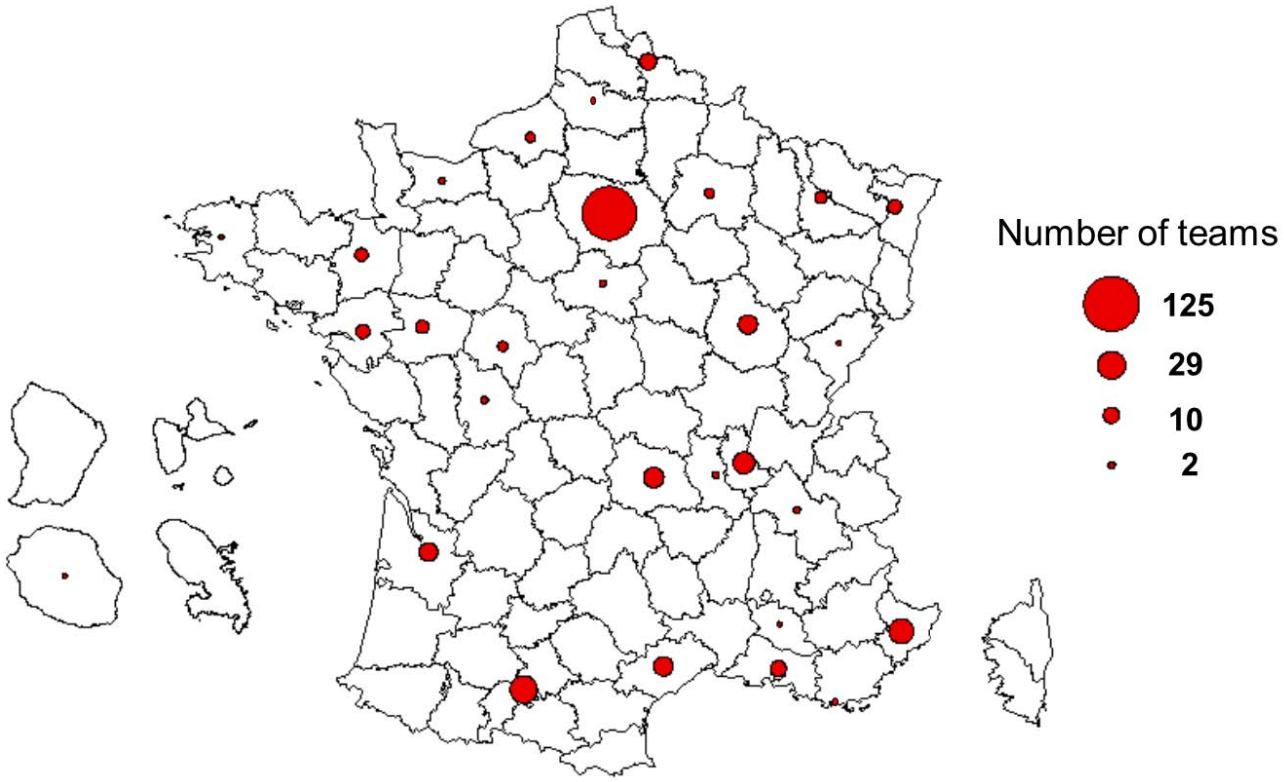
- 343 research teams
- 1,540 researchers
- 1,160 hospital practitioners
- 15,800 publications a year

Team distribution by domain

- The teams are distributed in the following domains:



Geographical distribution



- About 36% of ITMO PMN teams are based in the Paris area.
- Teams are affiliated to 38 universities (7 in Paris area) and 13 *Grandes Ecoles* (4 in Paris).

- Some spots display focused and specific research activities:
  - metabolism/nutrition in Bordeaux, Clermont-Ferrand, Dijon, Lyon and Nice
  - cardiovascular and metabolic diseases in Toulouse
  - diabetes in Lille
  - cardiometabolism in Nantes

- In the Paris area, the teams are spread out on 27 spots. Some of them are focused on specific field:
  - cardiovascular in Georges Pompidou European Hospital
  - cardiometabolism in Pitié Salpêtrière Hospital
  - diabetes in Cochin Hospital
  - metabolism/nutrition in Jouy-en-Josas and in Campus Paris Rive Gauche
  - hepato/gastroenterology in Bichat Hospital

Other research infrastructures

- Clinical Investigation Centres (CIC)

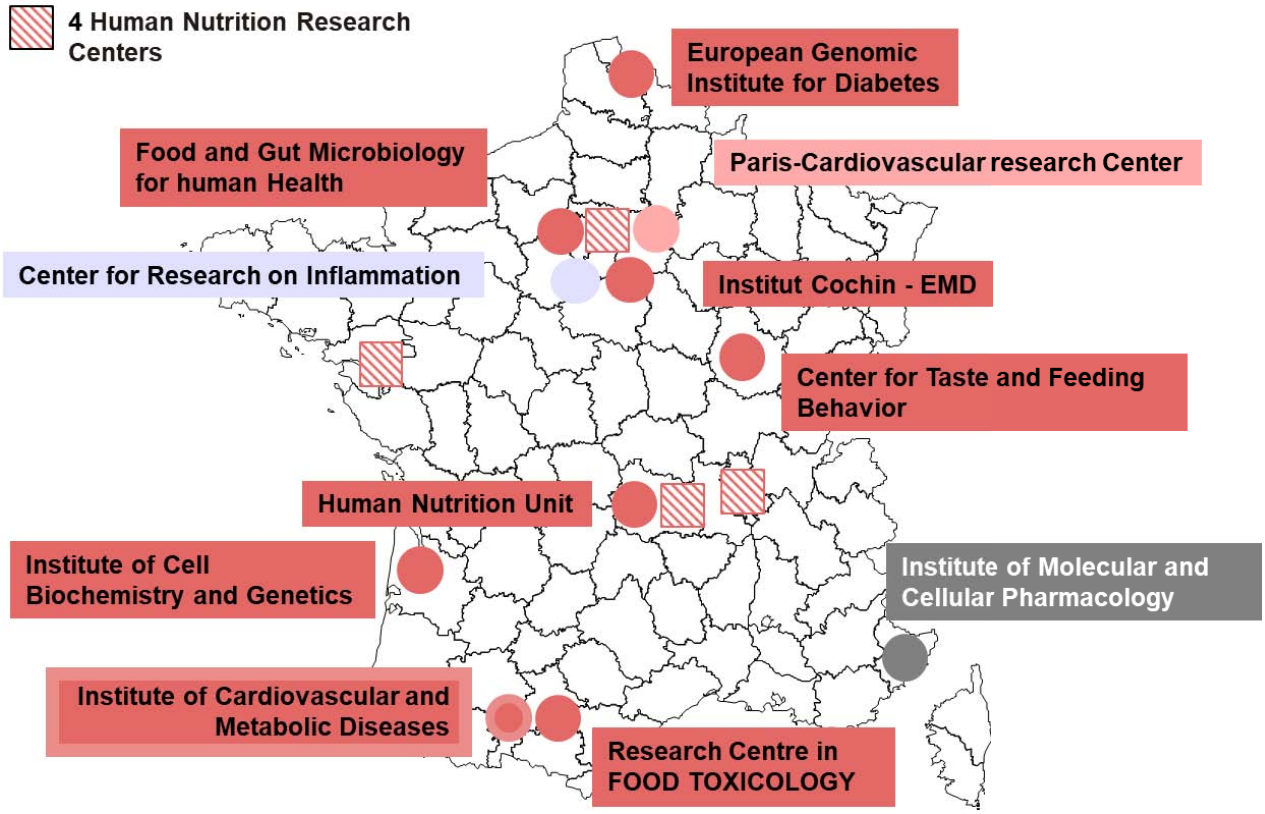
Set up by the Ministry of Health through the DGOS (Department for the supply of healthcare) and Inserm (the National Institute for Health and Medical Research), the CICs are clinical research infrastructures dedicated to the organisation, coordination and realization of physiology, pathophysiology and/or therapy protocols with the aim to increase knowledge of diseases, their prevention and treatments.
The CICs' activities are always closely linked to the University Hospital research programs. There are 36 CICs to date. They are organized into 54 theme-based modules and spread out in France. The CICs are connected through 9 national thematic networks, 3 of them displaying the following themes: "Thrombosis", "Cardiovascular diseases", "Hepatology and Gastroenterology".
More than 40% of protocols developed in CIC networks relate to one of the domains covered by ITMO PMN.

- Networks for excellence in clinical research

The national infrastructure for French clinical research F-CRIN approved networks for excellence in clinical research to lead original and internationally appealing scientific programmes. These programmes have targeted themes with major potential for development and benefit from renowned collective scientific and methodological expertise with a strong capacity for research. Out of the 19 approved Networks, 8 are specialized to the following themes: "Thrombosis", "Obesity", "Cardiovascular diseases", "Cardiovascular and renal diseases", "Autoimmune and autoinflammatory diseases", "Severe asthma", "Atopic dermatitis" and "Stroke".

- Human Nutrition Research Centers (HNRC)

The Human Nutrition Research Centers were set up to develop research on clinical nutrition in healthy human and out patients, to provide specific facilities regarding both investigation tools and specific food conditioning. The 4 centers were created in Lyon (Rhône-Alpes), Clermont-Ferrand, Nantes (Grand-Ouest) and Paris (Ile-de-France). Each of these centers is a combination of several research units from INRAe, INSERM, Universities and clinical units from University Hospitals with specific facilities.



French initiative « Investments for the Future »

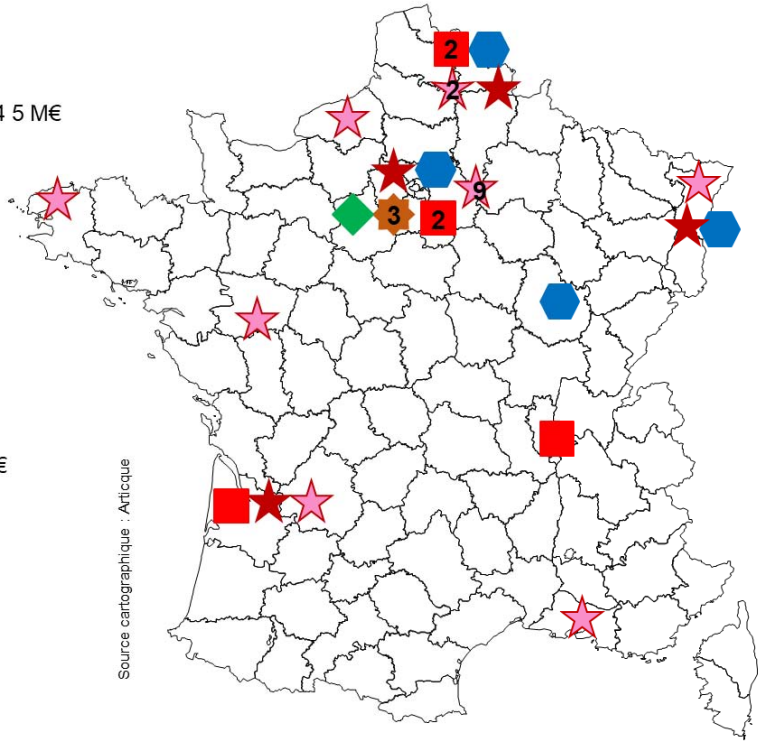
Launched in 2009 by the French Government, the Investments for the Future programmes are strategic initiatives which aim to boost French competitiveness by investing particularly in research and higher education. This strong financial support to research, higher education and innovation aimed at promoting excellence and the development of high-level projects and clusters and strengthening France's capacity for innovation.
Among others, the main programmes in the fields of the PMN institute are listed below and detailed in the following figure:

- Equipment of excellence, EQUIPEX (very high quality scientific facilities)
- Laboratories of Excellence, LABEX (internationally visible labs)
- Research Hospitals, IHU (centers of excellence in research, care, training and technology transfer in the health field)
- Cohort (long-term funding for cohorts with underlying health issues)
- Preindustrial Biotechnology Demonstrators (allowing faster achievement of the proof of commercial concept)
- National Infrastructures in Health and Biotechnology
- Hospital University research in Health, RHU (supporting translational health research projects or clinical research project)

RHU:
BOOSTER 9 M€
Cil'LICO 6 M€
DESTINATION 2024 5 M€
EVIRED 9 M€
COSY 5M€
FollowKnee 8 M€
iVASC 8,5 M€
iMAP 9 M€
Innov-CKD 6 M€
KTD-Innov 9 M€
PreciNASH 6 M€
QUID-NASH 9 M€
SHIVA 8,2 M€
STOP-AS 6,6 M€
SUccESS 9 M€
WillAssistHeart 6 M€
DELIVER 6,7 M€

IHU:
ICAN 45 M€
LIRYC 61 M€
MixSurg 80,3 M€

IHU-B:
PreciDIAB 5M€



National Infrastructures:
F-CRIN 23,4 M€
MetaboHub 12,9 M€
ECELLFRANCE 16,3 M€

Cohorts:
CKD rein 4 M€
E4N 7,9 M€
CONSTANCES 35 M€

Demonstration project:
MetaGenoPolis 19 M€

Labex:
EGID 26,7 M€
INFLAMEX 13,3 M€
LipStic 8,3 M€
Hepsys 3 M€

Equipex:
IVTV 2,7 M€
LIGAN 8 M€
MUSIC 3 M€
RE-CO-NAI 13 M€
ImaginExBioMed 6,8 M€
HEPATHER 10 M€

Circulatory system

C2VN
Centre de Recherche en CardioVasculaire et Nutrition

Marie-Christine Alessi
Pierre Emmanuel Morange

Thrombosis, platelets and vascular disorders

Aix-Marseille University
INRAE UMR 1260 INSERM UMR 1263
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Key facts

Team

- Researchers : 15
- Technicians : 6
- Postdoc fellows : 0
- PhD Students : 6

Translational approaches

- Patents : 3
- Clinical research grants : 2
- Industry partnerships : 5

International research links

- Ashford MLJ university of Dundee (UK)
- Gresele Paolo, university of Perugia (Italy)
- PhD Program (TICARDIO) between C2VN, university of mainz (germany) and Maastricht (Netherlands)

Keywords

- Thrombosis
- Platelets
- Haemostasis
- Cardiovascular
- Pathophysiology
- Biomarkers
- Adipose tissue
- Genome editing
- Cell culture
- Epidemiology
- Mice model
- Molecular biology

Biological Resources

- Animal models (mice and rat)
- Cohorts of patients (thrombosis) and families (rare haemostasis disease)
- Main laboratory cell lines
- Biobank (accredited biological resource center, Hemovasc)

Thrombosis is a major clinical problem. Through the study of large populations and rare diseases we aim to identify hereditary and non-hereditary components that contribute to haemostasis and thrombosis. Our major goal is to identify relevant biomarkers and new therapeutical targets.

Research Brief :

The formation of thrombi at sites of vessel lesions is a major clinical problem. Thrombosis results from the interaction of genetic and environmental risk factors. Progress in this field requires the identification of specific hereditary and environmental risk factors in affected individuals and of the design of new antithrombotic therapies. Emerging technologies are beginning to allow the unbiased characterization of variation in genes, RNA, proteins and metabolites associated with thrombotic conditions. These approaches will lead us to identify genes, epigenetic and metabolites variations that could be biomarkers themselves or will point to circulating markers of thrombosis for further exploration. Furthermore, by studying rare inherited diseases causing platelet dysfunction or low platelet counts, we aim to identify new pathways involved in thrombosis. We extend our objectives to environmental factors through the understanding of the role of platelets in tissue injury in various pathological contexts. We also examine how nutrition and obesity can affect thrombosis and the cardiovascular pathophysiology. During obesity, expansion of ectopic fat (epicardial and perivascular depots) may exert adverse lipotoxic, prothrombotic, and proinflammatory effects. Using noninvasive imaging we will unveil the direct myocardial and vascular targets of ectopic adipose tissue action.

- **Methodologies Used :**

Cohort evaluation / Genotyping platforms
genome editing
Rat model of metabolic syndrome / Murine models of thrombosis and obesity
Cell cultures, flow chamber, microscopy
Biological evaluation (cytometry, qPCR, cell culture...)
Magnetic Resonance Imaging (collaborative work)

Publications

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Main objectives of team 2 of the C2VN

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C2VN Centre de Recherche en CardioVasculaire et Nutrition

Françoise Dignat-George
Christophe Dubois

Endothelium, blood cells and vascular diseases

Aix-Marseille University
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Marie-Christine ALESSI
Marseille

Dysregulation of vascular homeostasis is a critical determinant of cardiovascular diseases. From mechanistic studies to translational and clinical research, our objective is to identify new molecular and cellular targets to improve diagnosis and therapy of vascular disorders.

Key facts

Team

- Researchers : 26
- Technicians : 9
- Postdoc fellows : 1
- PhD Students : 14

Translational approaches

- Patents : 13
- Clinical research grants : 20
- Industry partnerships : 4

International research links

- PhD program (TICARDIO) between C2VN, University of Mainz (Germany) and Maastricht (Netherlands)
- Pr Nigel Mackman, University of North Carolina, Chapel Hill, USA : Roles of TF-bearing microparticles in thrombosis associated with cancer (on going collaboration with a MTA)
- Rienk Nieuwland, Academic Medical Center, Laboratory of Experimental Clinical Chemistry (Vesicular Observation Center), Amsterdam, The Netherlands :\\\"Microparticle standardization by flow cytometry\\\"

Keywords

- Extracellular vesicles
- Thrombosis
- Vascular biology
- Vascular regeneration
- Endothelial cells
- Experimental animal models
- vascular imaging
- Intravital microscopy
- Molecular and cellular biology
- Angiogenesis models

Biological Resources

- In vivo models of thrombosis
- Vascular disease patients cohorts
- Animal models of ischemia
- Trangenic mouse
- Biobanks of patient-derived endothelial cells

Research Brief :

The dynamic interplay between endothelium cells and molecular and cellular and subcellular blood components is a key component of vascular homeostasis. Their dysregulations are at the crossroad of pathogenic processes underlying vascular thrombotic, inflammatory or ischemic diseases. Better knowledge of the molecular pathways and cellular effectors of these processes is challenging to develop biomarkers and therapeutic options targeting cardiovascular risk. Our research aims at addressing the contribution of leucocytes, endothelial progenitors, extracellular vesicles and Nets in immuno-thrombosis, vascular injury and regeneration. Based on original in vitro and in vivo models our goal is to transpose this knowledge to clinical practice through delineation of original biomarkers, imaging strategies and cell-based therapies allowing to promote a personalized approach of vascular medicine. Main topics include 1/ Understanding of the interactions of neutrophils platelets and nets at with endothelium and their contribution to thrombosis and cancer. 2/ Characterization of the structure-function relationship of extracellular vesicles that determine their role in the coagulolytic balance and their significance in vascular diseases 3/ Study of the progenitor cells-dependent endothelial repair processes in vascular diseases, and identification of innovative imaging strategies and cell-based therapies with clinical usefulness in ischemic vasculopathies.

Methodologies Used :

Molecular and cellular biology
Vascular cell culture
Vessels functional imaging
Angiogenesis models
Animals models of thrombosis
Intravital microscopy

Publications

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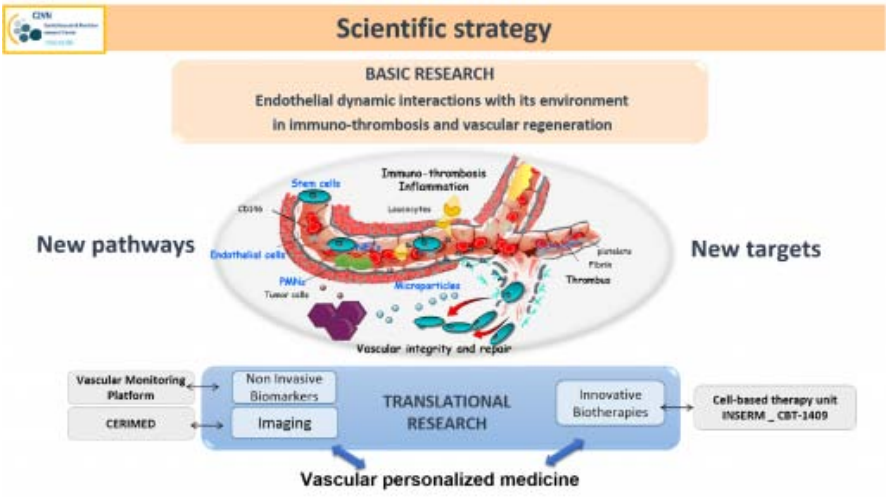
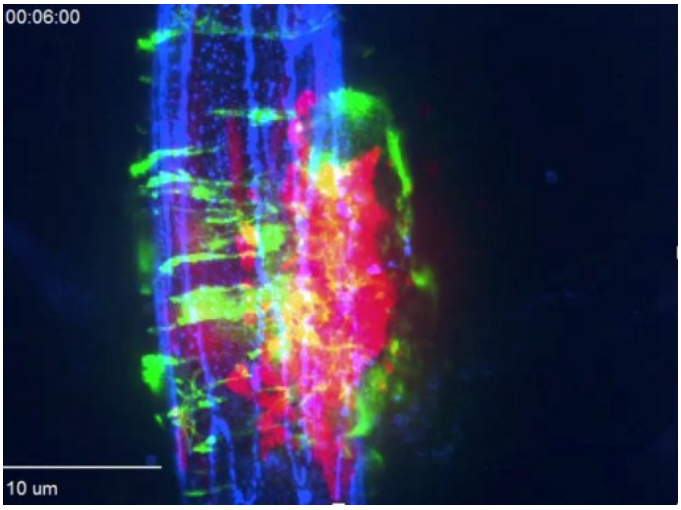
Research topic and strategy



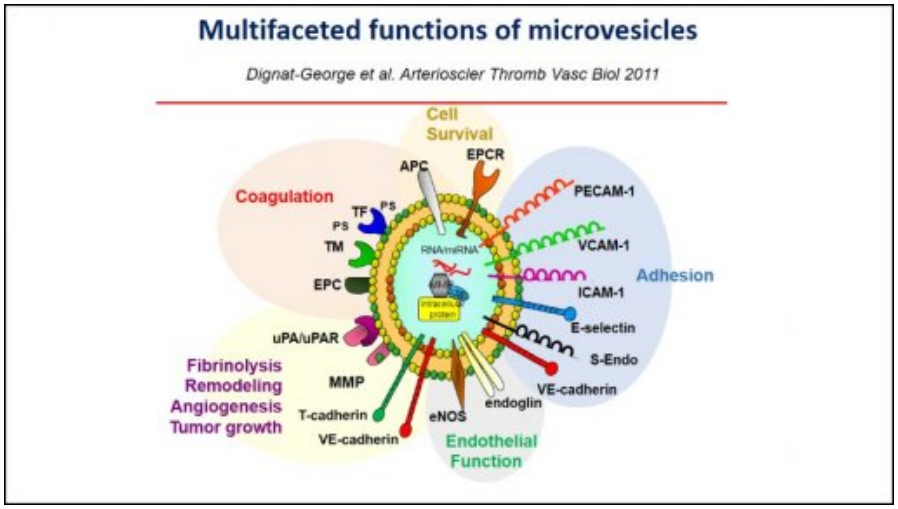
Our research strategy is focused on the mechanisms by which the endothelium dynamically interacts with its environment and their dysregulation in vascular disorders. From this basic knowledge we aim to identify new pathways and targets towards an innovative and personalized vascular médicine.

Real-time observation of a growing thrombus in a living mouse



A laser-induced injury was performed on arterioles of a living mouse leading to the activation of the endothelium (blue), the accumulation of platelets (red) at the site of injury and the generation of fibrin (depicted in green). Platelets, endothelial cells and fibrin were observed by real-time confocal intravital microscopy.

Microparticles



Endothelial microparticles are considered as a miniature version of endothelial cells. They express a large repertoire of endothelial molecules and biological functions that are related to their involment in the tuning of vascular homeostasis.

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C2VN
Centre de Recherche en CardioVasculaire et Nutrition

Régis Guieu

Dysoxia, purinergic system and inflammation

Aix-Marseille University
INSERM 1263 INRAE 1260
Marie-Christine Alessi
Marseille

Key facts

Team

• Researchers : 25
• Technicians : 6
• Postdoc fellows : 0
• PhD Students : 15

Translational approaches

• Patents : 2
• Clinical research grants : 4
• Industry partnerships : 2

International research links

• Spain and Denmark
• Italy and Belgium
• USA and Sweden

Keywords

• Adenosinergic system
• Dysoxia
• Coronary artery disease
• Cardiotoxicity
• Biomarkers
• Induced pluripotent stem cells
• Murine models
• Functional Genomics
• Translational Research

Biological Resources

• hiPSC clones for research on cardiotoxicity
• Cohorts of patients
• Biobanks for research on cardiotoxicity
• Animal models (mice and rat)

We have developped specific tools for the identification of spare adenosine receptors in cardiovascular diseases, and we have unique expertise in identification of pathophysiological mechanisms associated to immune cardiac adverse events of cancer therapies.

Research Brief :

The team studies the effects of inflammation and dysoxia in the pathophysiological mechanisms of arrhythmias, coronary artery disease and cardiotoxicity, with a translational approach based on recognized clinical research and the development of fundamental approaches using unique technologies in cellular and animal models. The research projects have been developed around three main axes:
1. The first axis addresses the role that the adenosinergic system plays in CVDs, primarily arrhythmias and coronary artery diseases. We have developed specific tools to evaluate adenosine metabolism and the expression and function of adenosine receptors.
2. The second axis addresses cardiovascular adaptation to extreme conditions of oxygenation and pressure and the role that adenosine and its receptors play in this adaptation. These studies are facilitated thanks to a unique technical platform including hypobaric hypoxia chambers and a hyperbaric chamber, which enable us to study all conditions of extreme oxygenation and/or pressure.
3. The third axis addresses the response of the cardiovascular system to inflammation and dysimmunity, primarily in the context of cardiotoxicity to anticancer treatments. The strength of our studies lies on the implementation of translational approaches from clinical studies to innovative cellular models of hiPSC. Pre-clinical in vivo models were developed to assess the involved pathophysiological mechanisms that are challenging to investigate in humans.

• **Methodologies Used :**

Hyperbaria chamber, chemical and physical model of hypoxia
Translational approaches
Cardiac differenciation of hiPSC
Functional genomics
Transcriptomics
Cardiac electrophysiology

Publications

Brignole M, Guieu R, Tomaino M, Iori M, Ungar A, Bertolone C, Unterhuber M, Bottoni N, Tesi F, Claude Deharo J (2017). Mechanism of syncope without prodromes with normal heart and normal electrocardiogram, Heart Rhythm. 14(2), 234-239

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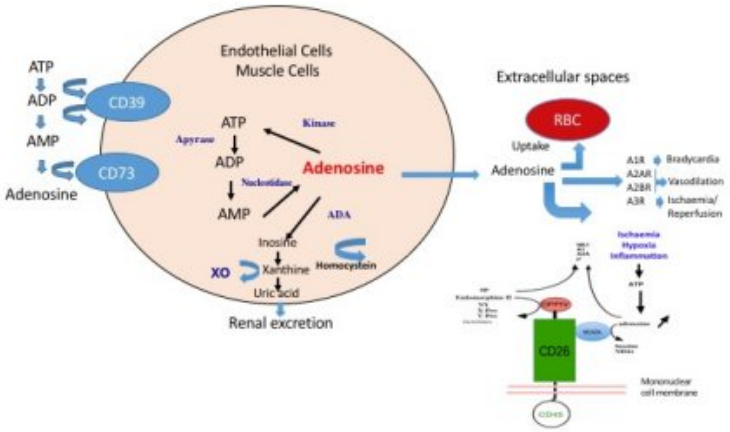
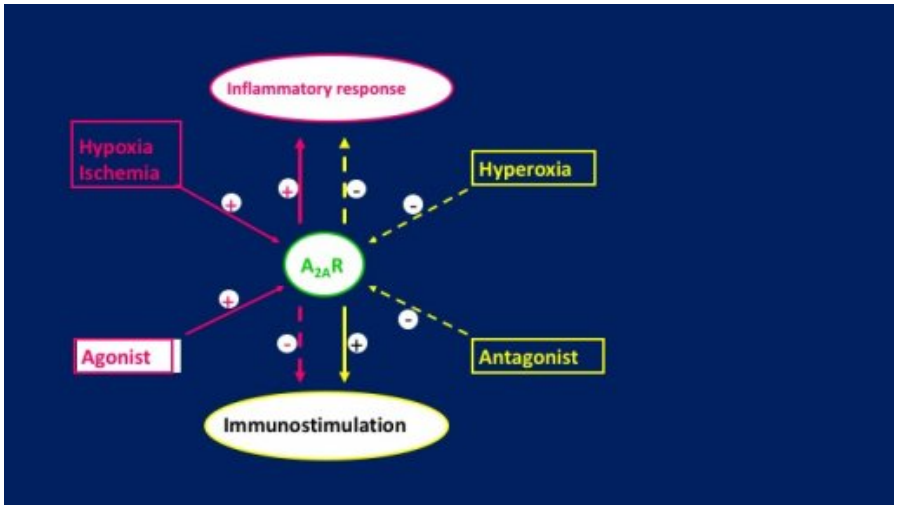
Simplified representation of the adenosinergic system



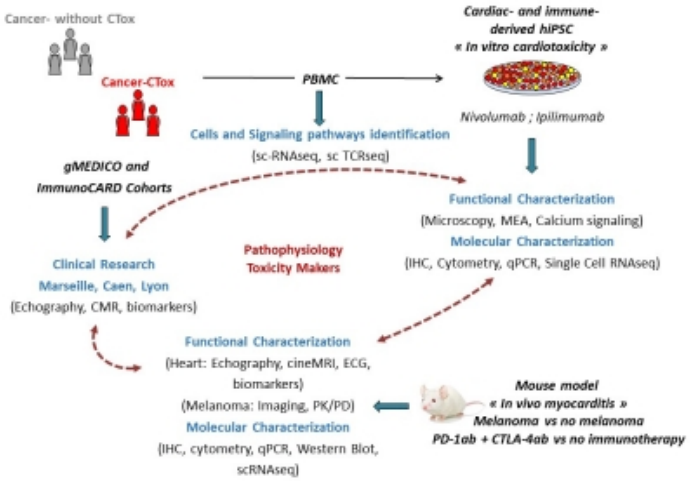
Simplified representation of the adenosinergic system and of its implication in the control of the cardiovascular system

A2A receptor and hypoxia



Simplified representation of the role of the A2A adenosine receptors on hypoxia-induced inflammation

Translational research on Myocarditis related to immune checkpoint inhibitors



Integrating data from multicentre patient cohorts, preclinical mouse model, and hiPSC cellular model to define the clinical profile of ICI-myocarditis, to better understand its pathophysiology, to identify predictive biomarkers of toxicity and of poor prognosis, to test new targeted therapeutic approaches.

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C2VN Centre de Recherche en CardioVasculaire et Nutrition

Stéphane BURTEY
Marcel BLOT-CHABAUD

New endothelial molecular targets (NEMOT)

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Marie-Christine Alessi
Marseille

This team identified two new endothelial molecules involved in inflammation, thrombosis and angiogenesis (aryl hydrocarbon receptor and CD146) with the objective of using them in personnalized medicine as biomarkers and therapeutic targets

Key facts

Team

- Researchers : 11
- Technicians : 5
- Postdoc fellows : 0
- PhD Students : 5

Translational approaches

- Patents : 7
- Clinical research grants : 4
- Industry partnerships : 2

International research links

- Belgium
- USA
- nederlands

Keywords

- Endothelium
- Uremic toxins
- Chronic kidney disease
- CD146
- Cancer
- Cellular biology/cytometry
- Molecular biology
- Translational medecine
- flow culture
- Animals models

Biological Resources

- Ahr KO mouse
- Antibodies against CD146 and recombinant CD146 proteins
- EVITHUP cohort
- Flow culture of endothelial cells
- CD146 KO mice
- Binational cohorts of hemodialysed patients (France/Algeria)

Research Brief :

The goal of the "New Endothelial Molecular Targets" team is to investigate two endothelial proteins identified by our group as new potential vascular therapeutic targets involved in inflammation, angiogenesis and atherothrombosis: the aryl hydrocarbon receptor (AhR) and CD146. AhR is a receptor for numerous solutes, including uremic toxins of indole family, and its activation in EC is associated with a procoagulant and proinflammatory phenotype leading to atherothrombosis. AHR plays a key role in the expression of PgP in the liver in response to uremic toxins. CD146 is a transmembrane glycoprotein belonging to the Ig superfamily, also detectable in the bloodstream as a soluble form (sCD146).The CD146/sCD146 system is expressed on both EC, where it is involved in angiogenesis and inflammation, and numerous tumor cells, where it induces tumor angiogenesis and growth.
The team IV project will combine the knowledge and know-how of two research groups sharing expertise in the original endothelial target identified by VRCM.
Our objectives for the next five years are 1/ to characterize the functions of these proteins in endothelial cells, 2/ to further elucidate their interrelationships and 3/ to validate them as targets in vascular diseases in relevant preclinical models, such as flow cell culture and "close-to-disease" mouse models, in order to generate innovative devices for diagnostic or therapeutic applications.

- **Methodologies Used :**

Mouse models, Flow culture, in vivo video microscopy, molecular biology.

Publications

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Dufies, Nollet, Ambrossetti, Traboulsi, Viotti, Borchiellini, Grepin, Parola, Helley-Rusick, Bensalah, Ravaud, Bernhard, Schiappa, Bardin, Dignat-George, Rioux-Leclercq, Oudard, Négrier, Ferrero, Chamorey, Pages, Blot-Chabaud* (2018). Soluble CD146 is a predictive marker of pejorative evolution and of sunitinib efficacy in clear cell renal carcinoma, Theranostics. 8(9), 2447-2458*

Dou L, Poitevin S, Sallée M, Addi T, Gondouin B, McKay N, Denison MS, Jourde-Chiche N, Duval-Sabatier A, Cerini C, Brunet P, Dignat-George F, Burtey S (2018). Aryl hydrocarbon receptor is activated in patients and mice with chronic kidney disease, Kidney Int. 93(4), 986

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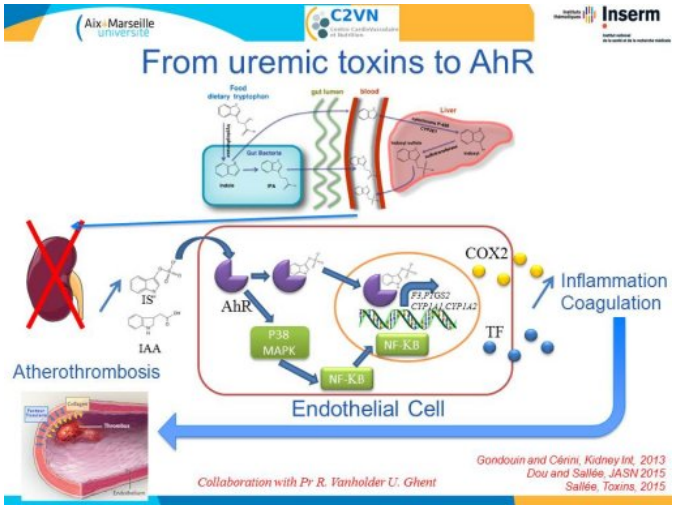
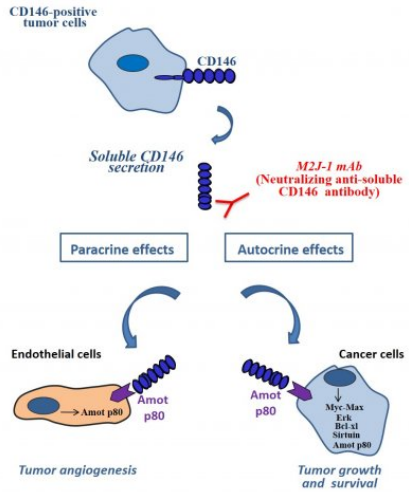
From uremic toxins to Atherothrombosis



Indoles (indoxyl sulfate and indole acetic acid) are uremic toxins derived from the tryptophan metabolism in the gut. They activate aryl hydrocarbon receptor in the endothelial cells. AhR activation induces endothelial dysfunction leading to inflammation and procoagulant profil. Endothelial dysfunction, mainly expression of Tissue Factor, could lead to atherothrombosis and explains the increased cardiovascular mortality observed during Chronic kidney disease.

Summary of the effects induced by soluble CD146 on cancer cells



CD146-positive tumors secrete soluble CD146 through shedding of the membrane form. This soluble CD146 generates both paracrine and autocrine effects trough binding to angiomotin. Paracrine effects involves proliferation of endothelial cells , leading to tumor angiogenesis. Autocrine effects are mediated through the induction of different factors in cancer cells, leading to tumor growth and survival.
All these effects can be antagonized by the neutralizing anti-soluble CD146 M2J-1 antibody.

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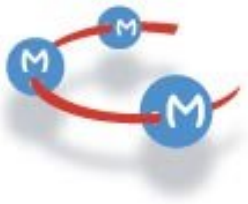

Giulia Chinetti
Jaap Neels

Immune cells and cardiometabolic disease

Université Côte d'Azur
Inserm U1065
Patrick Auberger
NICE

Key facts

Team

- Researchers : 8
- Technicians : 1
- Postdoc fellows : 1
- PhD Students : 1

Translational approaches

- Patents : 1
- Clinical research grants : 1
- Industry partnerships : 0

Keywords

- Immune cells
- Metabolism
- Cardiovascular disease
- Metabolic syndrome
- Nuclear receptors
- molecular biology
- biochemistry
- cell biology
- animal studies
- clinical studies

Biological Resources

- Transgenic mice for tissue-specific expression of PPARb
- Genetically modified Jurkat T cells
- Collection of carotid tissue, plasma, and PBMCs from a cohort of patients suffering from atherosclerosis
- Collection of aneurysmal tissue, plasma, and PBMCs from a cohort of patients suffering from abdominal aortic aneurysms.

The strong presence of clinical members in our team has allowed us to develop different sample collections from patients suffering from atherosclerotic plaques in their carotid arteries, abdominal aortic aneurysms, or myocardial infarctions.

Research Brief :

Our team studies the role of immune cells in cardiometabolic disease. More specifically, our research focuses on both macrophages and T cells and how they are implicated in different cardiometabolic pathologies such as obesity-associated inflammation and its connection with development of insulin resistance and type-2 diabetes, but also the involvement of these immune cells in atherosclerosis, abdominal aortic aneurysm, and cardiomyopathy. The role of members of the peroxisome proliferator-activated receptor (PPAR) family, in particular PPARbeta, in this context has been one of our main research interests. The role of these nuclear receptors in different aspects of immune cell biology (e.g. metabolism and polarization), in the context of cardiometabolic disease, has been a major research subject for us.

One of our more recent and current research interests focuses on vascular calcification (VC) and the role of macrophages, T cells, and PPAR members in VC development. One of the approaches that we use in this context is the application of artificial intelligence on patient data (imaging combined with biological and clinical characteristics) to develop predictive models of VC progression and post-operative outcomes.

To explore our research interests, we combine different approaches including in vitro cell biology, in vivo mouse models, ex vivo patient samples, clinical studies, and artificial intelligence.

- **Methodologies Used :**

Clinical studies
Animal studies
Cell biology
Biochemistry
Molecular biology

Publications

Rousseau AS, Sibille B, Murdaca J, Mothe-Satney I, Grimaldi PA, Neels JG (2016). Alpha-Lipoic acid up-regulates expression of peroxisome proliferator-activated receptor Beta in skeletal muscle: involvement of the JNK signaling pathway, FASEB Journal. 30(3), 1287-99

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Key facts

Team

• Researchers : 6
• Technicians : 4
• Postdoc fellows : 2
• PhD Students : 3

Translational approaches

• Patents : 3
• Clinical research grants : 0
• Industry partnerships : 1

International research links

• Germany, Austria, Italy, England, USA, Thailand

Keywords

• cardiac arrhythmias
• apoptosis
• ischemia-reperfusion injury
• electrophysiology
• pacemaker activity
• Mouse models of myocardial infarction and heart failure
• Cardiac exploration ex vivo (isolated heart) and in vivo (echocardiography; telemetry)
• Genetically-modified mouse models of dysfunction in cardiac pacemaking
• Optical mapping and confocal imaging of intracellular Ca2+ handling
• Cardiac and cellular electrophysiology

Biological Resources

• in vivo and in vitro models of heart disease
• surgical models
• genetic models

Matteo Mangoni Stéphanie Barrère - Lemaire

Cardioprotection, physiopathology of heart rhythm and ischemia

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CNRS UMR5203 Inserm U1191
Philippe Marin
Montpellier

We developed worldwide unique mouse models to investigate the mechanisms underlying dysfunction of heart automaticity and have identified putative targets in the signaling cascade downstream the FAS-receptor apoptotic pathway activated during ischemia-reperfusion injury.

Research Brief :

Our research aims to develop strategies to protect the heart from sinus node dysfunction and associated arrhythmias under conditions of cardiovascular disease and ageing. To this aim, we study the role of ion channels in the mechanisms underlying the genesis and regulation of heart rate. We were the first to develop in vitro electrophysiological studies on mouse sinus node (SAN) and atrioventricular (AVN) cells associated to confocal live imaging of calcium. Our strategy is based on the use of genetically modified mouse models to identify the contribution of the ion channels and intracellular calcium release in the generation and regulation of cardiac automaticity associated with in vivo experiments using telemetry on freely moving mice.
We seek to understand the mechanisms underlying reperfusion-induced cell death in ischemic tissues after myocardial infarction. We were the first to identify the FAS-DAXX apoptotic pathway as a target for cardioprotection and have developed therapeutic peptides to inhibit this cascade specifically activated during reperfusion injury. In parallel, we have developed cell-based therapeutics with improved therapeutic properties capable of inhibiting reperfusion injury. These innovative tools, administered as an adjunct to reperfusion therapy, will further reduce cardiac injury and lower morbidity and mortality rates in patients.

• **Methodologies Used :**

Patch clamp recording
Optical mapping
Confocal imaging of intracellular Ca2+ dynamics
Cardiac exploration ex vivo (isolated heart) and in vivo (echography, telemetry)
Genetically-modified mouse models of cardiac automaticity and impulse conduction
Mouse models of myocardial infarction

Publications

Torrente AG, Mesirca P, Neco P, Rizzetto R, Dubel S, Barrere C, Sinegger-Brauns M, Striessnig J, Richard S, Nargeot J, Gomez AM, Mangoni ME. (2016). L-type Cav1.3 channels regulate ryanodine receptor-dependent Ca2+ release during sino-atrial node pacemaker activity., Cardiovascular Research. 109(3), 451-61

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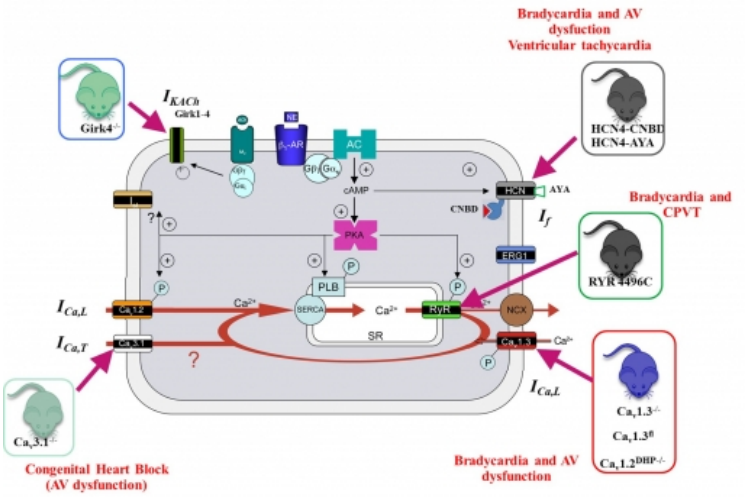
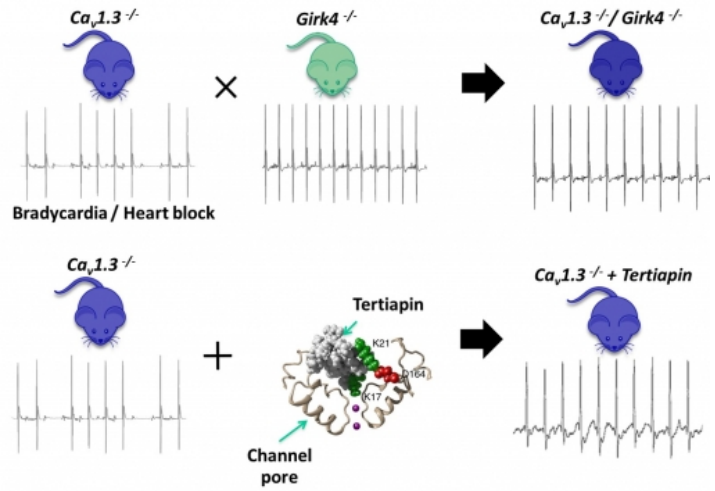
Mouse models of sino-atrial node dysfunction



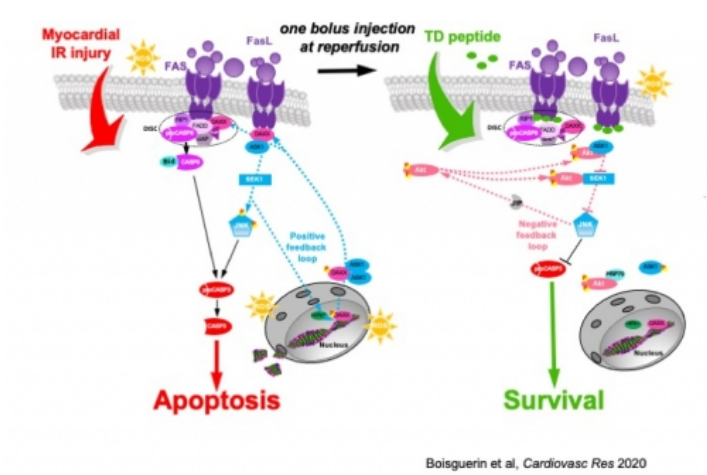
Mouse models of sino-atrial node dysfuction available in our research team. Models are generated by inducing constitutive or conditional loss-of-function in ion channels involved in the generation of sino-atrial pacemaker activity and atrioventricular conduction.

Targeting of GirK4 channels rescues sino-atrial dysfunction



Cav1.3 knockout (KO) mice show sinus bradycardia and 2nd degree atrioventricular block. Girk4 KO mice present with normal heart. Crossing these mouse lines produces Cav1.3/Girk4 KO animals with normal heart rate. When Cav1.3 KO mice undergo an intraperitoneal injection of the GIRK pore blocker tertiapin (represented bound to the channel pore) normalization of heart rate is observed. Girk4 targeting could be a future therapeutic approach for dysfunction of heart automaticity.

Pharmacological cardioprotective strategies to fight against myocardial Ischemia-reperfusion injury.



Boisguerin et al, *Cardiovasc Res* 2020

Our objective is to develop strategies that prevent cellular apoptosis following ischemia-reperfusion injury. Using innovative interfering peptide, we target the apoptotic extrinsic pathway downstream the FAS receptor and stimulate the cardioprotective pathways.

Mangoni Matteo - Matteo.Mangoni@igf.cnrs.fr - +33633181463 - https://www.igf.cnrs.fr/index.php/en/h-teams-en/h-barrere-en

Key facts

Team

- Researchers : 16
- Technicians : 15
- Postdoc fellows : 7
- PhD Students : 12

Translational approaches

- Patents : 4
- Clinical research grants : 1
- Industry partnerships : 1

International research links

- Europe
- United States

Keywords

- Intestine
- Circadian rhythm
- Adipose tissue
- Mitochondrial functions
- Transcriptional regulation
- Pharmacology
- Nuclear receptors
- Metabolic syndrome
- Liver
- Biochemistry
- Pharmacology
- Molecular biology
- Genetically-modified mice
- Cellular biology
- Mouse phenotyping

Biological Resources

- Animal tissues (from our different mouse models)
- Human biopsies (heart, liver and adipose tissue)

Bart Staels

Inter-organ cross-talk in cardiometabolic diseases

Université de Lille
Inserm - CHU de Lille UMR 1011 Institut Pasteur de Lille UMR 1011
Bart Staels
Lille

We combine a strong background in the field of nuclear receptors and metabolism, and a unique scientific environment and up-to-date technological platforms.

Research Brief :

The organism senses its energy status through the close communication of several organs which integrate multiple endocrine (hormones, cytokines) and metabolic (glucose, free fatty acids..) signals. Dysregulation of the tight control of metabolism leads to dyslipidemia, insulin resistance and obesity which predispose to the development of cardiovascular complications and atherosclerosis. We aim to better understand the metabolic functions of nuclear receptors (NRs), with a major focus on FXR, PPARs, Rev-erba and RORa, and to define the potential benefit of pharmacological agents acting via these NRs on human health.
The role of these NRs will be investigated by comparing total- or organ-specific deficient or over-expressing mice of these NRs to wild-type mice with respect to basal metabolic parameters, energy expenditure, gene and protein expression and pharmacological response. Cellular and molecular approaches will also be used to identify the molecular mechanisms at the basis of the identified physiological functions. Since NRs are potential pharmacological targets, the use of existing as well as the identification of novel synthetic ligands will allow us to study the biological effects of these compounds. Finally, the role of these NRs in human physiology will be investigated by analysis of tissue biopsies from subjects suffering from metabolic disorders. It is expected that these approaches will uncover new therapeutic strategies for the treatment of metabolic diseases.

- **Methodologies Used :**

In vivo mouse phenotyping, Cell culture (cell lines or primary cells), Molecular biology approaches (transfection, quantitative PCR, Western-blot, Chromatin Immunoprecipitation (ChIP), Gene silencing, DNA micro-array technology, ChIP-seq technology, Sc RNAseq), Immuno-histochemistry, Bioinformatics

Publications

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Deprince A., Hennuyer N., Kooijman S., Pronk A.C.M., Baugé E., Lienard V., Verrijken A., Dirinck E., Vonghia L., Woitrain E., Kloosterhuis N.J., Marez E., Jacquemain P., Wolters J.C., Lalloyer F., Eberlé D., Quemener S., Vallez E., Tailleux A., Kouach M., Goossens J.F., Raverdy V., Derudas B., Kuivenhoven J.A., Croyal M., Van de Sluis B., Francque S., Pattou F., Rensen P.C.N., Staels B., Haas J.T. (2022). Apoliprotein F is reduced in humans with steatosis and controls plasma triglyceride-rich lipoprotein metabolism., Hepatology. Epub(),

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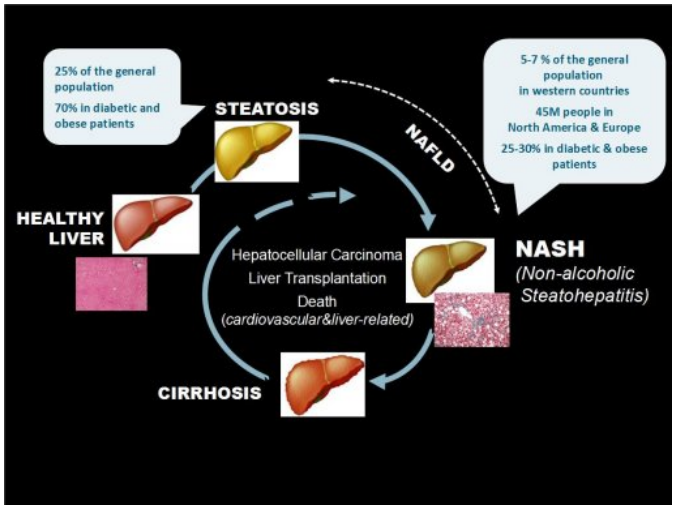
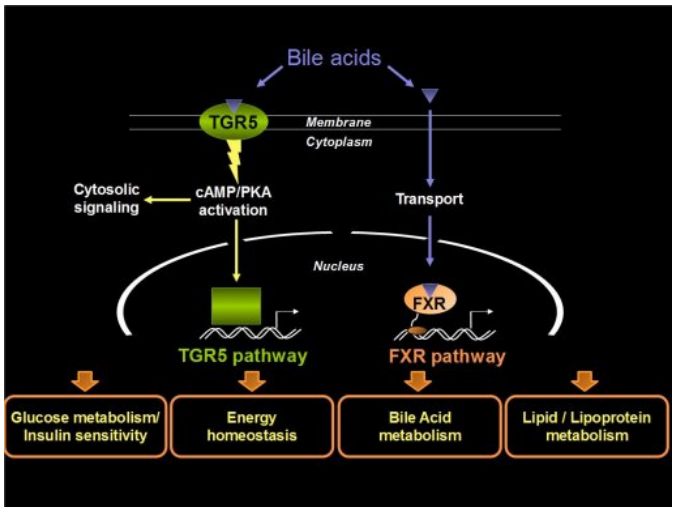
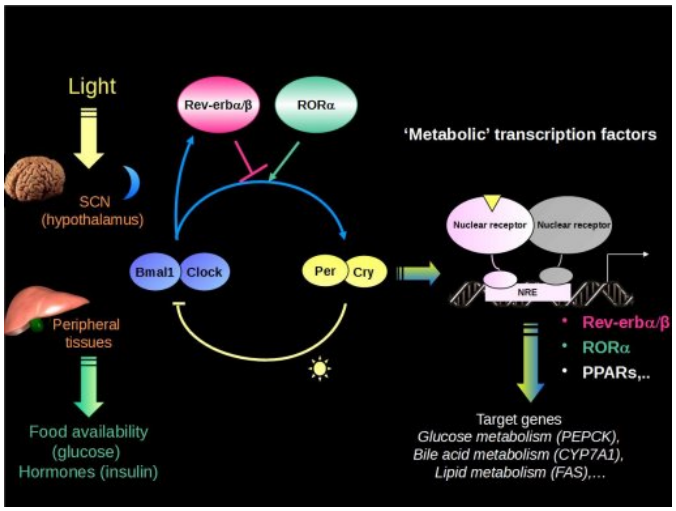
Non-Alcoholic Fatty Liver Disease (NAFLD): modulation by PPARs



Bile acids signal via FXR and TGR5



Transcriptional control of metabolic pathways by circadian oscillators



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Agnès VINET

LaPEC

Avignon University
UPR UPR-4278
Agnes VINET
Avignon

Key facts

Team

• Researchers : 12
• Technicians : 3
• Postdoc fellows : 1
• PhD Students : 5

Translational approaches

• Patents : 2
• Clinical research grants : 5
• Industry partnerships : 4

International research links

• UC Louvain (Bruxelles, Belgique)
• Miguel Hernandez University (Elche, Spain)
• University of Laval (Quebec, Canada)

Keywords

• Cardiovascular function
• Exercise
• Nurtition
• Adipose tissue
• Oxidative stress
• Cardiac and vascular ultrasonography
• Isolated organs
• In-vivo cardiovascular evaluation
• Biochemical assays
• Cellular experiments

Translational approach to study the effects of exercise and/or nutrition on cardiovascular dysfunctions in cardio-metabolic pathologies. The different research groups focus on myocardial function, the link between vascular function and adipose tissue and the crossplay between NO and oxidative stress

Research Brief :

The Laboratoire de Physiologie Expérimentale Cardiovasculaire (LaPEC, UPR-4278) focuses on vascular and myocardial dysfunctions and studies the effects of physical exercise and/or nutrition in prevention and rehabilitation of cardiometabolic diseases. The implication of the inflammatory status and the nitric oxide (NO) pathway in the genesis of the oxidative stress is central to these studies. Specific focus is also addressed on the effect of adipose tissue on cardiovascular function with regard to its different phenotypes and localizations, and its related inflammation and oxidative stress. The potential outcomes of our research fall within the scope of a better appraisal and therapeutic efficiency through:
- the identification of at risk populations at an early stage of vascular and myocardial dysfunction;
- the revelation of precursor signs impacted by exercise and/or nutrition, allowing better pharmacological targeting, working to the objective of synergetic and potentially additive effects.
The laboratory is composed of the 3 research groups
- ACTIV: Adipose tissue Cross-Talk wIth Vascular function
- NO-Stress: Nitric oxide, Oxidative and Metabolic Stress
- ReFoRM: Myocardial Remodeling and Regional Function

• **Methodologies Used :**

- Resting and stressed (dobutamin or exercise) echocardiography in humans and animals (Vivid Q, GE and Vevo, VisualSonic)
- Resting and stressed (exercise) Vascular ultrasonography in humans and animals (Vivid Q, GE and Vevo, VisualSonic)
- Laser Doppler in humans and animals (Perisoft and Pericam, Perimed)
- Isolated heart (Langerdorf)
- Myocardial ischemia-reperfusion
- Isolated artery (aortic, mesenteric)
- Biochemical assays (Western blot analysis,ELISA)
- ROS and NO fluorescence assays (histological, cellular, tissular)
- Mitochondrial function evaluation
- Isolated cardiomyocytes
- Cell culture

Publications

Jordan Loader, Cindy Meziat,* Rani Watts, Christian Lorenzen, Dominique Sigaudo-Roussel,Simon Stewart, Cyril Reboul, Gregory Meyer, Guillaume Walther. (2017). Effects of Sugar-Sweetened Beverage Consumptionon Microvascular and Macrovascular Functionin a Healthy Population., Arterioscler Thromb Vasc Biol.. 37(6), 1250-1260*

Philouze C, Obert P, Nottin S, Benamor A, Barthez O, Aboukhoudir F. (2018). Dobutamine Stress Echocardiography Unmasks Early Left Ventricular Dysfunction in Asymptomatic Patients with Uncomplicated Type 2 Diabetes: A Comprehensive Two-Dimensional Speckle-Tracking Imaging Study., J Am Soc Echocardiogr.. 31(5), 587-597

Reynès C, Beaume JB, Latil-Plat F, Ennaifer H, Rocher L, Antoine-Jonville S, Benamo E, Knapp Y, Vinet A. (2021). Concomitant peripheral neuropathy and type 2 diabetes impairs post-exercise cutaneous perfusion and flowmotion., J Clin Endocrinol Metab.. 106(10), 3979-3989

Boulghobra D, Dubois M, Alpha-Bazin B, Coste F, Olmos M, Gayrard S, Bornard I, Meyer G, Gaillard JC, Armengaud J, Reboul C. (2021). Increased protein S-nitrosylation in mitochondria: a key mechanism of exercise-induced cardioprotection., Basic Res Cardiol.. 116(1), 66

Bolea G, Philouze C, Dubois M, Risdon S, Humberclaude A, Ginies C, Charles AL, Geny B, Reboul C, Arnaud C, Dufour C, Meyer G. (2021). Digestive n-6 Lipid Oxidation, a Key Trigger of Vascular Dysfunction and Atherosclerosis in the Western Diet: Protective Effects of Apple Polyphenols., Mol Nutr Food Res.. 65(6), 487

Grandperrin A, Schnell F, Donal E, Galli E, Hedon C, Cazorla O, Nottin S. (2022). Specific alterations of regional myocardial work in strength-trained athletes using anabolic steroids compared to athletes with genetic hypertrophic cardiomyopathy., J Sport Health Sci.. 29(22), 2095-2546

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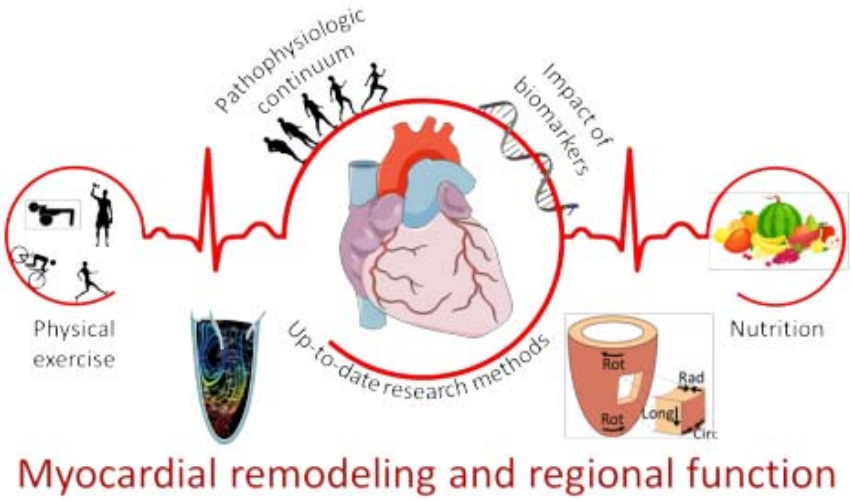
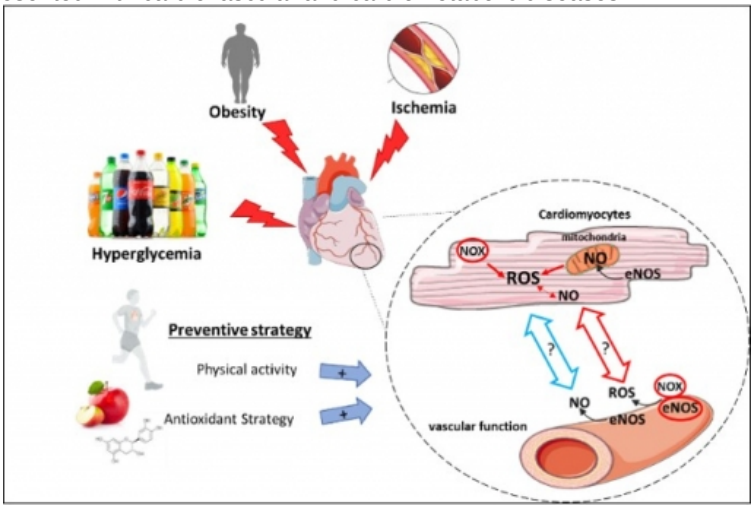
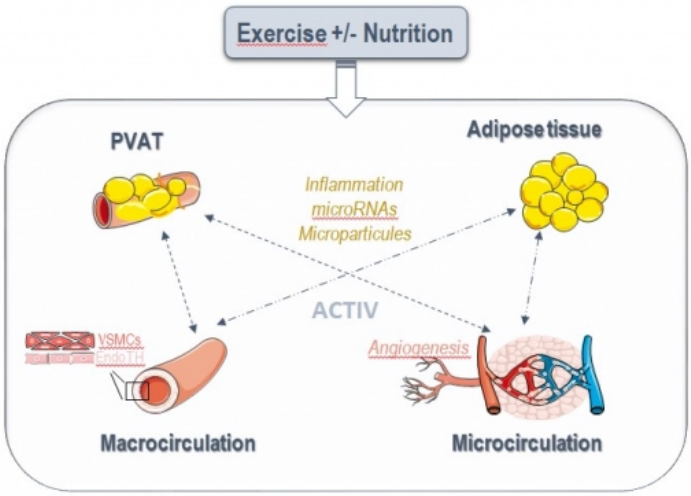
Translational approach in cardiometabolic disease



Based on up-to-date cardiac imaging technologies and biomarkers, the researchers of ReFoRM aim to assess myocardial remodeling and regional function in response to prophylactic approaches including physical exercise and nutrition in both healthy subjects (sedentary people or athletes) and patients presented with cardiovascular and cardiometabolic diseases.



The main objective of the NOStress group is to decipher how exercise and/or nutritional approaches are able to impact NO and cytosolic/mitochondrial ROS pathways both in the heart and the vascular system in response to physiological or pathological stress.



ACTIV group examines how physical exercise and/or nutrition modulate the cross-talk between vascular function (micro- and macrocirculation) and adipose tissue (perivascular, central, brown and white).

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Key facts

Team

- Researchers : 4
- Technicians : 2
- Postdoc fellows : 2
- PhD Students : 3

Translational approaches

- Patents : 4
- Clinical research grants : 3
- Industry partnerships : 1

International research links

- Austria, Belgium, Germany, Italy, Spain, Israel, Latvia, USA

Keywords

- Autophagy
- Biomarkers
- Heart failure
- Cardiac cells
- Oxidative stress
- MiRNAome
- Phosphorylation
- Proteome
- Mitochondrial respiration
- O-GlcNAcylation

Biological Resources

- Plasma and serum biobanks (heart failure patients, myocardial infarction, abdominal aorta aneurysm)
- Macrophages and smooth muscle cells from patients with abdominal aorta aneurysm.
- Human aorta normal and diseased tissue biobank

Florence Pinet

Identification of molecular determinants of cardiovascular diseases

Université de Lille
Institut Pasteur de Lille UMR1167
Philippe Amouyel
Lille

Translational research involved in the search of potential biomarkers of cardiac diseases using differential "Omics" technologies :proteomic, miRNAomic

Research Brief :

The research project of our group is translational with the aim to find new biomarkers of left ventricular remodeling post-infarction and heart failure. The team has expertise on coordinating recruitment of patients with cardiac disorders, clearly phenotyped for left ventricular remodeling post-infarction (REVE 1 (n=266) and REVE 2 (n=246) studies) or heart failure (PTHF (n=60) and INCA (n>2000) studies. These clinical studies allow recuperating plasma and serum samples that are used for differential proteomic and transcriptomic (miRNA and lncRNA) analyses. We have developed techniques allowing access and detection of plasma ?deep? proteome. We have the expertise in discovery and validation of targets from proteomic (SELDI-TOF, 2D-DIGE, multiplex, ELISA) and miRNAomic (arrays, Q-RT-PCR). Two approaches are currently developed: 1) a clinical approach with the purpose to develop clinical diagnostic applications for which we analyzed all the data obtained by biostatistics and system biology analyses and; 2) a molecular approach with the purpose to understand the physiopathological mechanisms underlying the targets (proteins, post-translational modified proteins, miRNA, lncRNA) modulation in the pathologies studied. The discovery of new biological factors involved in the different cardiovascular pathologies would help to a better stratification of patients at risk.

- **Methodologies Used :**

Tissues, cells and plasma/serum (depleted for major proteins) proteomic.
2D-gel electrophoresis, mass spectrometry
Arrays and Q-RT-PCR for miRNAs and lncRNAs, ELISA, multiplex assays
Primary culture of neonatal rat cardiomyocytes, human smooth muscle cells (aorta), macrophages
Isolation of extracellular vesicles
Laser-microdissection laser, cells and tissues imaging
System biology analysis
Mitochondrial respiration (seahorse)
Oxidative stress
Autophagy, mitophagy

Publications

Turkieh A, Porouchani S, Beseme O, Chwastyniak M, Amouyel P, Lamblin N, Balligand JL, Bauters C, Pinet F. (2019). Increased clusterin levels after myocardial infarction protects cardiomyocytes from apoptosis induced by a defect in protein degradation systems activity, Cellular Death Disease. 10(8), 608

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Bouvet M, Dubois-Deruy E, Turkieh A*, Mulder P, Peugnet V, Chwastyniak M, Beseme O, Dechaumes A, Amouyel P, Richard V, Lamblin N, Pinet F. (2021). Desmin aggrephagy in rat and human ischemic heart failure through PKCzeta and GSK3 as upstream signaling pathways., Cell Death Discovery. 7(1), 153*

Peugnet V, Chwastyniak M, Mulder P, Lancel S, Bultot L, Fourny N, Renguet E, Bugger H, Beseme O, Loyens A, Heyse W, Richard V, Amouyel P, Bertrand L, Pinet F, Dubois-Deruy E (2022). Mitochondrial-targeted therapies require mitophagy to prevent oxidative stress induced by SOD2 inactivation in hypertrophied cardiomyocytes, Antioxidants. 11(4), 723

Abou Zeid F, Charrier H, Beseme O, Michel JB, Mulder P, Amouyel P, Pinet F, Turkieh A (2022). Lim Domain Binding 3 (Ldb3) Identified as a Potential Marker of Cardiac Extracellular Vesicles, International Journal Molecular Science. 2(), 7374

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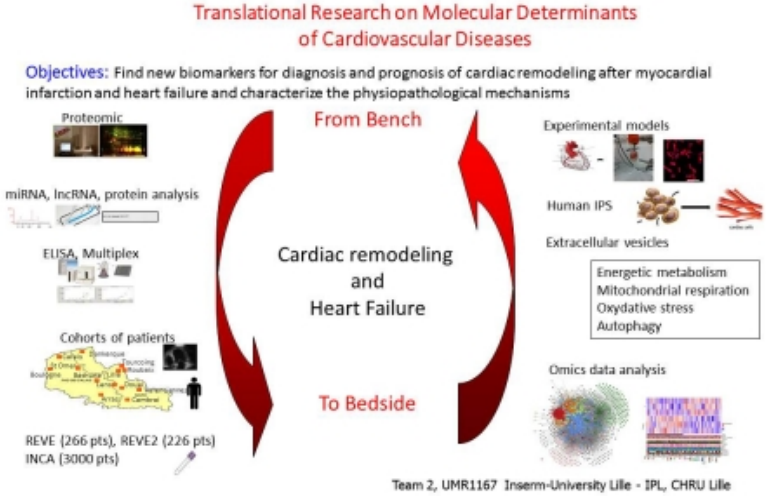
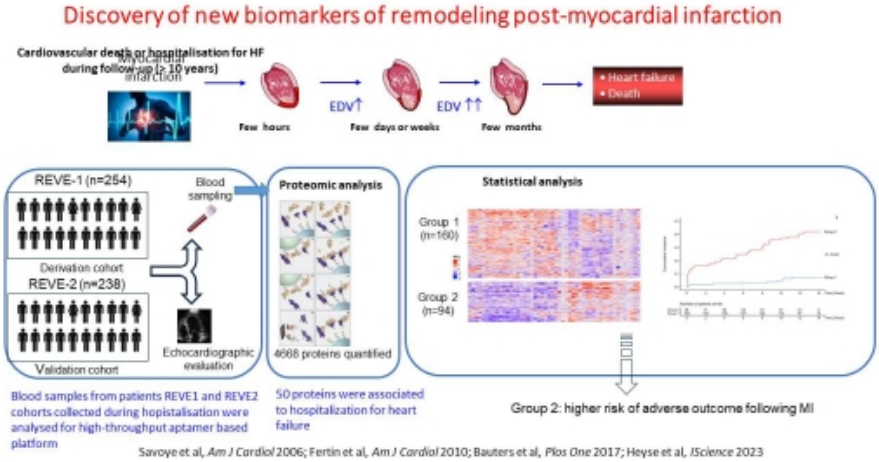
Activity of team 2

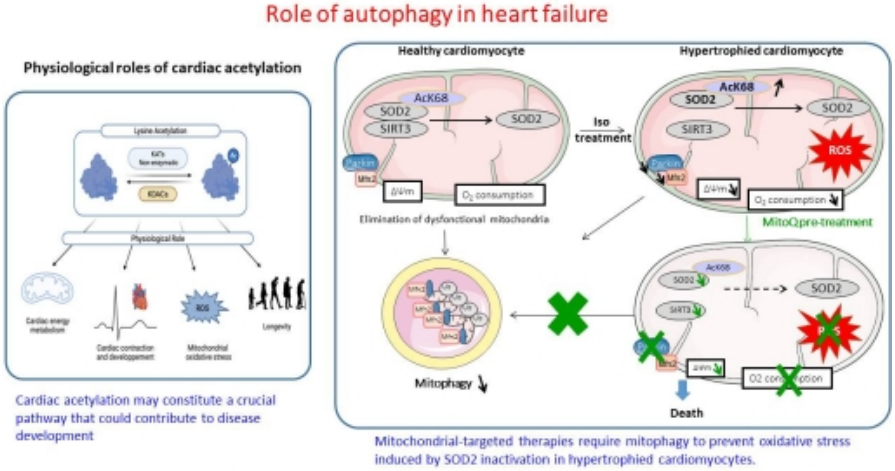


Major results using REVE and REVE2 cohorts



Savoye et al, *Am J Cardiol* 2006; Fertin et al, *Am J Cardiol* 2010; Bauters et al, *Plos One* 2017; Heyse et al, *IScience* 2023

Major results of autophagy in HF



Turkieh et al, *Cells* 2021; Peugnet et al, *Antioxidants* 2021; Dubois-Deruy et al, *Biomedicines* 2022

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Carmen Martinez

Extracellular vesicles and metabolic diseases

Université de Montpellier
Inserm 1046 CNRS UMR 9214
Alain Lacampagne
Montpellier

The team has a unique expertise in the identification of mechanisms by which extracellular vesicles participate in cardiovascular consequences of obesity and diabetes by associating fundamental and translational research. Developing pioneering therapies based on extracellular vesicles

Key facts

Team

- Researchers : 3
- Technicians : 2
- Postdoc fellows : 0
- PhD Students : 3

Translational approaches

- Patents : 3
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- Extracellular vesicles
- Metabolic diseases
- Oxidative stress
- Myography
- Confocal Microscopy
- Ultracentrifugation

Research Brief :

Translational research depicting the role of extracellular vesicles (EVs) as novel effectors to elucidate disease-specific pathway in metabolic diseases. Therapeutic strategies to fight against metabolic dysfunctions with new design of EVs in the field of nanomedicine as well as nutritional approaches.

Extracellular vesicles (EVs) and metabolic dysfunctions: interrelationship between obesity and diabetes. The main goal is to predict cardiovascular consequences of obese and diabetic patients as well as define new therapeutic opportunities from the delivery of "specific" vesicle subsets. Thus, the focal point of the project is EVs bringing novelty, and establishing possibly a selling point in view of concepts uniqueness. For disease outcome, the focus will be of common downstream consequences of obesity such as increased cardiovascular diseases and diabetes.
Therapeutic strategies to fight against cardiovascular and metabolic dysfunctions using EVs. EVs will be engineered to over-express different therapeutic players (proteins, mRNA or miRNA) by driving the synthesis of the relevant EV-producing cells. A goal will be the selection of specific EV subsets to assess their therapeutic potential in proof-of-concept analyses.

Methodologies Used :

- In vivo (echography, telemetry, plethysmography) and ex vivo (myography, arteriography, langerdorff) approaches: animal models (pharmacology, knock out).
- Cell culture (primary cells and cell lines) and biology (flow cytometry, confocal microscopy, patch clamp, oxygraphy). Molecular biology (quantitative PCR, Western blot, gene silencing). ROS measurements.
- Clinical studies (epidemiology, pharmacology, genetics).

Publications

Perdomo L, Vidal-Gómez X, Soleti R, Vergori L, Duluc L, Chwastyniak M, Bisserier M, Le Lay S, Villard A, Simard G, Meilhac O, Lezoualc'h F, Khantalin I, Veerapen R, Dubois S, Boursier J, Henni S, Gagnadoux F, Pinet F, Andriantsitohaina R, Martínez MC; Metabol study Group. (2020). Large Extracellular Vesicle-Associated Rap1 Accumulates in Atherosclerotic Plaques, Correlates With Vascular Risks and Is Involved in Atherosclerosis., Circulation Research. 127(), 747-760

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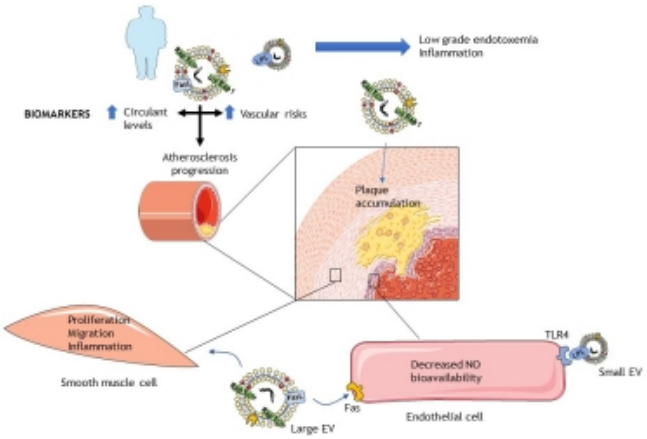
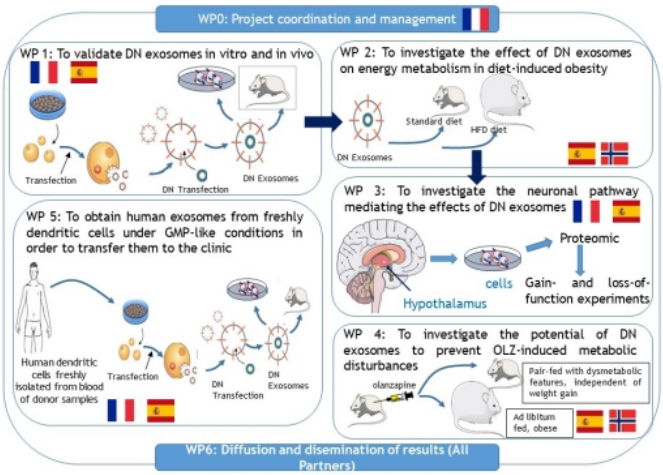
EVs play a key role on atherosclerosis development



Extracellular vesicles are biomarkers and induce endothelial and vascular smooth muscle dysfunction in metabolic syndrome

Extracellular vesicles as therapeutic tools against obesity



European consortium working on the proof of concept of extracellular vesicles are tools acting of central regulation of obesity

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David Masson

Lipid and Lipid transfer in sterile and septic inflammation (LIPNESS)

Université de Bourgogne Dijon
Inserm UMR1231
Francois Ghiringhelli
Dijon

Key facts

Team

- Researchers : 15
- Technicians : 9
- Postdoc fellows : 3
- PhD Students : 8

Translational approaches

- Patents : 1
- Clinical research grants : 2
- Industry partnerships : 0

Keywords

- Lipids
- Lipoproteins
- inflammation
- Lipidomic
- LPS quantification

Our Teams is dedicated to study the link beteween lipoproteins, lipid and the inflammatory response

Research Brief :

We are studying the role of Lipoproteins and lipid molecules, as well as the impact of lipid exchanges in the modulation of inflammation with applications in chronic inflammation (atherosclerosis) and acute inflammatory diseases including sepsis.

Lipopolysaccharides (LPS) bind and activate Toll like receptor 4 at the surface of immune cells, leading to the release of pro-inflammatory cytokines and to inflammation. Alternatively, bacterial blebs forming large LPS aggregates can be disrupted and molecular transfer of LPS towards lipoproteins can occur. It results in its neutralization and elimination back to the liver, namely the reverse LPS transport pathway (RLT). Recent observations suggest that PLTP and CETP, as members of the lipid transfer/lipopolysaccharide binding protein gene family play a driving role in RLT, thus modulating inflammation and innate immunity.

Phospholipids are continuously remodeled through deacylation and reacylation by the opposite actions of phospholipase A2, and lysophospholipid acyl-transferases (LPLATs). LPLATs affect both the PUFA content of phospholipids and the availability of free fatty acids such as arachidonic acid used for eicosanoid synthesis. By using specific mouse models and samples from human patients, we assess the impact of phospholipid and fatty acid metabolism in myeloid cells on inflammation and atherosclerosis development.

- **Methodologies Used :**

Lipidomics
Cell culture
Animal models
Translational research

Publications

Lebrun LJ, Lenaerts K, Kiers D, Pais de Barros J-P, Le Guern N, Plesnik J, Thomas C, Bourgeois T, Dejong CHC, Kox M, Hundscheid IHR, Khan NA, Mandard S, Deckert V, Pickkers P, Drucker DJ, Lagrost L, Grober J. . (2017). Enteroendocrine L Cells Sense LPS after Gut Barrier Injury to Enhance GLP-1 Secretion., Cell Rep. (21), 1160-68

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Lipness
UMR 1231

David MASSON, Pharm.D., PhD
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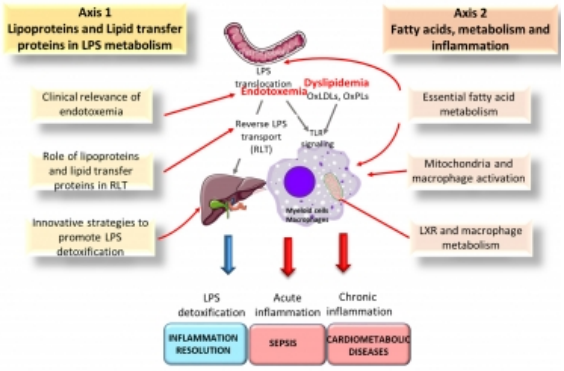
Clinical Chemistry departement

LIPNESS team – CSS3

Lipids and lipid transfer in sterile and septic inflammation



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Daniel Henrion

Cardiovascular Mechanotransduction (CarMe)

Université d' Angers
Inserm U1083 CNRS UMR 6015
Guy Lenaers
Angers

Key facts

Team

- Researchers : 30
- Technicians : 11
- Postdoc fellows : 2
- PhD Students : 18

Translational approaches

- Patents : 2
- Clinical research grants : 12
- Industry partnerships : 2

International research links

- Germany, Gret-Britain, USA, Spain, Canada, Hungary

Keywords

- blood flow
- ischemia/reperfusion
- GPCRs
- endothelium
- mechanotransduction
- Microcirculation
- limb ischemia
- electrophysiology
- Local blood flow
- bio-computing
- resistance arteries
- remodeling

Study of small resistance arteries mechanotransduction in ischemic diseases (limb and heart ischemia, hypertension, diabetes, obesity)

Research Brief :

Resistance arteries are located upstream capillaries, are crucial to the delivery of blood to vital tissues at relevant flow and pressure. Disorders of these small arteries can raise capillary pressure and cause downstream organ damage such as that seen in diabetes, neurovascular disorders or kidney disease. We aim a) to define how structure and function of small arteries change in ischemic disorders associated with ageing and the related risk factors and aa) to identify the specific changes in pathways involved in resistance artery homeostasis leading to the identification of novel targets/biomarkers for intervention and disease prevention.
We have 3 specific objectives:
1- investigate flow-mechanotransduction in resistance arteries in order to better define the pathways involved with a special focus on the mechanosensitive channels and on the mechanosensitive receptors.
2- determine in resistance arteries the mechanism of remodelling involved in ischemic disorders
3- investigate the mechanisms involved in ischemia-reperfusion injury and to bring forward new strategies to prevent its occurrence.
Finally, ischemic disorders are investigated using mouse models of ischemia/reperfusion in healthy and diseased ageing and in human vessels from patients with severe limb ischemia and healthy volunteers.

• Methodologies Used :

Arteriography and myography for resistance arteries (in vitro function)
In vivo microcirculatory function (Laser-Doppler flow metry, arteriography...)
Molecular biology of resistance arteries and mitochondria
electrophysiology (patch-clamp on tissue slices, microelectrodes on xen. oocytes)
confocal microscopy (fixed tissues and real-time)
Molecular modeling and dynamics, bioinformatics

Publications

Caillon A, Grenier C, Grimaud L, Vessieres E, Guihot AL, Blanchard S, Lelievre E, Chabbert M, Foucher ED, Jeannin P, Beauvillain C, Abraham P, Loufrani L, Delneste Y, Henrion D (2016). The angiotensin II type 2 receptor activates flow-mediated outward remodelling through T cells-dependent interleukin-17 production, Cardiovascular research. 81(1), 515-25

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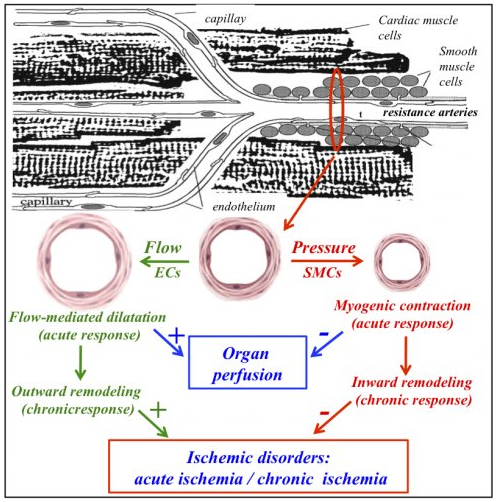
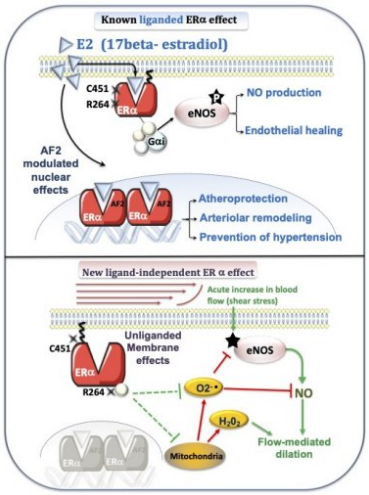
Vascular response to pressure and flow



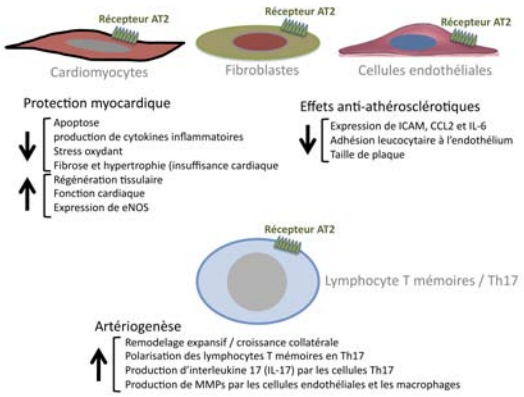
Schematic representation of the research project of CarMe: Acute and chronic vascular response to pressure and flow determine a proper tissue perfusion. A desiquilibrium between pressure- and flow-dependent tone and wall structure is involved in cardiovascular disorders.

Membrane-ERalpha in flow-mediated dilation



Flow stimulates endothelial cells resulting in the production of NO, which in turn induces relax-ation of the smooth muscle and thus dilation. Flow also activates membrane-associated ERalpha, which reduces oxidative stress. This results in enhanced NO bioavailability. The absence of membrane-associated ERalpha leads to the production of O2-°, which attenuates NO-dependent dilation despite a remaining dilation due to a rise in H2O2 production (eLife. 2021 Nov 29;10:e68695)

Vascular effects of the angiotensin II type 2 receptor



From Caillon et al., Cardiovasc Res. 2016;112(1):515-25

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GETBO
Groupe d'Étude de la Thrombose de Bretagne Occidentale

Francis COUTURAUD

Venous Thromboembolism study Group of Western Brittany

Université de Bretagne Occidentale Brest
Inserm UMR1304
Francis COUTURAUD
Brest

Key facts

Team

• Researchers : 41
• Technicians : 20
• Postdoc fellows : 3
• PhD Students : 9

Translational approaches

• Patents : 1
• Clinical research grants : 10
• Industry partnerships : 30

International research links

• Netherland, Switzerland, Belgium, Germany, Italia, Spain, Sweden, Austria
• Canada, USA
• Australia

Keywords

• Venous Thromboembolism
• immune-thrombosis/endothelial dysfunction
• pregnancy - estrogen exposure
• cancer associated thrombosis
• pulmonary vascular obstruction
• clinical trial (phase I, II, II, IV)
• biostatistics, IE
• animal models on recurrent VTE
• nuclear radio-marking
• radiomics

Biological Resources

• Larges cohorts of patients with VTE with biobank (>30 000 patients) and imaging database in 5000 patients
• in vitro and in vivo models on recurrent VTE (mouses)
• Chemistry-physical clot structure
• Nuclear medicine (functional imaging, new radio-marking)
• ultrasound and omics
• radiology (Xray) and omics

Identification of cellular and molecular mechanisms involved in venous thromboembolism (VTE) and recurrent VTE. The research is focused on patients at high risk of recurrent VTE (ie, unprovoked VTE) with bio-molecular, chemistry/physical approaches, larges clinical randomized trials and cohorts.

Research Brief :

Research program:
Objective: identification of cellular and molecular mechanisms involved in venous thromboembolism (VTE) and recurrent VTE.
Three scientific questions through 3 centered axes:
Axis 1: Pathophysiology-heritability of VTE phenotypes at high risk of recurrent VTE (Group leader: Francis Couturaud, MD, PhD): who and why is at high risk of recurrent VTE.
Axis 2: Inflammation and Immunopathology of VTE (Groupe leader: Catherine Lemarié, CR-INSERM): how VTE occurs and recurs - role of endothelial dysfunction.
Axis 3: Women and hormonal exposure: risk of VTE and vasculo-placental complications (Group leader: Karine Lacut, MD, PhD): impact of hormonal exposure on VTE.
Three functional work packages:
WP1 (Strategic Work-package): elaboration and strategic organization of the 3 scientific thematic axes
WP2 (Clinical Investigation Work-package): clinical studies
WP3 (Basic Science Investigation Work-package): biomolecular pathophysiological mechanisms - clot structure
Translational approaches to address these questions including:
Investigation of biological factors and novel biomarkers,
Identification of functional role of these mediators in target cells (in vitro cellular models) and in wild-type or transgenic murine models of VTE and recurrent VTE,
Translation/validation: large national and international cohorts and databases.

• **Methodologies Used :**

- Larges clinical trials and prospective cohorts with biological and imaging database, expertise in méthodology, biostatistics, bioinformatic, AI
- In vivo: animal models on venous thromboembolism recurrence (mouses)
- In vitro biomolecular technics: GentleMACS for tissue homogenization, MultiMACS magnetic bead cell selection, Automated cell counter, Neodot nano-spectrometer for DNA, RNA and protein concentration, Thermal cycler, Spectophotometer, Centrifuges microcentrifuges, Freezer -80°C/ -20°C, Hybridization Incubator, Western Blot, Immunofluo- immunohistochemistry equipment
- Chemistry-physical clot structure
- Nuclear medicine and ultrasound

Publications

Couturaud F, Leroyer C, Tromeur C, Julian JA, Kahn SR, Ginsberg JS, Wells PS, Douketis JD, Mottier D, Kearon C (2014). Factors that predict thrombosis in relatives of patients with venous thromboembolism, BLOOD. 124(13), 2124-30

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Najem MY, Couturaud F, Lemarié CA (2020). Cytokine and chemokine regulation of venous thromboembolism, . J Thromb Haemost. 18(5), 1009-1019

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Morange PE, Peiretti F, Gourhant L, [...], Lemarié CA, Frontini M, Alessi MC, Trégouët DA, Couturaud F. (2021). A rare coding mutation in the MAST2 gene causes venous thrombosis in a French family with unexplained thrombophilia: The Breizh MAST2 Arg89Gln variant., PLoS Genet. 17(1), e1009284

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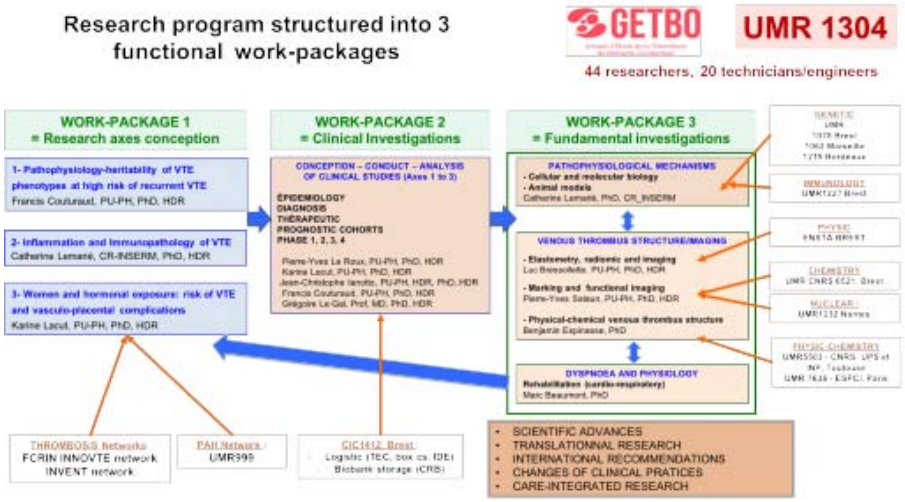
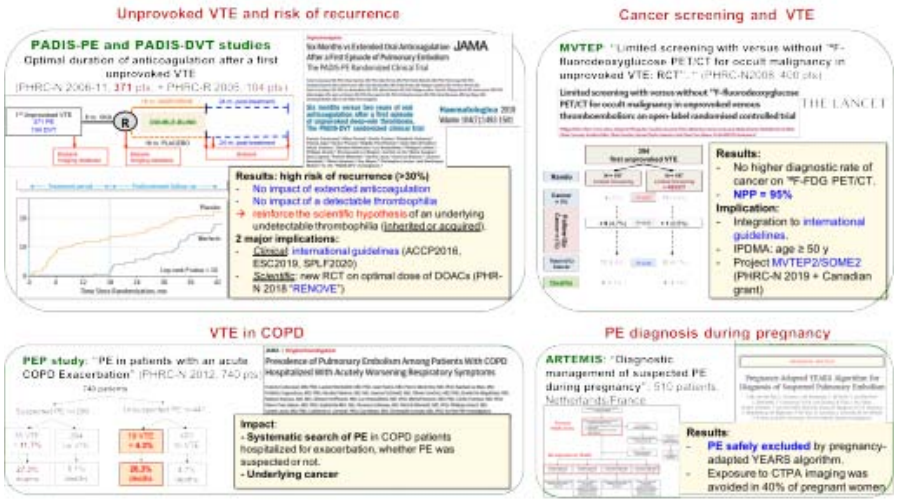
Research structuration (work packages)



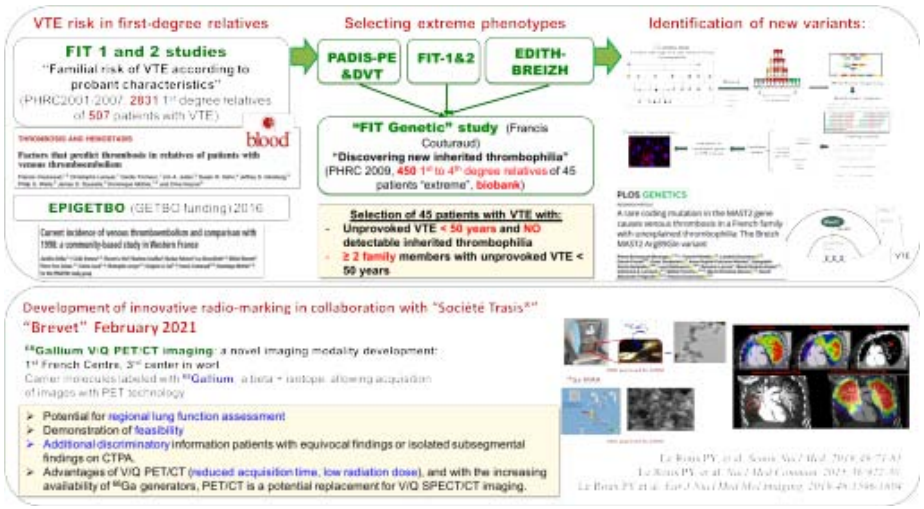
Research program (3 scientific axes) structured into 3 work packages - UMR1304 - GETBO
Local, national and international collaborations - National and international network

Clinical research results



Results on 1-Optimal duration of anticoagulation in patients with a first unprovoked VTE (double-blind randomized trials) 2-PE prevalence in COPD patients (prospective cohort) 3-Systematic cancer screening in patients with unprovoked VTE (randomized clinical trial) 4-Validation of PE diagnostic strategy in pregnant women (management study).

Translational and basic science results



Results on 1-VTE risk in first degree relatives of patients with VTE 2-Selection of families at high thrombosis risk without detectable thrombophilia 3-Identification of new inherited thrombophilias 4-Brevet on new isotope 68 Gallium for VTE diagnosis with nuclear medicine

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Key facts

Team

• Researchers : 18
• Technicians : 6
• Postdoc fellows : 1
• PhD Students : 17

Translational approaches

• Patents : 3
• Clinical research grants : 6
• Industry partnerships : 7

International research links

• ERANET : Netherlands, Poland, Belgium, Spain - OTHER: Finland, Germany, USA

Keywords

• endothelium
• lymphatics
• aortic stenosis
• heart failure
• transcatheter aortic valve implantation (TAVI)
• vascular high-resolution echography
• myograph
• echocardiography
• magnetic resonance imaging
• arteriograph

Biological Resources

• patients : heart failure, septic shock, antiphospholipid syndrome, hypertension, diabetes, polycystic kidney disease, kidney transplantation.

Jeremy Bellien

EnVI; Endothelium, Valvulopathy and Heart Failure

Rouen Normandy University
Inserm U1096
Jeremy Bellien
Rouen

Unique translational (both experimental and clinical) expertise in the functional evaluation of vascular and cardiac dysfunction, major innovation in the field of aortic stenosis, unique research on cardiac lymphatics

Research Brief :

Our cardiovascular research focuses on 3 aspects: vascular protection, treatment of aortic stenosis and improvement of cardiac contractile function/reduction of heart failure. This research is translational, performed both in experimental/pre-clinical models and in humans (healthy volunteers and patients).
Our vascular research concerns protection of vascular endothelial cells against injury or dysfunction induced by risk factors (hypertension, diabetes) or cardiovascular diseases (myocardial infarction, heart failure, septic shock etc.). Pharmacological targets currently evaluated include in particular protein tyrosine phosphatase 1B, soluble epoxide hydrolase, and dopamine receptors
Regarding aortic stenosis, our work is based on the Rouen discovery and development of transcatheter aortic valve implantation (TAVI); we attempt to uncover new mechanisms and new pathways for prevention or slowing of aortic stenosis development. We also address the links between endothelial dysfunction and aortic stenosis. This research is performed within the frame of the FHU REMOD-VHF and RHU STOP-AS both placed under the leadership of our group.
Finally, our cardiac research concerns the evaluation of new treatments of diastolic dysfunction or heart failure and the cardiac consequences of aortic stenosis or its reversion. In particular, we focus on the benefits of lymphangiogenic therapy in heart failure, within the frame of an ERA-NET project under our leadership.

• **Methodologies Used :**

- Experimental and clinical cardiac and vascular imaging (echocardiography, echo-tracking, tonometry, tissue Doppler, Holter)
- Magnetic resonance imaging for small animals
- In vitro vascular functional evaluation (arteriograph, myograph)
- Experimental models of cardiovascular diseases in rats and mice (myocardial infarction, heart failure, hypertension, aortic stenosis, insulin resistance etc.)
- Evaluation of oxidative stress
- culture aortic valve cells
- evaluation of cardiac lymphatic network & lymphangiography

Publications

Banquet S, Gomez E, Nicol L, Edwards-Lévy F, Henry JP, Cao R, Schapman D, Dautreaux B, Lallemand F, Bauer F, Cao Y, Thuillez C, Mulder P, Richard V, Brakenhielm E. (2011). Arteriogenic therapy by intramyocardial sustained delivery of a novel growth factor combination prevents chronic heart failure., CIRCULATION. 124(1059), 1069

Eltchaninoff H, Prat A, Gilard M, Leguerrier A, Blanchard D, Fournial G, Iung B, Donzeau-Gouge P, Tribouilloy C, Debrux JL, Pavie A, Gueret P; FRANCE Registry Investigator (2011). Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry., EUROPEAN HEART JOURNAL. 32(191), 197

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Lorthioir A, Joannidès R, Rémy-Jouet I, Fréguin-Bouilland C, Iacob M, Roche C, Monteil C, Lucas D, Renet S, Audrézet MP, Godin M, Richard V, Thuillez C, Guerrot D, Bellien J. (2015). Polycystin deficiency induces dopamine-reversible alterations in flow-mediated dilatation and vascular nitric oxide release in humans., KIDNEY INTERNATIONAL. 87(465), 1472

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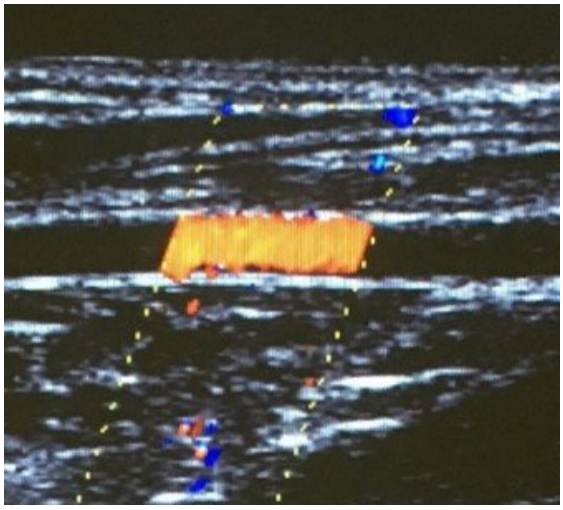
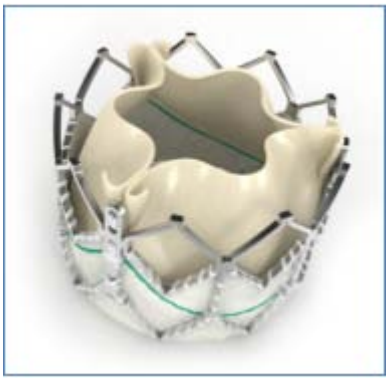
noninvasive evaluation of human arterial diameter



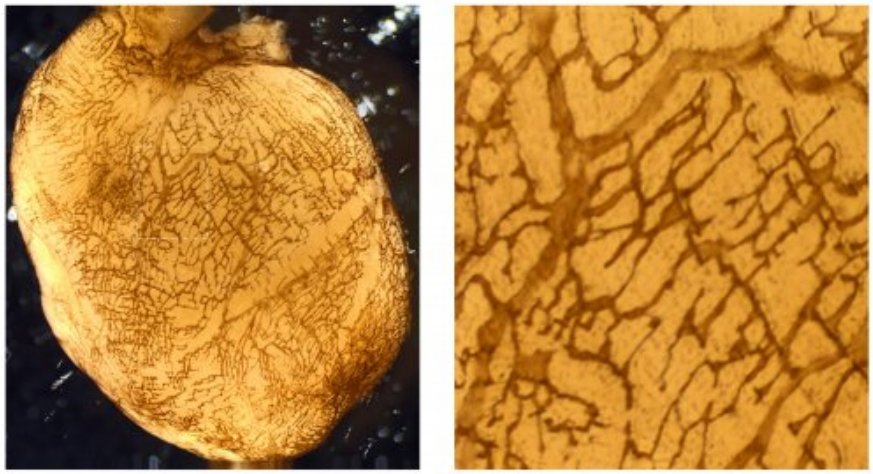
Non invasive, dynamic, echo-tracking based imaging of human radial artery diameter, allowing evaluation of changes in vascular tone and thus of endothelial-dependent dilatation and endothelial dysfunction

Transcatheter Aortic Valve



Aortic Valve designed for Transcatheter Aortic Valve Implantation (TAVI)

Cardiac lymphatics network



Immunohistochemical imaginf of cardiac lymphatic network (rat left ventricle)

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Frank Lezoualc'h

Signaling and pathophysiology of heart failure and aging

Université de Toulouse III
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Toulouse

Our team is specialized in the functional analysis of key proteins and their signaling networks and checkpoints in heart failure in the context of cardiac ischemia, metabolic dysregulation and aging. Our aim is to identify new therapeutical targets for the treatment of heart failure.

Key facts

Team

- Researchers : 3
- Technicians : 1
- Postdoc fellows : 3
- PhD Students : 3

Translational approaches

- Patents : 11
- Clinical research grants : 1
- Industry partnerships : 3

International research links

- USA
- The Netherlands

Keywords

- Cyclic AMP
- Heart failure
- Signalling
- Therapeutic innovation
- Senescence
- Epigenetic
- Biochemistry
- Molecular biology
- Viral gene transfer
- Chemical screening assay
- Chip seq

Biological Resources

- animal models of cardiac hypertrophy, myocardial infarctus, aging
- Epac, MAO transgenic and knowckout mice

Research Brief :

Our team aims at determining the pathophysiological mechanisms leading to heart failure (HF), one of the major causes of death worldwide with an increased prevalence in the Ederly. The long-term objective is to obtain a comprehensive knowledge of key signaling system (i.e cAMP, reactive oxygen species, Ca2+) alterations and epigenetic mechanisms that promote pathological cardiac remodeling and HF. Our goal also encompasses the identification of the mechanisms of cardiomyocyte senescence and cardiac ageing that strongly impact HF development. The final aim is to identify and exploit novel therapeutic strategies against HF. To achieve these goals, our research programs are conducted from molecular to the most integrative levels of cardiac pathophysiology using cutting-edge technologies.

- **Methodologies Used :**

Molecular and cellular biology methods (PCR, immunocytochemistry, cell culture (neonatal cardiac myocytes, adult cardiac myocytes, cell lines), infection and transfection,
Biochemistry (Immunoblot, immunoprecipitation, affinity precipitation assay,)
RNAseq & ChipSeq
Calcium imaging
Experimental animal models (conditional knock-out mouse models, models of cardiac hypertrophy and Failure, aging)

Publications

Lezoualc'h F, Fazal L, Laudette M, Conte C (2016). Cyclic AMP Sensor EPAC Proteins and Their Role in Cardiovascular Function and Disease, Circulation research. 118(5), 881-897

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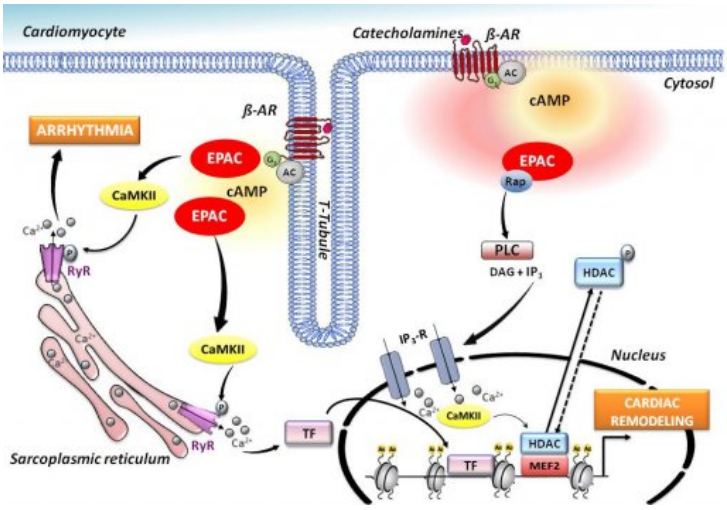
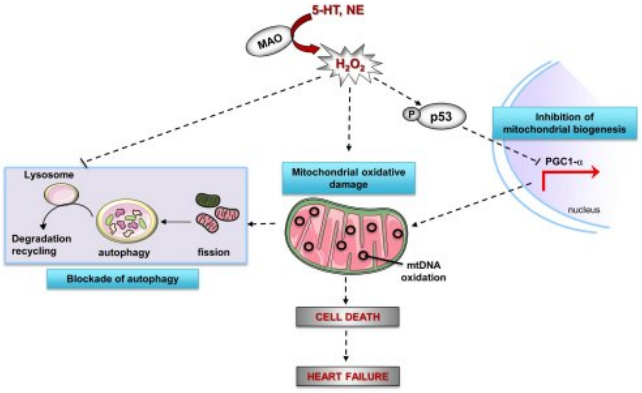
Epac signalling leads to pathological cardiac remodeling and heart failure



Beta-adrenergic receptors (B-AR) activate Epac which induces Ca2+ dysregulation via the ryanodine receptor (RyR) leading to arrhythmia. Epac also regulates the activity of transcription factors (TF) which are involved in pathological cardiac remodelling.

Deleterious effect of MAO-A on mitochondrial damage, cardiomyocyte death and heart failure.



MAO-A-generated oxidative stress triggers p53 activation leading to down-regulation of peroxisome proliferator-activated receptor-gamma coactivator-1a (PGC-1a), a master regulator of mitochondrial biogenesis. On the other hand, MAO-A-generated oxidative stress impairs lysosome function and acidification leading to autophagic flux blockade and altered mitochondrial quality control

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Chantal Boulanger

Endothelial Physiopathology and Extracellular Vesicles

Université de Paris
Inserm UMR 970
Chantal Boulanger
Paris

Associating molecular and integrated physiology to decipher new avenues in the field of endothelial dysfunction

Key facts

Team

- Researchers : 4
- Technicians : 3
- Postdoc fellows : 1
- PhD Students : 1

Translational approaches

- Patents : 3
- Clinical research grants : 5
- Industry partnerships : 1

Keywords

- Exosomes
- microRNA
- Microvesicle
- Endothelial activation
- Heme
- Tunable resistive pulse sensing
- flow cytometry
- myograph

Research Brief :

An initial step in cardiovascular disease development is the loss of vasculo-protective functions of the endothelium. Thus, we need to decipher the mechanisms regulating endothelial dysfunctions to identify new therapeutic targets in vascular diseases. In addition, early detection of dysfunctional endothelial cells will help stratify cardiovascular risk and treatment of asymptomatic subjects.
In the past decade we have pioneered research on the release of membrane vesicles from dysfunctional endothelial cells. We have demonstrated that circulating endothelial microparticles (EMP) are potentially useful clinical indicators of dysfunctional endothelium and a prognostic marker of cardiovascular mortality. But extracellular release of membrane vesicles is not only a sign of cell injury, these vesicles are also a new mediators affecting the function of target cells. Indeed we have demonstrated that EMP are paracrine signals for vascular repair in ischemic diseases. In addition, microparticles promote pro-inflammatory and pro-angiogenic responses in human atherosclerotic lesions.

Our current research integrates new research avenues in the field of endothelial dysfunction:
1/ the role of autophagy in endothelial activation and vesicle release (C. Boulanger)
2/ micro-RNA packaging in endothelial vesicles in atherosclerosis and myocardial infarction (X. Loyer, CRCN; C. Boulanger)
3/ endothelial activation by erythrocyte vesicles in hemolytic disorders (O. Blanc-Brude, CRCN)

- **Methodologies Used :**

Flow cytometry for cell and extracellular vesicle analysis
Tunable resistive pulse sensing
Endothelial cell culture (murine, human)
Endothelial culture under shear stress
Fluorescence microscopy
Myograph for studying isolated blood vessel reactivity
Original murine models with specific endothelial deletion

Publications

Amabile N, Cheng S*, Renard JM, Larson MG, Ghorbani A, McCabe E, Griffin G, Guerin C, Ho JE, Shaw SY, Cohen KS, Vasan RS, Tedgui A, Boulanger CM**, Wang TJ**. (2014). Association of circulating endothelial microparticles with cardiometabolic risk factors in the Framingham Heart Study, European Heart J.. 35(), 2972-79*

Camus S, Moraes JA, Bonnin P, Abbyad P, Le Jeune S, Lionnet F, Loufrani L, Grimaud L, Lambry JC, Charue D, Kiger L, Renard JM, Larroques C, Le Clesiau H, Tedgui A, Bruneval P, Barja-Fidalgo C, Alexandrou A, Tharaux PL, Boulanger CM, Blanc-Brude O (2015). Circulating Cell Membrane microparticles Transfer Heme to Endothelial Cells and Trigger Vaso-Occlusions in Sickle Cell Disease., Blood. 125(), 3805-14

Loyer X, Paradis V, Vion AC, Colnot N, Devue C, On S, Scetbun J, Romain M, Paul JL, Rothenberg M, Marcellin P, Durand F, Bedossa P, Prip-Buus C, Baugé E, Staels B, Boulanger CM, Tedgui A, Rautou PE. (2016). Liver microRNA21 is overexpressed in non-alcoholic steatohepatitis and contributes to the disease in experimental models by inhibiting PPARalpha expression., Gut. 65(), 4850-60

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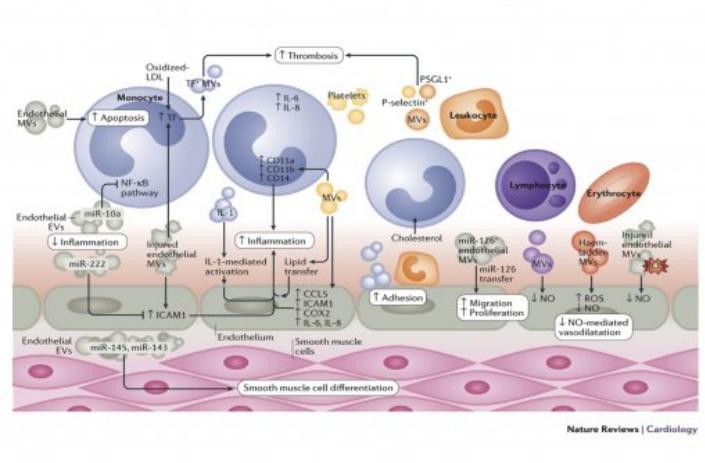
Pro- and anti-atherogenic effects of in vitro generated extracellular vesicles



Potential in vitro harmful or beneficial effects of extracellular vesicles (EVs) on inflammation, thrombosis and endothelial function. MVs: microvesicles; EMVs: endothelial MVs; NO: nitric oxide; ROS: reactive oxygen species; IL: interleukin; ICAM-1: intercellular adhesion molecule-1; RANTES: CCL5, Cox-2: cyclooxygenase type-2; miR: microRNA; PSGL1: P-selectin glycoprotein ligand-1 (Adapted from Boulanger et al. Nature Rev. Card 2017, 14(5):259-272)

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Jean-Sébastien Silvestre
Philippe Menasché

Regenerative therapies for cardiac and vascular diseases

Paris University
Inserm UMR 970
Chantal Boulanger
Paris

The team spans a fully integrated spectrum encompassing basic, preclinical and translational research to develop efficient approaches of cell and non cell-based strategies to circumvent the adverse remodeling occurring in patients with cardiovascular ischemic diseases.

Key facts

Team

• Researchers : 4
• Technicians : 3
• Postdoc fellows : 1
• PhD Students : 5

Translational approaches

• Patents : 2
• Clinical research grants : 1
• Industry partnerships : 2

International research links

• USA, Germany, United Kingdom

Keywords

• Extracellular membrane vesicles
• Heart failure
• Myocardial infarction
• Cell therapy
• inflammation
• Regeneration
• hindlimb ischemia
• Flow Cytometer
• echocardiography
• myocardial infarction
• microangiography

Biological Resources

• In vivo model of critical limb ischemia
• In vitro model of cardiac cell differentiation
• Neonatal model of cardiac regeneration
• In vivo model of myocardial infarction
• In vivo model of heart failure

Research Brief :

The team is based on the complementary expertise contributed by a group (Dr JS Silvestre) experienced in deciphering of signaling pathways involved in post-ischemic tissue remodeling and a group (Pr P Menasché) with a long standing experience in the preclinical, translational and clinical aspects of stem cell research. Together, we form an ideal platform of expertise and technical know-how, ranging from the basic features of cell injury, regeneration and remodeling to the clinical applications of cell- and non cell-based therapies complying with the increasingly stringent regulatory requirements. The background of the group members (both basic scientists and practising clinicians) as well as their respective expertises allow the team to cover a spectrum of activities from the mechanisms of postischemic tissue remodelling and regeneration at the molecular level to the development of therapeutic strategies to mimick and boost these processes. Through the use of tools ranging from molecular biology methods to small and large animal models, the team spans a fully integrated spectrum encompassing basic, preclinical and translational research. Our main objectives are to decipher the molecular and cellular mechanisms involved in post-ischemic tissue remodeling and to develop efficient approaches of cell- and non cell-based strategies to circumvent the adverse remodeling occurring in patients with cardiovascular ischemic diseases.

• **Methodologies Used :**

- Pathophysiological models of cardiovascular ischemic diseases: hindlimb ischemia induced by right femoral artery ligation and cardiac ischemia induced by occlusion of the proximal left anterior descending coronary artery
- Vessel growth analysis by high definition microangiography, immunohistochemistry and laser Doppler imaging to analyze flow recovery
- Transthoracic echocardiography to follow non-invasively systolic and diastolic ventricular function
- Transthoracic echo-guided injection
- Flow cytometer: FACS sorter, Image stream

Publications

Howangyin KY, Zlatanova I, Pinto C, Ngkelo A, Cochain C, Rouanet M, Vilar J, Lemitre M, Stockmann C, Fleischmann BK, Mallat Z, Silvestre JS (2016). Myeloid-Epithelial-Reproductive Receptor Tyrosine Kinase and Milk Fat Globule Epidermal Growth Factor 8 Co-Ordinately Improve Remodeling After Myocardial Infarction via Local Delivery of Vascular Endothelial Growth Factor, Circulation. 133(9), 826-39

El Harane N, Kervadec A, Bellamy V, Pidial L, Neametalla HJ, Perier MC, Lima Correa B, Thiébault L, Cagnard N, Duché A, Brunaud C, Lemitre M, Gauthier J, Bourdillon AT, Renault MP, Hovhannisyan Y, Paiva S, Colas AR, Agbulut O, Hagège A, Silvestre JS, Menasché P, Renault NKE. (2018). Acellular therapeutic approach for heart failure: in vitro production of extracellular vesicles from human cardiovascular progenitors., Eur Heart J. 39(20), 1835-1847

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Lima Correa B, El Harane N, Desgres M, Perotto M, Alayrac P, Guillas C, Pidial L, Bellamy V, Baron E, Autret G, Kamaleswaran K, Pezzana C, Perier MC, Vilar J, Alberdi A, Brisson A, Renault N, Gnecchi M, Silvestre JS, Menasché P. (2021). Extracellular vesicles fail to trigger the generation of new cardiomyocytes in chronically infarcted hearts., Theranostics. 11(20), 10114-10124

Correa BL, Harane NE, Gomez I, Hocine HR, Vilar J, Desgres M, Bellamy V, Keirththana K, Guillas C, Perotto M, Pidial L, Alayrac P, Tran T, Tan S, Hamada T, Charron D, Brisson A, Renault NK, Al-Daccak R, Menasché P, Silvestre JS. (2021). Extracellular Vesicles from Human Cardiovascular Progenitors Trigger a Reparative Immune Response in Infarcted Hearts., Cardiovasc Res. 117(1), 292-307

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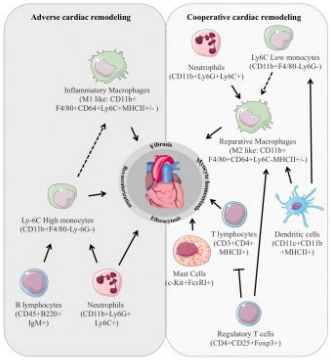
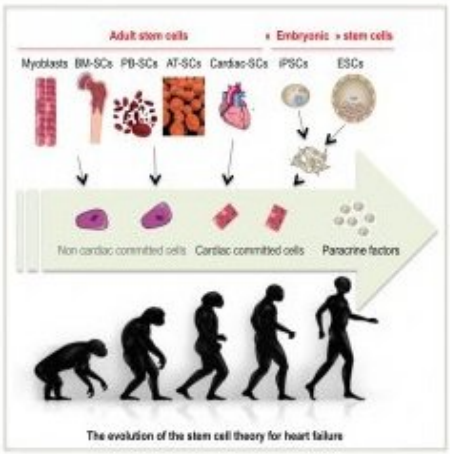
Inflammation and cardiac repair



Immune cell stimulation is among the earliest responses detectable in the injured cardiac tissue and plays an instrumental role in the coordination of multiple processes governing cardiac remodeling. In animal models, the number, type and activation state of the different subclasses of inflammatory cells dictate their impact on cardiac repair leading to either positive or deleterious cardiac remodeling. (From Zlatanova et al, Front Cardiovasc Med, 2016)

The evolution of the stem cell theory for heart failure



The recent big bang in the evolution of the stem cell theory suggests that therapeutic cells rather act as reservoirs of a wide array of bioactive entities that trigger multiple and synergic endogenous repair pathways. Abbreviations: BM: bone marrow, PB: peripheral blood; AT: adipose tissue; iPSCs: induced pluripotent stem cells; ESCs: embryonic stem cells; SCs: stem cells. (From Silvestre JS/P Menasché, Ebiomedicine, 2015)

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Jean-Sébastien Hulot

Cellular, molecular and physiological mechanisms of heart failure

Université de Paris Cité
Inserm UMR970
Chantal Boulanger
Paris

Alliance of high-level basic research and translational medicine

Key facts

Team

- Researchers : 4
- Technicians : 3
- Postdoc fellows : 3
- PhD Students : 4

Translational approaches

- Patents : 4
- Clinical research grants : 2
- Industry partnerships : 5

International research links

- United States
- Germany
- Netherlands

Keywords

- Heart Failure
- Stem Cells
- Stiffness
- Fibrosis
- Tissue Engineering
- Patient-specific iPS cells
- Stem cell biology
- Cytometry / FACS
- cardiomyocyte relaxation
- Genome Editing

Biological Resources

- Library of patient-specific hiPSC
- in vivo models: cardiac hypertrophy, myocardial infarction
- Advanced stages of heart failure

Research Brief :

Heart Failure (HF) remains a leading cause of mortality and morbidity in Europe. Our general aims are to understand the molecular and cellular mechanisms involved in the transition to heart failure and to identify relevant targets to reverse the adverse remodeling process or alternatively promote myocardial tissue repair.
During the last years, the team has consequently set up animal and cellular models to study ischemic heart failure (the most prevalent form of HFrEF) as well as cardiac hypertrophy, an adaptive cardiac response to stress (particularly hemodynamic overload) that progressively leads to heart failure (and mimics some stages of HFpEF). In these murine models of heart failure, we have notably identify a new population of adult stem cells that reside in the myocardium and are identified by the expression of PW1/Peg3 gene. We found that these cells are involved in the fibrotic remodelling of the myocardium in response to stress, thus identifying a new target to limit injury-induced adverse remodelling.
More recently the team has developed innovative tools based on human induced pluripotent stem cells to further model cardiac disorders in a dish. This human cellular platform allows to perform pharmacological investigations, model mono- or multigenic forms of cardiomyopathy, investigate underlying pathological pathways and perform direct intervention (genome editing) to correct or introduce punctual genomic changes and perform functional analyses.

• Methodologies Used :

Biology of adult stem cells with appropriate tools to isolate and identify PW1+ cells in all organs including the cardiovascular system
Human cellular models of cardiac disorders using patient-specific hiPSC
Targeted genome editing using TALENS and/or CRISPR/Cas9
Gene transfer in the cardiovascular system using AAV and adenovirus;
Calcium signalling and calcium sources in cardiovascular cells;
Experimental mouse models for heart failure

Publications

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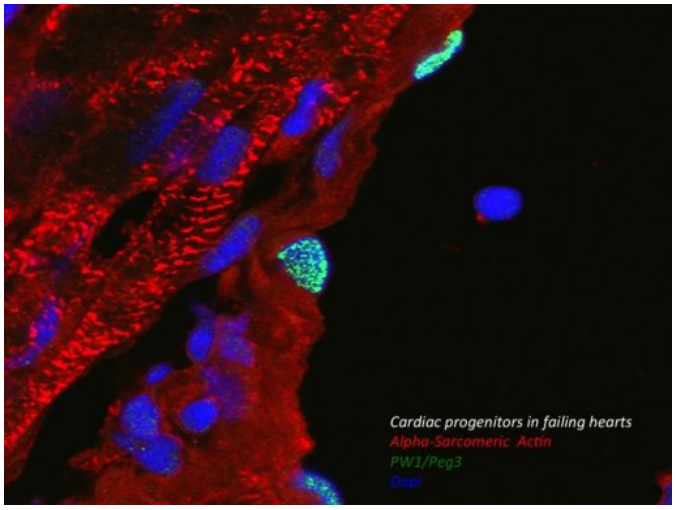
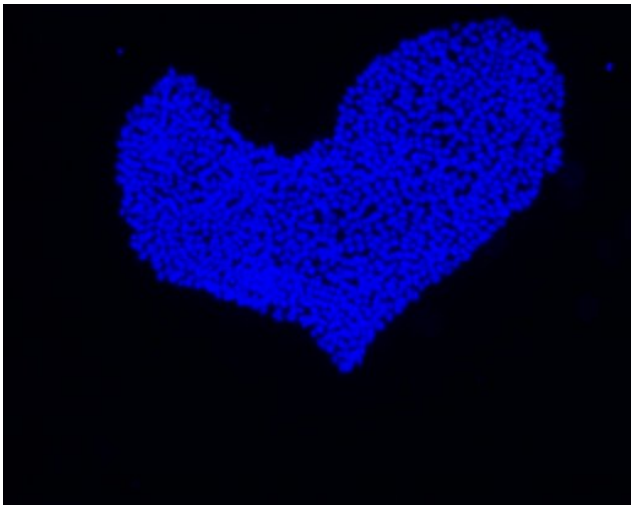
Endogenous Cardiac Stem Cells



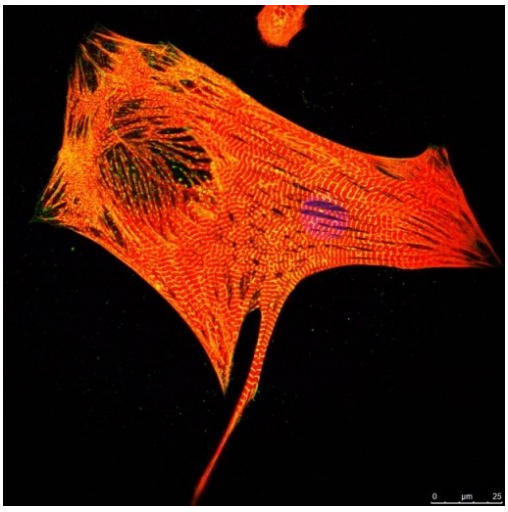
PW1 expression identifies cardiac adult stem cells with fibrogenic potential

Human Models of Cardiac Diseases



A heart-shape colony of human iPS cells

Cardiomyocytes Generated from hiPSC



Human iPS-cell derived cardiomyocytes model cardiac diseases in a dish

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Key facts

Team

• Researchers : 5
• Technicians : 5
• Postdoc fellows : 2
• PhD Students : 2

Translational approaches

• Patents : 0
• Clinical research grants : 6
• Industry partnerships : 1

Keywords

• Rare arterial diseases
• Mitral Valve Prolapse
• Genetics
• Fibromuscular dysplasia
• Gene expression
• Exome sequencing studies
• Genetic association studies
• Knock-out mouse model

Biological Resources

• DNA collection and cohort of patients and families with arterial fibromuscular dysplasia
• DNA collection and cohort of patients and families with vascular Ehlers Danlos syndrome
• DNA collection and cohorts of patients with rare inherited vascular disorders
• DNA collection and tissue collection of patients with cardiac valvular diseases (mitral valve prolapse)

Xavier Jeunemaitre

Genes and rare arterial diseases

Université de Paris 05
(Université Rene Descartes)
Inserm U970
Chantal Boulanger
Paris

Integrated translational research based on several unique patients cohorts, the constitution and exploitation of DNA and tissue biobanks, the use of the most recent genetic technologies to identify new disease-causing genes and variants, the creation and characterization of cellular and mouse models

Research Brief :

Our team aims to identify causative genes and understand mechanistic basis of several rare arterial diseases. We are interested in rare forms of hypertension (Pseudohypoaldosteronism, type II: PHAII) and Fibromuscular Dysplasia: FMD) and rare vascular diseases : vascular Elhers-Danlos Syndrome (vEDS) and inherited forms of aortic aneurysms (TAA). We have also high interest in understanding the genetics and the biology of mitral valve prolapse (MVP) for which we have recently identified several genetic risk loci.
We apply three complementary strategies to achieve these goals:
1) High throughput genetic and genomic approaches, which are exome sequencing and genome-wide association to families and large cohorts of patients recruited at the Hypertension Department and the National Reference Centre for Rare Vascular Diseases
2) Molecular and physiological investigation in CRISPR-Cas9 engineered cells and animal models of genes involved in the regulation of hypertension and vascular tone: WNK pathway, KLHL3-CUL3 ubiquitin ligase complex and collagen 3 alpha 1 gene COL3A1, mutated in vEDS.
3) Clinical investigation and complications follow-up search of circulating biomarkers and vascular tone assessment for vEDS and FMD patients.

• **Methodologies Used :**

- Human genetic studies : genome-wide association and linkage studies, families and population based cohorts, Exome and targeted sequencing
- Mouse models : transgenesis, gene inactivation, tissue-specific inactivation, in vivo blood pressure monitoring, metabolic cages, arterial myograph, creation of original mouse models
- Tissue characterization : Immunohistochemistry, In situ hybridisation, Confocal microscopy imaging, mRNA quantification, Western blotting, RNA-seq, chromatine interaction
- Cellular models : classical cellular characterization, cell trafficking, inhibition by siRNA and shRNA, original cellular models (SDHB inactivation), ubiquitination process, BRET imaging.

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Publications

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Key facts

Team

• Researchers : 6
• Technicians : 1
• Postdoc fellows : 1
• PhD Students : 6

Translational approaches

• Patents : 1
• Clinical research grants : 0
• Industry partnerships : 1

International research links

• USA - Suisse - Angleterre - Espagne - Allemagne - Israel - Mexique -Brésil

Keywords

• heart
• excitation-contraction coupling
• RyR
• Ca2+ sparks
• Ca2+ channel
• Epac
• small G proteins
• aldosterone
• arrhythmia
• heart failure
• cardiac hypertrophy
• confocal microscopy
• molecular biology
• patch-clamp
• biochemistry
• bilayers

Biological Resources

• adult rodent cardiac myocytes
• neonatal cardiac myocytes
• adenovirus
• mouse sinus node preparation
• transgenic mice breeding
• cardiomyocyte humain dérivé d'IPS

Jean-Pierre Benitah

Calcium Signaling and Cardiovascular Physiopathology

Université Paris Saclay
Inserm UMR-S 1180
Ana Maria Gomez
ORSAY

Our team has the internationally recognized expertise in cardiac excitation-contraction coupling in physiologic and pathologic conditions and in molecular basis of arrhythmia. We are one of the rare teams that combine simultaneous recordings of patch-clamp and confocal microscopy in cardiomyocytes.

Research Brief :

Cardiovascular disease still places a heavy burden on society due to poor understanding of the molecular mechanisms involved. All cellular processes are controlled by signal transduction pathways, the defects of which can be involved in pathologies. Ca2+ is a major and proximal player in the physiology and pathophysiology of the cardiovascular system. As a primary regulator of cardiac excitation-contraction coupling, deregulation of Ca2+ signaling is directly related to contractile dysfunction associated with heart failure (HF) and arrhythmias. It is therefore essential to elucidate the mechanisms that maintain Ca2+ homeostasis. In fact, Ca2+ signaling is regulated by Ca2+ channels, transporters and exchangers, working in synergy with Ca2+ dependent proteins. Through integrated approaches from the molecule to the organism, organized around different experimental models, transgenic, and human cardiomyocytes derived from pluripotent stem cells, our project aims to define the mechanisms underlying changes in Ca2+ signaling involved in HF and arrhythmias with 3 axes: 1/ Analysis of the regulation of the expression and function of Ca2+ influxes via Cav1.2 and Orai1/) during HF; 2/ The role of RyR2 at the ventricular and sinus node level in the development of normal rhythm and arrhythmias during HF and CPVT; 3/ The role of Epac on Ca2+ signaling, and its implication in cardiac dysfunction linked to diabetes and cardiotoxicity associated with anticancer treatments.

• **Methodologies Used :**

- Electrophysiology : microelectrode, patch-clamp and lipid bilayers
- Confocal Microscopy (alone or coupled to patch-clamp)
- Superresolution Gated STED
- Biochemistry, molecular and cellular biology.
- Transgenic animal breeding
- Holter telemetry
- calcium imaging

Publications

Wang YY, Mesirca P, Marqués-Sulé E, Zahradnikova A Jr, Villejoubert O, D'Ocon P, Ruiz C, Domingo D, Zorio E, Mangoni ME, Benitah JP, Gómez AM (2017). RyR2R420Q catecholaminergic polymorphic ventricular tachycardia mutation induces bradycardia by disturbing the coupled clock pacemaker mechanism., JCI Insight. 2(8), e91872

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Grégoire Vandecasteele

Cyclic Nucleotide Signaling and Cardiovascular Pathophysiology

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Ana-Maria Gomez
Châtenay-Malabry

Our team demonstrated that cAMP signalling in heart and vessels is highly compartmentalized through the activity of specific cAMP-PDEs and that a loss in cAMP compartmentation occurs during cardiac pathological hypertrophy and contributes to the development of heart failure.

Key facts

Team

- Researchers : 7
- Technicians : 3
- Postdoc fellows : 2
- PhD Students : 5

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 1

International research links

- Germany
- United States
- Italy

Keywords

- cAMP-dependent protein kinase
- phosphodiesterase
- ion channels
- heart failure
- compartmentation
- electrophysiology
- excitation-contraction coupling
- FRET-based imaging
- echocardiography
- vascular reactivity

Biological Resources

- Rat/mouse models of heart failure (genetic, surgical, drug-induced)

Research Brief :

Heart failure (HF) is the only cardiovascular disease that is increasing in prevalence in Europe and the USA. Most cases of HF are caused by diseases of heart muscle that result in pathologic hypertrophy ("remodeling" at the ventricular chamber level) and contractile dysfunction. The majority of HF in patients under 70 years of age reflects impaired systolic function resulting from dilated cardiomyopathy. Beta-adrenergic receptor/cAMP cascade is centrally involved in the pathophysiology of HF, as demonstrated by the correlation between elevated norepinephrine and mortality and the beneficial effect of beta-blockers in this pathology. However, such medications are effective in only 40-50% of HF patients. In the recent past, our team has crucially contributed to the understanding that physiological cAMP signaling is confined in specific subcellular domains and suggested that drawbacks of HF treatments are due to their bypass of compartmentalization. The goal of our team is to provide an in-depth analysis of cAMP signaling in pathologic hypertrophy and to define defective cAMP signaling events that underlie HF. Since HF is associated with anomalies of the vasomotor tone, we also explore the organization of the cAMP signaling cascade in vascular smooth muscle.

- **Methodologies Used :**

Our studies are conducted in rat, mouse and humans. Experimental approaches combine assessment of cardiac function in vivo (echocardiography, ECG) and at the organ level (Langendorff perfused heart), and single cell (patch-clamp, fluorescence imaging) and biochemical studies. A major focus is placed on cAMP phosphodiesterases (PDE) and protein kinase A because our previous work has demonstrated that these enzymes play a key role in the organization of the intracellular cAMP cascade. Through the development of molecules that activate specific cardiac PDE isoforms, our project will attempt to provide new treatments of HF acting on localized cAMP signaling to improve heart function and clinical outcomes.

Publications

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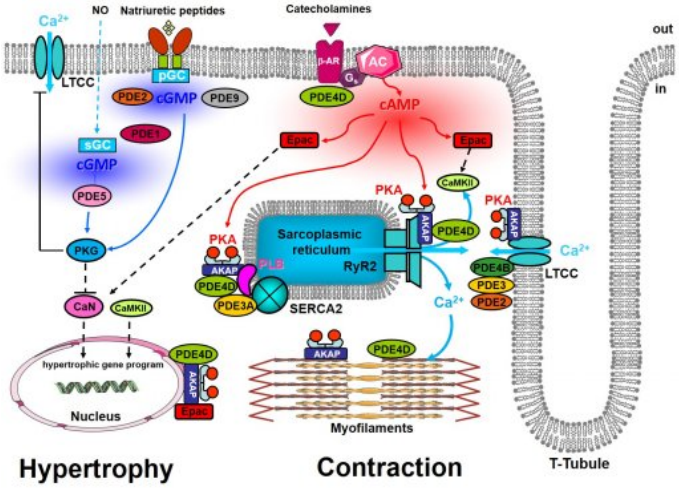
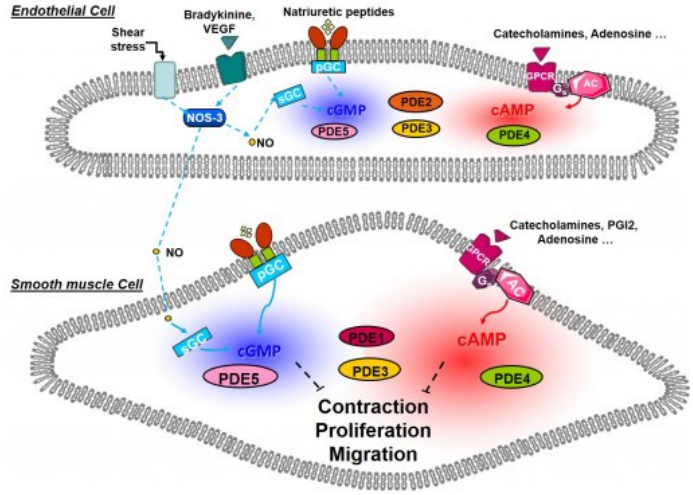
Cyclic nucleotides metabolism in cardiac myocytes.



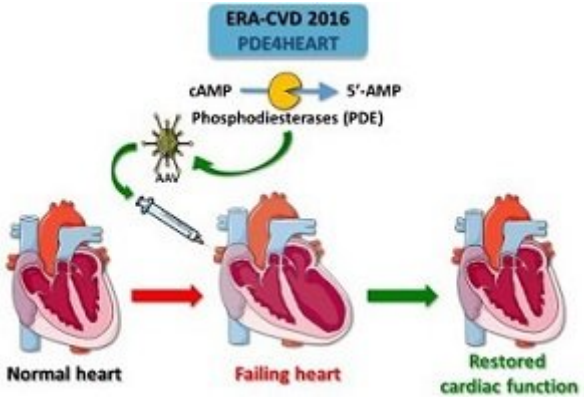
The major phosphodiesterases (PDEs) expressed in cardiac myocytes are indicated, together with their subcellular localization in relation to their role in regulating hypertrophic growth and excitation-contraction coupling. AC: adenylate cyclase; AKAP: A-kinase anchoring protein; CaMKII: Ca2+/calmodulin-dependent kinase II; cAMP: cyclic adenosine monophosphate. Adapted from Bobin et al. Arch Cardiovasc Dis. 2016.

Cyclic nucleotide metabolism in vascular endothelial and smooth muscle cells.



Cyclic nucleotide metabolism in vascular endothelial and smooth muscle cells. For each cell type, the main pathways leading to cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) synthesis and the major phosphodiesterase (PDE) families involved in their degradation are indicated. GPCR: G-protein coupled receptor; Gs: heterotrimeric G-protein stimulating AC; NO: nitric oxide; NOS: NO synthase; pGC: particulate guanylate cyclase.

Gene therapy with phosphodiesterases to treat heart failure



The figure illustrates one of the current research project of the team which was supported by the European Research Area Network (ERA-Net) on Cardiovascular diseases and involving three other european teams (FO Levy, Norway; V Nikolaev, Germany; E Hirsch, Italy). Our goal is to test whether augmenting the activity of a cAMP phosphodiesterase (PDE) in the heart by gene therapy with adeno-associated virus (AAV) is beneficial in heart failure.

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Mathias Mericskay Anne Garnier

Energy signalling and cardiovascular pathophysiology

Université Paris-Saclay
INSERM UMR1180
Ana-Maria Gomez
Châtenay-Malabry

We have an internationally recognized expertise in the characterization of energy metabolism and specifically mitochondrial dysfunction in cardiac fibers.

Key facts

Team

• Researchers : 6
• Technicians : 1
• Postdoc fellows : 1
• PhD Students : 2

Translational approaches

• Patents : 1
• Clinical research grants : 0
• Industry partnerships : 0

International research links

• Canada
• Austria
• USA

Keywords

• Heart failure
• Mitochondria
• AMPK
• Nicotinamide Adenine Dinucleotide
• Sirtuin
• Animal models of heart failure (transgenics, TAC, MI)
• Mitochondrial Respiration
• Echocardiography
• Mitochondrial ROS production
• RTqPCR, Western blots

Biological Resources

• Transgenic models (AMPKciko, SIRT1ciko, SRF-HKO, NMRK2 KO
and TG
• Heart failure models induced by cardiac surgery (myocardial infarction, transverse aorta constriction)

Research Brief :

The severity of energy deficit of the failing myocardium proved to be a prognostic factor of mortality in HF patients. Key questions remain open as regard the contribution of different factors to the establishment of the perturbations in energy metabolism and mitochondrial dysfunction in the failing heart. The team is studying several axis in this field from basic to translational research.

1: Energy metabolism signalling in heart failure and its different regulation in males and females. The team is studying cardiac-specific mouse models of SIRT1 and AMPKalpha2 deletion, which are key regulatory pathways driving mitochondrial biogenesis and metabolic adaptation and that we found to be differently active in males and females.

2: Interactions between endoplasmic reticulum stress and mitochondrial dysfunction in cardiac injury. We try to understand the link between these two process and energy signalling pathways, notably the link between Sirt1 deacetylation of eIF2alpha translation factor and its activity in ER-stress, a new mechanism identified by team members.

3: Developing metabolic therapies of HF. We characterized a drop in myocardial NAD coenzyme levels as a typical feature of the failing heart. We identified a new targetable pathway mediated by the nicotinamide riboside kinase 2 to restore NAD in the context of ischemic and non ichemic diated cardiomyopathy. We combine vitamins and new polyphenols screenings to target metabolic perturbation and ER stress.

• **Methodologies Used :**

- Respirometry
- Cardiac surgery on rodents (TAC; MI)
- Echocardiography
- Transcriptomics
- Metabolomics

Publications

Diguet N, Trammell SAJ, Tannous C, Deloux R, Piquereau J, Mougenot N, Gouge A, Gressette M, Manoury B, Blanc J, Breton M, Decaux JF, Lavery GG, Baczkó I, Zoll J, Garnier A, Li Z, Brenner C, Mericskay M. (2018). Nicotinamide Riboside Preserves Cardiac Function in a Mouse Model of Dilated Cardiomyopathy., Circulation. 137(21), 2256-2273.

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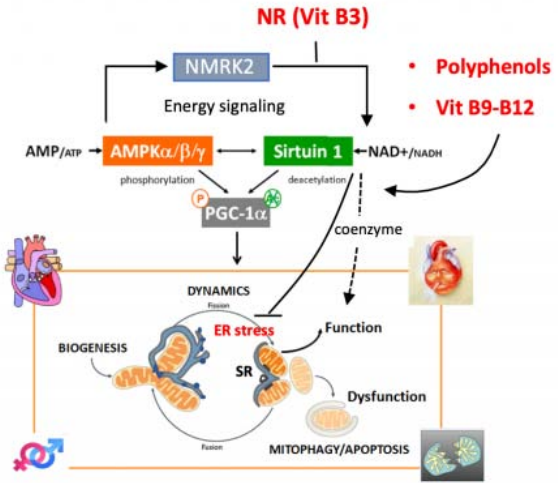
Grimbert L, Sanz MN, Gressette M, Rucker-Martin C, Novotova M, Solgadi A, Karoui A, Gomez S, Bedouet K, Jacquet E, Lemaire C, Veksler V, Mericskay M, Ventura-Clapier R, Piquereau J, Garnier A. (2021). Spatiotemporal AMPK?2 deletion in mice induces cardiac dysfunction, fibrosis and cardiolipin remodeling associated with mitochondrial dysfunction in males only, Biol Sex Differ. 12(1), 52

Team 1 projects summary



Different regulatroy mechanisms govenr the life cycle of mitochondria among which AMPK (activated by high AMP/ATP ratio) and SIRT1 (activated by high NAD+/NADH ratio) play a preponderant role, notably through activation of the PGC1alpha transcriptional coactivator. NAD synthesis can be stimulated by nicotinamide riboside (NR), a specific type of vitamin B3 phosphorylated by the NMRK2 kinase characterized as a new alternative NAD salvage pathway.

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IRIS team

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Hubert Vidal
Pierre Bénite

IRIS team gathers scientists and clinicians at the hospital, has a strong interaction with the Center for Clinical Investigation of Lyon and a labelled platform for in vivo experimentation. This makes IRIS team the best environment for translational research in the field of ischemia-reperfusion.

Key facts

Team

- Researchers : 34
- Technicians : 8
- Postdoc fellows : 3
- PhD Students : 6

Translational approaches

- Patents : 2
- Clinical research grants : 4
- Industry partnerships : 5

International research links

- USA, SWITERZLAND
- UK, LEBANON
- ITALY, SOUTH AFRICA

Keywords

- ischemia-reperfusion
- myocardial infarction
- stroke
- cardiorenal syndrome
- cardiometabolic syndrome
- Animal models
- photon microscopy
- molecular and cellular biology
- MRI, PET, CT, US
- Ca2+ imaging

Biological Resources

- in vivo/in vitro models
- biobanks from CRB
- cohorts from CIC

Research Brief :

The IRIS team focuses on the physiopathology of the ischemia-reperfusion (I/R) syndromes in the heart, kidney and brain, by combining fundamental, translational and clinical approaches. Our strategy relies on three main aims:
1/ Imaging of cell death and inflammation
2/ Molecular mechanisms of ischemia-reperfusion: Ca2+, metabolism and inflammation
3/ Molecular mechanisms & conditioning engineering of organ preservation and biomarkers detection.
Although important therapeutic progress has been made over the last two decades, ischemic pathologies such as myocardial infarction and stroke remain one of the first causes of death worldwide. Due to the aging of the population and the progression of comorbidity factors like diabetes, obesity and arterial hypertension, the occurrence of ischemia-reperfusion syndromes should continue and even worsen.
The clinical research group is composed of cardiologists, neurologists, nephrologists, surgeons and anesthetists-resuscitators who work in several hospitals from the Hospices Civils de Lyon. Its main objective is to conduct clinical trials aiming to test the effect of therapeutic molecules on ischemia-reperfusion syndromes.
The fundamental research group is made of INSERM and CNRS researchers, university teaching-researchers and clinicians-researchers, covering a wide range of expertise from molecular biology and biophysics to human physiopathology through medical imaging and in vivo experimentation.

• Methodologies Used :

Academic researchers and clinicians work conjointly to give rise to a translational research based on two complementary approaches: "from bench to bedside" and "from patient to bench".
By mean of molecular and cellular biology, cell lines and primary cells, ex vivo organs, in vivo animal models, we are studying the dynamics of mechanisms triggers by the ischemia-reperfusion sequence.
At the animal level, we are combining static analysis like OMICS, photon microsocpy to longitudinal follow-up with multimodal imaging of edema, perfusion, metabolism and inflammation.
Final, at the patient level, we are planning and developing ancillary studies based on the biobanks obtained from the clinical trials.

Publications

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3. Bochaton, T., Paccalet, A., Jeantet, P., Crola Da Silva, C., Cartier, R., Prieur, C., Jossan, C., Bonnefoy-Cudraz, E., Mewton, N. and Ovize, M. (2020). Heat Shock Protein 70 as a Biomarker of Clinical Outcomes After STEMI, J Am Coll Cardiol. (),

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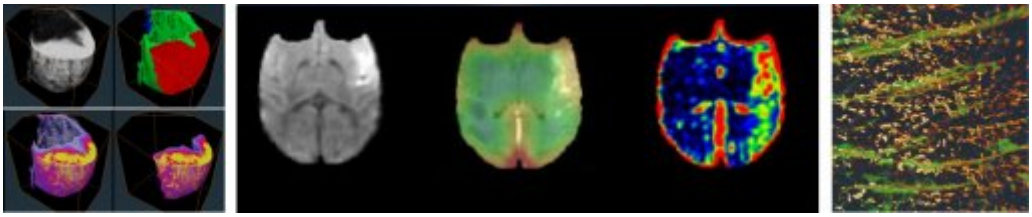
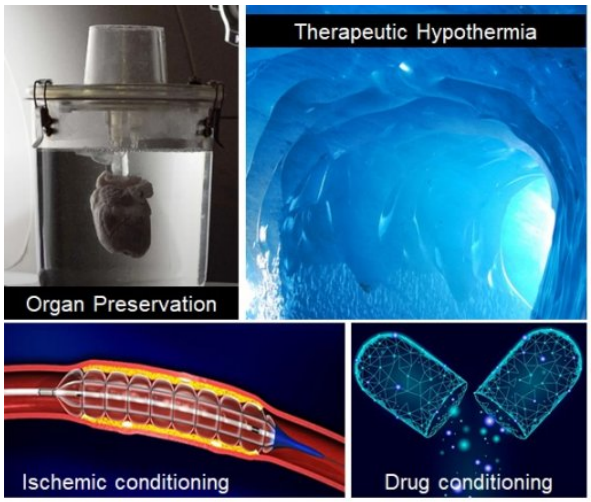
Imaging cell death and inflammation



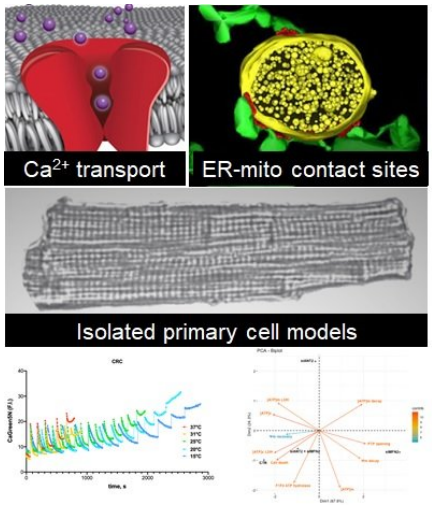
We propose to reveal the determinants of I/R injuries via molecular imaging tools that characterize and monitor tissue damage in a longitudinal and individual manner. To this aim, we build upon our long-term expertise for multimodal imaging of edema, perfusion, metabolism and inflammation, in particular macrophage imaging and blood brain barrier dysfunction. Developing companions imaging tools and their associated imaging biomarkers should favor the clinical transfer of our findings.

Molecular mechanisms of ischemia-reperfusion (IR): Ca2+, mitochondria, metabolism and inflammation



The mitochondrial permeability transition pore(PTP) opening has been shown to be crucial in cell death regulation during I/R injury. However, its inhibition in clinics did not afford a beneficial prognostic to patients undergoing myocardial infarct or cardiac arrest. We have refocused our research on cardioprotection upstream of the PTP: on reticular Ca2+ channels, on the mitochondrial Ca2+ entry and on some signaling mechanisms, together with determining their metabolic and inflammatory impact.

Mechanisms of organ conditioning, preservation & engineering



Among the I/R protection strategies, therapeutic hypothermia is routinely applied in the clinic. Even if the ischemic conditioning has been protective, it suffers from the lack of knowledge on the molecular mechanisms involved. To optimize clinical protocols using cold as a cytoprotective therapy, our research is based on unsupervised high-throughput approaches and innovative targets. We are also developing innovative solutions to optimize the preservation of grafts in deep hypothermia.

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Flavien Charpentier

Ion channels and cardiac arrhythmias

Université de Nantes
Inserm UMR1087 CNRS UMR6291
Richard Redon
Nantes

The strength of our team relies on the diversity of its members, from biophysicists and cell biologists to clinical electrophysiologists, and its strong collaboration with the team of genetics and cardiologists, allowing the development of gene-to-bedside research programs on cardiac arrhythmias.

Key facts

Team

- Researchers : 11
- Technicians : 8
- Postdoc fellows : 0
- PhD Students : 5

Translational approaches

- Patents : 0
- Clinical research grants : 2
- Industry partnerships : 1

International research links

- Canada
- Switzerland
- Germany

Keywords

- ion channel
- cardiac conduction
- cardiac arrythmia
- Brugada syndrome
- long QT syndrome
- cardiac channelopathies
- aging
- human induced pluripotent stem cell
- proteomics
- cellular electrophysiology
- DGE-Seq, RNA-Seq
- in vivo electrophysiology

Biological Resources

- original transgenic mouse models of arrhythmias
- human induced pluripotent stem cell lines of genetically inherited arrhythmias
- cardiac myocytes and fibroblasts in primary culture

Research Brief :

Our team projects are based on our expertise in cardiac arrhythmias and in heart cell biology and differentiation of human induced pluripotent stem (iPS) cells into cardiomyocytes. Our goal is to understand the function and regulation of cardiac ion channels in physiological conditions and in the context of cardiac arrhythmias, to identify new therapeutic targets.
Our strategy is organized around 4 main research programs:
1. Cardiac arrhythmias and sudden death (I. Baró & N. Gaborit)
The goal is to identify pathophysiological mechanisms of hereditary cardiac arrhythmias, based on cellular models developed from patient induced pluripotent stem cells and knock-in mouse models
2. Fibrosis and cardiac conduction diseases (F. Charpentier)
This program aims to identify therapeutic targets based on the signaling pathways that we have shown to be involved in the development of fibrosis during aging in hereditary progressive cardiac conduction diseases
3. Post-translational regulation of Nav1.5 (C. Marionneau)
We are evaluating the involvement of the phosphorylation sites that we identified by a phosphoproteomic approach on Nav1.5 in the posttranslational regulation of this channel
4. Cardiac ionic channels: from biophysics to therapeutic applications (G. Loussouarn)
This program aims to develop therapeutic tools targeting the peptide sequences controlling the opening of voltage-gated ion channels involved in cardiac channelopathies.

- **Methodologies Used :**

Molecular and cellular biology: Taqman low density arrays, RNA-Seq, DGE-Seq, ChIP-Seq immunostaining, time laps videomicroscopy
Proteomics: pull-down assay, yeast two-hybrid interaction assay, in-solution mass spectrometry
Electrophysiology: conventional and high-throughput automated (384 wells) patch-clamp, high-throughput action potential recording with voltage-sensitive dyes, microelectrodes, MultiElectrode Arrays, electrocardiogram, in vivo intracardiac recording and pacing, telemetry
Target discovery and pharmacological screening

Publications

Portero V, Le Scouarnec S*, Es-Salah-Lamoureux Z*, Burel S, Gourraud JB, Bonnaud S, Lindenbaum P, Simonet F, Violleau J, Baron E, Moreau E, Scott C, Chatel S, Loussouarn G, O'Hara T, Mabo P, Dina C, Le Marec H, Schott JJ, Probst V, Baró I, Marionneau C, Charpentier F*, Redon R*. (2016). Dysfunction of the voltage-gated K+ channel beta-2 subunit in a familial case of Brugada syndrome., journal of the American Heart Association. 5(6), e003122*

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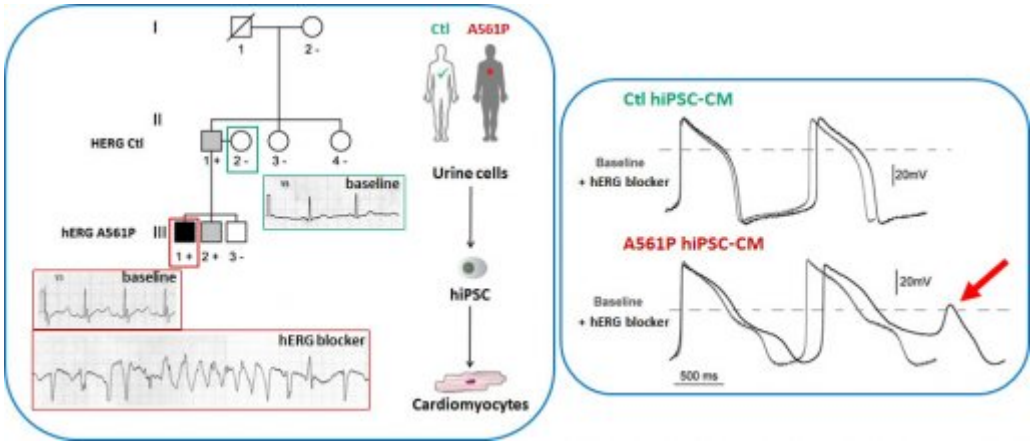
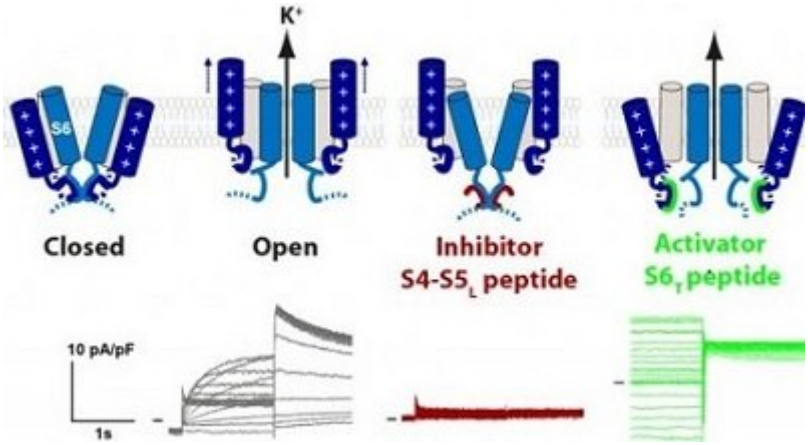
Phenotype of cardiomyocytes derived from iPS cells of a patient with type 2 long QT syndrome



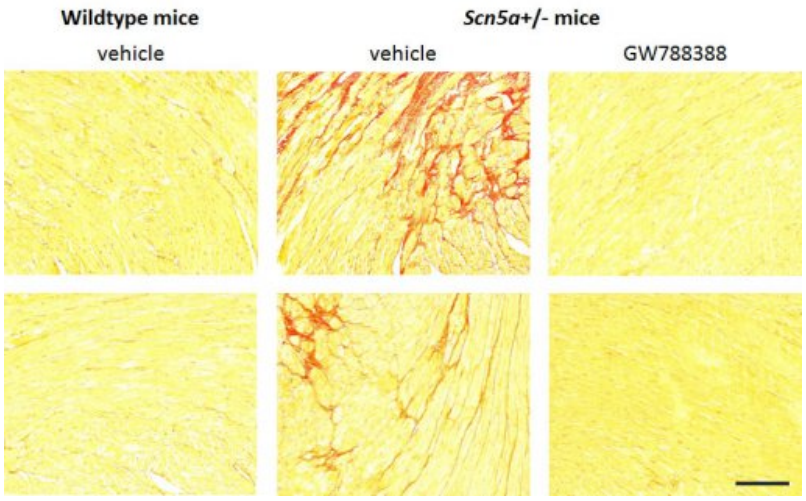
Action potentials (right panel) recorded in cardiomyocytes differentiated from induced pluripotent stem cells (hiPSC-CM) derived from urine cells of a patient with type 2 QT syndrome (p.A561P mutation of hERG channel) and his healthy mother (Ctl). Action potentials in A561P hiPSC-CM were longer than control ones. A hERG channel blocker induced ventricular arrhythmias in the patient and early afterdepolarizations (red arrow) in the patient's hiPSC-CMs.

Coupling mechanism between voltage sensors and the gate in the voltage-gated potassium channel hERG



hERG is formed by a tetrameric pore (S5-S6) surrounded by 4 voltage sensor domains (S1-S4). Covalently binding a peptide mimicking the S4-S5 linker (S4-S5L) to the channel S6 C-terminus (S6T) inhibits hERG. Conversely, covalently binding a peptide mimicking S6T to S4-S5L renders the channel voltage-independent. We thus show that S4-S5L acts as a voltage-controlled ligand that binds S6T to lock the channel in a closed state, elucidating the coupling between voltage sensors and the gate in hERG.

Inhibition of TGF-beta pathway prevents ageing-related fibrosis in heterozygous Scn5a knockout mice



Representative histological sections stained with picrosirius red from 60-week-old wildtype and heterozygous Scn5a knockout (Scn5a+/-) mice, a model of SCN5A-related progressive cardiac conduction disease, treated with either vehicle or GW788388, a blocker of TGF-? receptors, from the age of 45 weeks.

Charpentier Flavien - flavien.charpentier@inserm.fr - https://umr1087.univ-nantes.fr/research/research-teams/iia-ion-channels-and-cardiac-arrhythmias

Gervaise Loirand

Signaling in vascular and pulmonary pathophysiology

Université de Nantes
Inserm UMR 1087 CNRS UMR 6291
Richard Redon
Nantes

A specific strenght of the team is the strong interaction between basic scientists , interventional cardiologists/neurologists and vascular surgeons, and the close relationships between research and clinical departments allowing translational programs spanning from basic science to human disease.

Key facts

Team

- Researchers : 10
- Technicians : 6
- Postdoc fellows : 2
- PhD Students : 4

Translational approaches

- Patents : 4
- Clinical research grants : 2
- Industry partnerships : 1

Keywords

- G protein coupled receptor
- signal transduction
- intracranial aneurysm
- asthma
- hypertension
- airway
- artery
- smooth muscle
- pulmonary
- Cardiovascular
- contraction
- Rho proteins
- target discovery
- animal models
- functional exploration
- biochemistry
- molecular biology
- cell biology
- proteomics

Biological Resources

- - Primary culture (rodent en human bronchial and arterial vascular smooth muscle cells; human and rodent endothelial cells))
- - Ex vivo models of vascular and airway function analysis (arterial rings, bronchial ring, perfused kidney)
- - Animal models of vascular and pulmonary disease (hypertension, pulmonary hypertension, intracranial aneurysm, atherosclerosis, restenosis, asthma)
- - Original transgenic mice

Research Brief :

Our team projects are based on our previous work and acquired expertise on the small G proteins of the Rho family and their regulation in vascular smooth muscle cells and arterial diseases, but also more recently, in pulmonary pathologies. Our projetc relies on four main research programmes:
1. Regulation of RhoA activity: arterial pathologies and remodelling associated with aging (G. Loirand). This program particularly focus on the RhoA exchange factor, Arhgef1, identified as a target of interest in hypertension, and in the regulation of RhoA by phosphorylation
2. Role of Rac1 in arterial and bronchial smooth muscle cells (V. Sauzeau). The main objective is (i) to understand how Rac1 controls the contraction of bronchial smooth muscle cells, (ii) to define the mechanisms responsible for the activation of Rac1 in asthma, and (iii) to develop Rac1 inhibitors.
3. Physiopathology of intracranial aneurysms (G. Loirand). Based on our collaboration with the genetic team and the identification of rare causal variants in humans, our objective is to understand the pathophysiological mechanisms of intracranial aneurysms, through the development of relevant cellular and animal experimental models.
4. Inflammation/bronchial hyperreactivity relationship (A. Magnan). Particular interest is given to the relationship between Rac1/inflammation/contraction in asthma and to the confirmation of these pathways in the human pathology.

- **Methodologies Used :**

- Cell culture, cell biology
- Gene/function analysis (molecular biology, transfection, mutagenesis)
- Protein expression and function analysis, proteomics
- Animal models of human vascular and pulmonary diseases
- Transgenic mice, functional exploration (cardiovascular, pulmonary and metabolic)
- Ex vivo vascular and airway function analyses
- Imaging
- Target discovery
- Pharmacological screening

Publications

Guilluy C, Bregeon J, Toumaniantz G, Rolli-Derkinderen M, Retailleau K, Loufrani L, Henrion D, Scalbert E, Bril A, Torres RM (2010). The Rho exchange factor Arhgef1 mediates the effects of angiotensin II on vascular tone and blood pressure, Nat Med.. 16(2), 183-190

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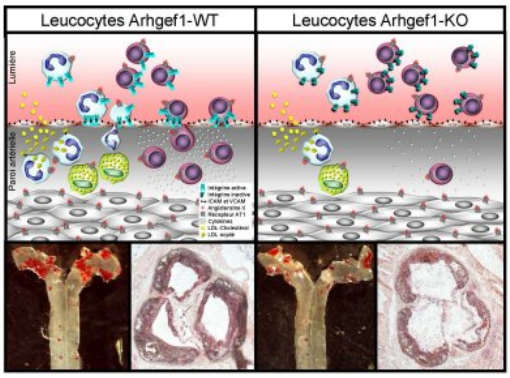
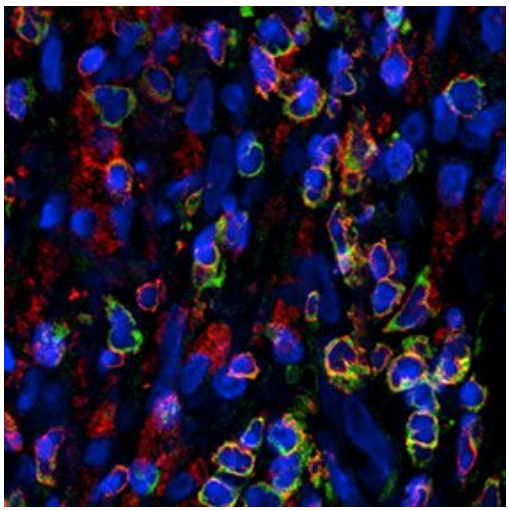
Loirand Gervaise - gervaise.loirand@univ-nantes.f r -

Arghef1 deletion limits atherosclerosis.



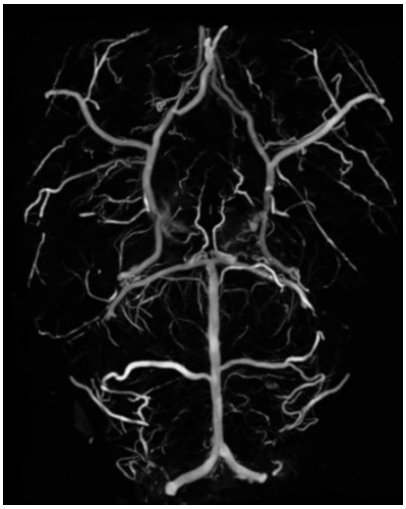
Atherosclerotic plaque formation is initiated by the penetration of LDL-cholesterol into the subendothelium and its oxidation which activates the endothelium and induces the expression of the adhesion molecules ICAM and VCAM. The stimulation of leukocytes (monocytes:light blue; T lymphocytes: violet) by Ang II/AT1 receptors activates Arhgef1, which induces the change in conformation of leukocyte integrins (left), high affinity for ICAM and VCAM, binding of leukocytes and their penetration.

Arghef1 expression in human atherosclerotic plaque



Immunostaining of cross section of human atherosclerotic carotid showing Arhgef1 expression in T cells in atherosclerotic lesion (CD3 red; Arhgef1 green).

Mouse cerebral vasculature



Micro-CT image of mouse (C57bl6) cerebral vasculature

Loirand Gervaise - gervaise.loirand@univ-nantes.f r -

Key facts

Team

• Researchers : 8
• Technicians : 0
• Postdoc fellows : 2
• PhD Students : 3

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 5

International research links

• United States, Sweden, United Kingdom

Keywords

• stroke
• coronary artery disease
• clinical trials
• registries

Biological Resources

• GENIC: Cohort of stroke patients and matched controls with careful phenotypic and genotypic characterization and a comprehensive biobank
• REACH : International cohort of 68 000 ambulatory outpatients with atherothrombosis from 44 countries, with follow-up up to 4 years
• BIOCORE: 3 parallel cohorts of patients with unstable, stable and no coronary artery disease, with careful phenotypic and genotypic characterisation from coronary angiography and intravascular ultrasound to proteomics
• CLARIFY: International registry of 33000 patients with stable coronary artery disease
• ODYSSEY OUTCOMES: phase 3 international trial of alirocumab, a PCSK9 inhibitor, in patients with elevated atherogenic lipoproteins after acute coronary syndromes

Philippe Gabriel Steg

Clinical Research in Atherothrombosis Laboratory for Vascular Translational Science

Université de Paris
Inserm U1148 CHU AP-HP
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Paris

integration of the stroke and myocardial infarction research teams

Research Brief :

Clinical epidemiology of coronary artery disease
- large scale registries
- clinical trials of new therapies
- comparative effectiveness of management strategies
- interrelations between cerebrovascular disease and coronary artery disease
Pathogenesis of acute coronary syndromes and stroke

• **Methodologies Used :**

International multicenter registries and clinical trials
Cerebrovascular and coronary invasive and noninvasive imaging of plaques

Publications

FUTURA/OASIS-8 Trial Group , Steg PG, Jolly SS, Mehta SR, Afzal R, Xavier D, Rupprecht HJ, López-Sendón JL, Budaj A, Diaz R, Avezum A, Widimsky P, Rao SV, Chrolavicius S, Meeks B, Joyner C, Pogue J, Yusuf S (2010). Low-dose vs standard-dose unfractionated heparin for percutaneous coronary intervention in acute coronary syndromes treated with fondaparinux: the FUTURA/OASIS-8 randomized trial., JAMA : the journal of the American Medical Association. 304(12), 1339-49

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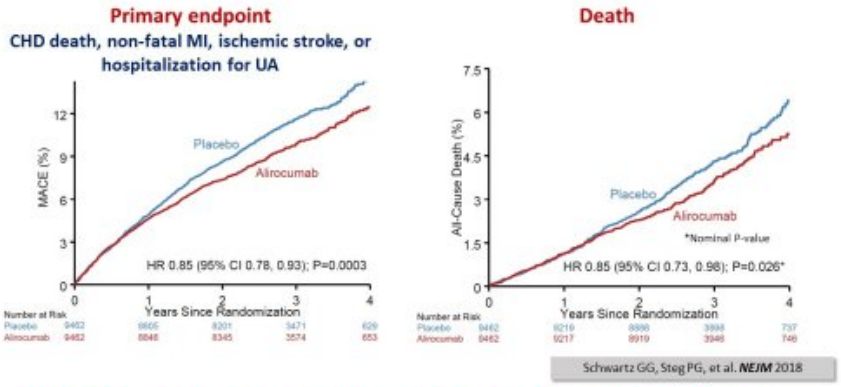
ODYSSEY OUTCOMES: a double blind randomized trial of alirocumab in pts with ACS

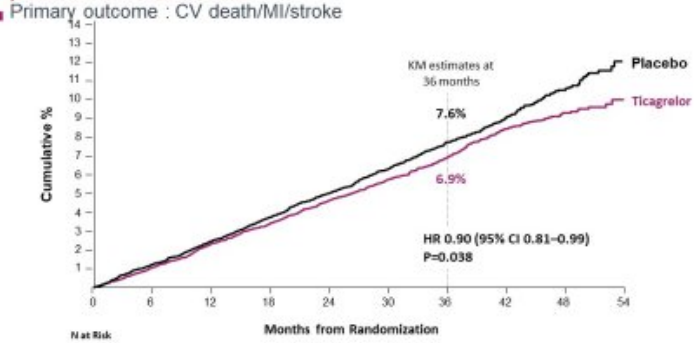
18,924 patients with recent ACS on maximum tolerated high intensity statin Rx



Schwartz GG, Steg PG, et al. *NEJM* 2018

THEMIS: a randomized trial of ticagrelor vs placebo added to ASA in diabetic patients with stable CAD

Primary outcome : CV death/MI/stroke



CI=confidence interval; HR=hazard ratio; KM=Kaplan-Meier; MI=myocardial infarction; N=number of patients

Steg PG, Bhatt DL, et al. *NEJM* 2019; 381:1309-20

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Key facts

Team

- Researchers : 3
- Technicians : 2
- Postdoc fellows : 2
- PhD Students : 3

Translational approaches

- Patents : 1
- Clinical research grants : 2
- Industry partnerships : 0

Keywords

- hypoxia
- angiogenesis
- ischemic cardiovascular diseases
- vascular biology
- cancer
- microscopy
- biomarkers
- animal models
- cell culture
- Translational Studies

Biological Resources

- Biobank (DNA, serum and plasma): Tumor bank (Hopital Saint-Louis); Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS)
- Human vascular tissues and cell biobank
- Animal models of angiogenesis and lymphangiogenesis (tumor models, metastatic models, ischemic models, lymphangioma)
- Primary culture (Venous and arterial endothelial and vascular smooth muscle cells)
- Ex vivo models of angiogenesis and lymphangiogenesis (arterial rings, lymphatic thoratic duct assay)
- Experimental models of acute myocardial infarction and stroke (mouse, rat and rabbit)

Stéphane Germain

Role of Matrix Proteins in Hypoxia and Angiogenesis

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Paris

Our goal is to understand how endothelial cells respond to hypoxia in order to identify new specific markers of hypoxia-induced angiogenesis and new potential therapeutic targets in cancer and ischemic cardiovascular diseases

Research Brief :

Biological events that permits an organism to maintain tissue viability in hypoxia remains poorly understood. How hypoxic endothelial cells integrate chemical signals with mechanical cues from their local microenvironment to protect vascular integrity during ischemic insult and/or induce functional capillary networks that exhibit specialized form remains an open question. A key role of hypoxia in regulating endothelial function is nevertheless established and growing evidence shows that angiogenesis, blood vessels formation by sprouting or growth of preexisting vessels, can be triggered by hypoxia, both during development and in pathological conditions.
Our efforts have recently been focused on characterizing the role of Lysyl Oxidase-like 2, Thrombospondin-1 and Angiopoietin-like 4 in regulating angiogenesis and vascular integrity. The complementary technical expertise of the members of the team together with the established collaborations with clinicians (Pathology, Urology, Cancer and Biochemistry departments, Hopital Saint-Louis and HEGP) led to the definition of angptl4 mRNA as an accurate marker for primary ccRCC diagnosis. Altogether, our studies aimed at better understanding of the complex interplay between endothelial cells and soluble growth factors and mechanical factors from the extracellular matrix will certainly have significant implications for understanding the regulation of developmental and pathological angiogenesis driven by hypoxia.

- **Methodologies Used :**

Multidisciplinary approach combining gene discovery approach for complex human diseases
- Cell culture, cell biology: vascular cell proliferation, adhesion, migration, cell velocity, videomicroscopy, 2-D and 3-D angiogenesis models, normoxia, hypoxia
- Gene/protein structure function analysis (molecular biology, transcriptomics, extracellular matrix proteomics, transfection, mutagenesis)
- Animal models, transgenic mice, cardiovascular functional exploration, cancer, metastases
- Vascular development (animal models, zebrafish studied by confocal, second harmony, bi-photon, and electron microscopy)

Publications

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The interaction of HSPGs with endothelial transglutaminase-2 limits VEGF165--induced angiogenesis

Online Cover This week features a Research Article that shows that transglutaminase-2 prevents heparan sulfate from potentiating signaling by a specific VEGF isoform, thereby attenuating blood vessel formation. The image shows retinal vascularization in a mouse deficient in transglutaminase-2

Germain Stéphane - stephane.germain@college-de-fr ance.fr - 0144271664 - https://www.college-de-france.fr/site/en-cirb/germain.htm

Key facts

Team

• Researchers : 6
• Technicians : 2
• Postdoc fellows : 1
• PhD Students : 1

Translational approaches

• Patents : 6
• Clinical research grants : 1
• Industry partnerships : 1

International research links

• Canada, USA, Spain, Switzerland

Keywords

• Vasopressin/water balance
• G-protein coupled receptors
• Monozinc aminopeptidases
• Apelin
• Brain
• Angiotensins
• Cardiac function
• Blood pressure
• Molecular modelling
• molecular biology
• cellular biology
• binding
• signaling
• [Ca2+]i mobilization
• internalization
• immunohistochemistry
• in situ hybridization
• Confocal microscopy
• expression of proteins
• Western-blot
• neuropeptide radioimmunoassay
• enzymatic activity
• drinking behavior
• diuresis
• vessel vasoreactivity
• blood pressure
• cardiac function
• hypertension
• myocardial infarction
• heart failure

Biological Resources

• experimental model of hyponatremia
• experimental model of hypertension (rat)
• experimental model of heart failure after myocardial infarction (mouse)

Catherine Llorens-Cortes

Neuropeptides Centraux et Régulations Hydrique et Cardiovasculaire -Central neuropeptides in the regulation of body fluid homeostasis and cardiovascular functions

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Our work is to identify new therapeutic targets (enzymes involved in the metabolism of (neuro)vasoactive peptides or their receptors) involved in water balance and cardiovascular functions control. The synthesis of compounds acting on these targets leads to the development of therapeutic agents.

Research Brief :

BRAIN RENIN-ANGIOTENSIN SYSTEM (RAS). We showed in the brain RAS that aminopeptidase A (APA) generates angiotensin III (AngIII) from AngII and that brain AngIII exerts a tonic stimulatory effect on the control of blood pressure (BP) in hypertensive animals. In coll. with the team of B. Roques (U640), we designed the first specific and selective APA inhibitor, EC33 and we showed that the inhibition of brain APA decreases BP. Brain APA constitutes a potential therapeutic target for the treatment of hypertension. We produced a new APA inhibitor, RB150 able, after administration by oral route, to cross the intestinal, hepatic and blood brain barriers, to block the activity of the brain RAS and to normalize BP in hypertensive animals. We pursue the preclinal development of RB150 with Quantum Genomics. APELINERGIC SYSTEM. We isolated an orphan receptor which was shown to be the receptor of a new peptide, apelin. We demonstrated that apelin and its receptor are expressed together with vasopressin (AVP) in hypothalamic neurons. We showed that the icv injection of apelin in lactating rats decreased the activity of these neurons and the systemic secretion of AVP, resulting in aqueous diuresis. Apelin is a natural inhibitor of the anti-diuretic effects of AVP. We showed that in rats and humans, apelin and AVP are regulated in opposite manners by osmotic stimuli. In addition, apelin decreases BP, improves cardiac contractility. Apelin controls water balance and cardiovascular functions.

• **Methodologies Used :**

Molecular modeling and molecular biology: 3D model of enzyme or GPCRs and site-directed mutagenesis studies - Screening of chemical libraries - Pharmacological studies of GPCRs stably expressed in eukaryotic cells : binding, cAMP production, [Ca2+]i mobilization, internalization followed by confocal microscopy - Neuroanatomical studies: immunohistochemistry, in situ hybridization - Purification of peptides by HPLC and radioimmunoassay - Enzymatic studies: expression of recombinant enzymes, purification, Western-blot analysis, enzymatic activity - Physiological studies: measurement of vasopressin release, drinking behavior, diuresis, plasma and urinary electrolytes Vessel vasoreactivity - Blood pressure - Cardiac function

Publications

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Elise Balse

Molecular and Cellular Plasticity in Cardiovascular Diseases

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Our team combines cutting-edge techniques (high resolution imaging, lineage tracing models, human trabeculae contraction) and new scientific concepts (ion channel trafficking, progenitor cells, protective macrophages) to study cardiovascular remodeling cellular and molecular players.

Key facts

Team

• Researchers : 6
• Technicians : 2
• Postdoc fellows : 0
• PhD Students : 5

Translational approaches

• Patents : 1
• Clinical research grants : 0
• Industry partnerships : 3

International research links

• Other: Lebanon, Australia
• Europe: Germany, Great Britain, Switzerland, Austria, Netherlands
• America: Canada, USA

Keywords

• Cardiovascular remodeling
• Atrial fibrillation
• Progenitor cells
• Heart failure
• Pulmonary hypertension
• Calcium imaging
• Lineage tracing
• High resolution imaging
• Electrophysiology
• Chronic hypoxia

Biological Resources

• Chronic hypoxia chamber for mice and rats
• Hypertrophic remodeling and transition to heart failure via chronic adrenergic infusion (Alzet pump) or pressure overload (transverse aortic constriction)

Research Brief :

Cardiovascular diseases are often intricate diseases that share pathophysiological mechanisms. Remodeling processes are associated with complex rearrangement at the tissue and at the cellular levels. We aim at understanding the drivers of the molecular and cellular plasticity that characterize cardiovascular remodeling during atrial fibrillation (AF), heart failure (HF), senescence and pulmonary hypertension (PH).
Our projects focus on:
- The plasticity of cellular composition of cardiovascular tissues. We notably study the capacity of progenitor and stem cells to be recruited, to differentiate in various mesenchymal cell lineages and to contribute to atrial and vascular remodeling.
- The plasticity of macromolecular protein complexes regulating cardiac function and their role in pump dysfunction and arrhythmias. We focus on the regulation of ion channels trafficking and targeting in cardiomyocytes.
- The role of cellular metabolic shifts in regulating myocardial remodeling and atrial electrical properties.
- The role of immune and inflammatory cells during cardiovascular remodeling leading to HF. We study the mechanisms of macrophages protective role during early adaptive cardiac hypertrophy.
-The role of oxidative stress and inflammation during age-associated cardiovascular remodeling and transition to heart failure.
- The role of the GCN2 gene loss of function in the development of Pulmonary Veno-Occlusive Disease, a particular form of pulmonary hypertension.

• **Methodologies Used :**

- Adult Cardiac Myocytes preparation (rat and mouse)
- Immune cell isolation / FACS analysis and sorting
- TIRF microscopy / High resolution 3D deconvolution Imaging
- Lineage tracing mouse models / Calcium imaging / Echocardiography
- percutaneous intramyocardial injections under echographic guidance
- Pulmonary and systemic hemodynamic measurements
- Pulmonary and epicardial progenitor and stem cells isolation and culture
- Transcriptomic analysis / Lipidomic analysis / Chronic hypoxia
- Contractility and hemodynamic measurements in rat isolated working heart model and Langendorff models
- In vitro measurements of human atrial trabeculae contractility

Publications

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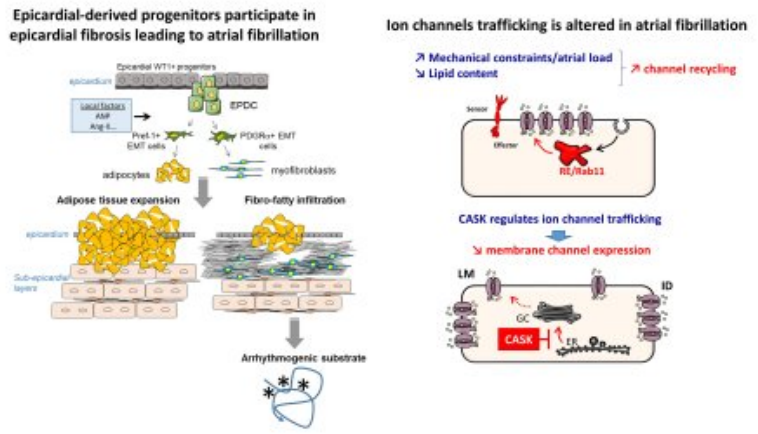
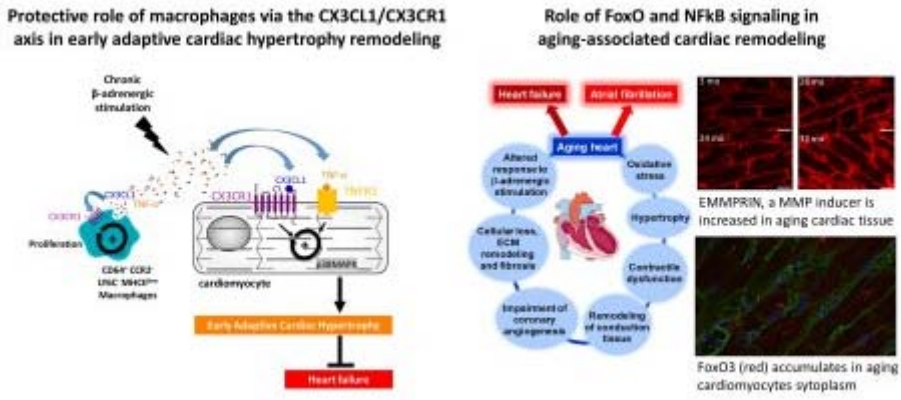
CELLULAR AND MOLECULAR PLAYERS IN ATRIAL FIBRILLATION



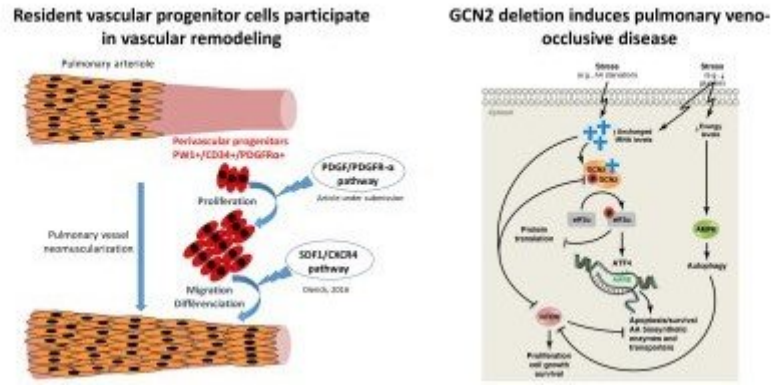
During atrial cardiomyopathy, epicardium is reactived. The recruitment of cells derived from epicardial progenitors engaged in adipocyte or fibroblastic lineages results in the arrhythmogenic fibro-fatty infiltration of atrial subepicardial layers. Atrial fibrillation is also associated with alterations of ion channel trafficking in the cardiomyocyte. We have shown that cholesterol, mechanical strain or scaffold proteins such as CASK regulate ion channel expression at the plasma membrane.

MECHANISMS IN CARDIAC REMODELING



Chronic ?-adrenergic stimulation or pressure overload elicits early adaptative cardiac remodeling which limits evolution towards heart failure. Macrophages produce CX3CL1 and TNF-? leading to cardiac macrophages proliferation and cardiomyocyte hypertrophy. Activation/inactivation of NF-?B and FoxO transcription factors, by reactive oxygen species, plays a central role in the transition from cardiac hypertrophy to heart failure at advanced ages.

MECHANISMS IN PULMONARY ARTERIAL HYPERTENSION ASSOCIATED VASCULAR REMODELING



We have identified important players of the pulmonary vascular remodeling, a major determinant of pulmonary arterial hypertension. Resident vascular progenitors are recruited and proliferate via PDGFR? activation, and produce new vascular smooth muscle cells via activation of the CXCR4 pathway. We have identified GCN2 as the gene causing the hereditary form of the pulmonary veno-occlusive disease and we are investigating the mechanisms underlying the development of the disease.

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INSTITUT MONDOR DE RECHERCHE BIOMÉDICALE

France Pirenne

Transfusion and red blood cell diseases

Université Paris-Est Créteil
Val de Marne
Inserm U955
JORGE BOCZKOWSKI
CRETEIL

Key facts

Team

• Researchers : 16
• Technicians : 6
• Postdoc fellows : 1
• PhD Students : 6

Translational approaches

• Patents : 2
• Clinical research grants : 9
• Industry partnerships : 5

International research links

• United States, Canada
• The Netherlands, Belgium
• England, Italy, Mali, Togo

Keywords

• Red blood cells
• Transfusion and Delayed Hemolytic transfusion reaction
• Sickle cell disease, Hemoglobinopathies and hemolysis
• Mechanism of Red blood cell alloimmunization
• Auto-immune cytopenia
• Biochemistry
• cellular and immunological techniques

Biological Resources

• Partnership with the Reference center of the Auto Immune Cytopenia (Cohort PHYSIOCAI) (Henri Mondor Hospital).
• Patients followed at the Sickle cell referral Center (Henri Mondor hospital Créteil) with sickle cell disease (Erythropédie) and thalassemia

Our Team develops fundamental and translational research on the pathology of the red blood cells (RBCs) in the context of sickle cell disease, thalassemia and transfusion, and also on B-cell biology in autoimmune responses to platelets and RBCs with a follow-up of patients with these pathologies.

Research Brief :

The team studies genetic red blood cell (RBC) diseases and the effects of transfusion in these diseases, focusing specifically on sickle cell disease (SCD). This team brings together scientists with complementary expertise in the field, including (i) researchers from the French Blood Agency (EFS), specializing in transfusion medicine, (ii) researchers from the Institute of Health and Medical Research specializing in hemoglobin (Hb) disorders, (iii) physicians from Assistance Publique-Hôpitaux de Paris at Creteil.
Four main topics are explored: 1) Immune and genetic background of immunization following the transfusion of RBCs 2) Innovative therapies, hemolysis-related vasculopathies, including transfusion reactions in SCD 3) Alpha-Hb pool and hemoglobinopathies 4) Autoimmune cytopenia.
Our team develops fundamental and translational research on the pathology of the RBC in the context of SCD, thalassemia and transfusion, a major therapeutic support for these diseases and also to a new research on B-cell biology in autoimmune responses to platelets and RBCs. We study on a large cohort of patients for which the high quality of phenotyping and follow-up are recognized worldwide. All historical data for transfusion in these patients are available through the regional information system of the EFS. New measurement methods have developed such as free alpha-Hb, fetal Hb content in RBCs for assessment of the effects of new treatment strategies in SCD and in post-transfusion reactions.

• **Methodologies Used :**

- Patient and new therapeutic evaluation
- spectrophotometry, cellular immunology, molecular biology
- Protein expression, and function analysis, biochemistry
- Flow cytometry, and fluorescence microscopy
- Flow adhesion assays
- Measurement of hemolysis parameters
- Measurement of alpha-hemoglobin pool

Publications

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Pierre-Yves Marie

Personalized medicine of heart failure and cardiovascular ageing

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Patrick Lacolley
Nancy

Development of innovative bioprofile-guided therapies of heart failure and frailty on a multi-organ scale, and including bridge-to-recovery strategies.

Key facts

Team

- Researchers : 18
- Technicians : 6
- Postdoc fellows : 4
- PhD Students : 10

Translational approaches

- Patents : 2
- Clinical research grants : 7
- Industry partnerships : 4

International research links

- N. Lopez (Spain), T. Thum (Germany), M. Bäck (Sueden), A. Aviv (Rutgers University, USA), R. Asmar (Lebanon), D. Perrea, Dr Chrysochoou and Pr Stefanadis (Greece).

Keywords

- Cardiovascular aging
- Cardiovascular shock
- Aldosterone
- Heart failure
- Inflammation and fibrosis
- Molecular imaging
- Bioprofiling
- Telomere dynamics
- Experimental models
- Patient cohorts

Research Brief :

The main objective is to elaborate innovative personalized strategies mechanistically targeted at cardiovascular ageing with the aim of improving the health care of age-related cardiovascular diseases, especially acute and chronic heart failure. More specific projects are as follows:

1) Identifying personalized bioprofiles of heart failure and cardiovascular aging, with a special focus on
- systemic biomarkers of fibrosis and inflammation (cardiotrophin, galectin, NGAL, miRNA, Trem1 ...)
- telomeres considered as a major biodeterminant of age-related cardiovascular diseases
- cross phenotyping with functional and molecular biomarkers from cardiovascular imaging (PET, MRI and echography).

2) Developing and testing bioprofile-guided therapies of heart failure, cardiovascular ageing and frailty, on a multi-organ scale and including bridge-to-recovery strategies for acute heart failure.

The program is supported by a number of grants obtained at the national and international level and corresponding to a global funding of more than 35 million euros. It uses a number of dedicated experimental models and readily available/accessible or on-going cohorts and databases in cardiovascular ageing research (a total of 40.000 subjects or patients).

• Methodologies Used :

Mechanistic approach of heart failure development, as a function of age and across a number of co-morbid conditions and with a special emphasis on 1) inflammation and interrelations with the activations of the mineralocorticoid and adrenergic systems, 2) remodeling and fibrosis, considered in a balanced risk-to-benefit approach, 3) arterial stiffening and its evolution from childhood and 3) a cardiovascular phenotyping provided by crossed information from blood-systemic and imaging-focal biomarkers.

Publications

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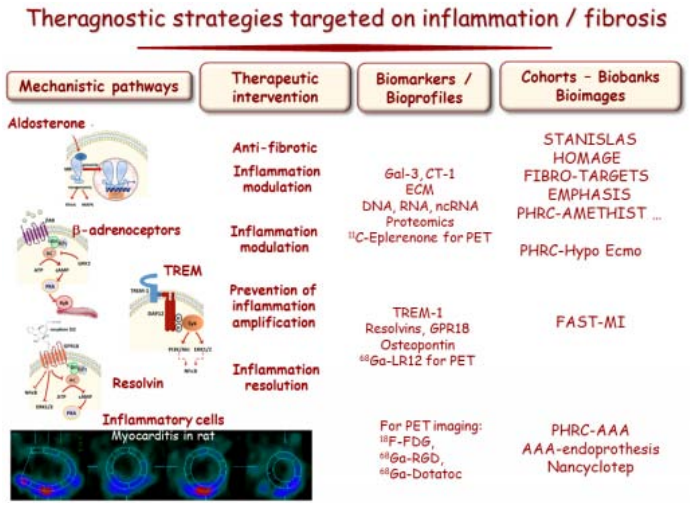
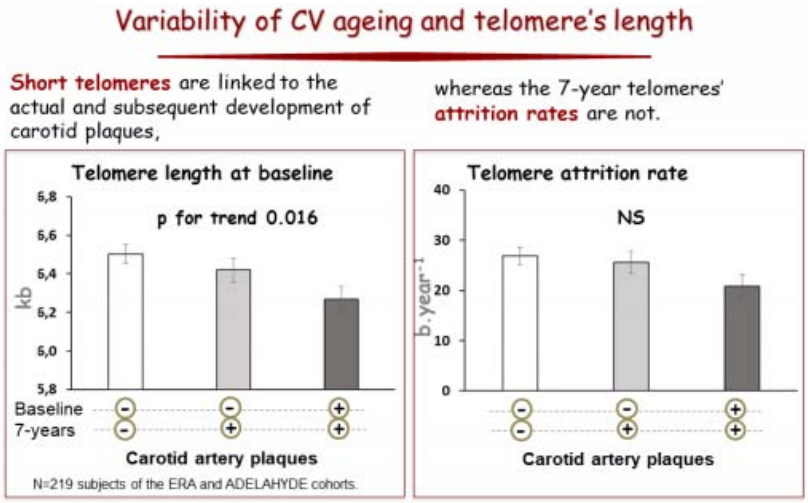
Theme "Personalized strategies to prevent, monitor and treat chronic HF"



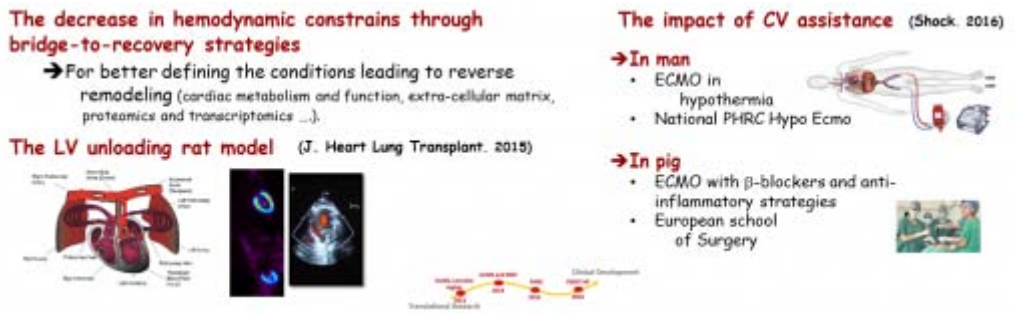
The project is focused on selected mechanisms of chronic heart failure (HF) development with especially kidney dysfunction, activation of mineralocorticoid receptors (MR), inflammation and hemodynamic constrains, and by using a mixing of information from blood-systemic and imaging-focal biomarkers. The clinical aim is to develop strategies of HF management using omics research and imaging technologies and by taking into account co-morbidities (chronic kidney disease, hypertension, obesity...).

Theme "Telomere dynamics and vascular aging".



The progressive life-long ageing of the CV system is markedly involved in the high rates of CV diseases documented in older people. Our studies have contributed to establish: (i) the associations between short leucocyte telomere length (TL) and several age-related arterial diseases and (ii) that TL is mainly determined before adulthood. Our ongoing project is aimed providing complementary information on TL dynamics and on the relationship between cardiovascular aging and TL.

Theme "Acute heart failure and cardiovascular shock"



Optimization of cardiac assistance, as swell as adrenergic inhibition and associated immune-modulator effects, are key points for cardiovascular protection. Our ongoing project is centered on bridge-to-recovery strategies leading to assist and/or protect the integrity of heart and vessels, with a special emphasize on the modulation of the adrenergic system, considered alone or in association with assistance techniques.

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Véronique Regnault

Vascular stiffness - inflammation - thrombosis

Université de Lorraine
Inserm U1116
Patrick Lacolley
Vandoeuvre-lès-Nancy

Interaction and integration of basic and clinical research in the cardiovascular biology field based on the combination of expertises on vascular stiffness, inflammation, immunothrombosis and human cohorts.

Key facts

Team

- Researchers : 10
- Technicians : 5
- Postdoc fellows : 1
- PhD Students : 5

Translational approaches

- Patents : 5
- Clinical research grants : 3
- Industry partnerships : 1

International research links

- Europe
- United States
- Australia

Keywords

- arterial stiffness
- vascular smooth muscle cells
- hypercoagulability
- mechanotransduction
- TREM-1
- vascular echotracking
- thrombin generation assay
- isolated vessels

Biological Resources

- Validated cohorts (antiphospholipid, heart failure, systolic hypertension
- Cardiovascular tissues and blood samples from human (aortic aneurysms), rat and mouse models

Research Brief :

Our general objective is the identification of key-drivers of accelerated vascular ageing and atherothrombosis and understanding molecular and cellular mechanisms.

A first aim is to delineate the mechanisms by which intramural cells sense and regulate their interaction with the extracellular matrix that endows arteries with their mechanical functionality and structural integrity. We aim also at refining the role of mechanosensing in vascular calcification which accelerates age-induced arterial stiffening.

Our second aim is to provide a molecular understanding of the interplay between arterial stiffness and hypercoagulability, in particular the role of vascular smooth muscle cells and their integrin receptors in thrombin generation both in the blood compartment and in the vascular wall, in order to identify new pathophysiological mechanisms than can be targeted to prevent early vascular aging.

The third aim is to unravel factors favoring the transition of acute to chronic inflammation and how to promote the healing of nonresolving inflammation as a novel cardiovascular therapeutic strategy.

Every program benefit from (i) our established expertise in vascular mechanostransduction, tissular thrombin generation, TREM-1-mediated inflammatory pathways and pro-resolving lipid mediators, (ii) the in-house availability of genetically modified mouse model, (iii) access to clinical biobanks and pathological tissues and (iv) strong national and/or international networks.

- **Methodologies Used :**

Methods to measure parameters of arterial stiffness and thrombin generation in vivo and in vitro: echotracking, pulse wave velocity, calibrated automated thrombography (whole blood, plasma)
Appropriate animal models (pharmacology, transgenic)
Primary cultures of human, rat and mouse vascular smooth muscle cells (cyclic stretch, siRNA, confocal and second harmonic generation microscopy)
Flow cytometry for extracellular vesicles, calcium and cell phenotypic markers
Cohorts, pharmacological trials, genetics

Publications

1. Zuily S, Regnault V, Selton-Suty C, Eschwège V, Bruntz JF, Bode-Dotto E, De Maistre E, Dotto P, Perret-Guillaume C, Lecompte T, Wahl D. (2011). Increased Risk for Heart Valve Disease Associated With Antiphospholipid Antibodies in Patients With Systemic Lupus Erythematosus: Meta-Analysis of Echocardiographic Studies., Circulation. 124(2), 215-224

2. Galmiche G, Labat C, Mericskay M, Ait Aissa K, Blanc J, Retailleau K, Bourhim M, Coletti D, Loufrani L, Gao-Li J, Feil R, Challande P, Henrion D, Decaux J-F, Regnault V, Lacolley P and Li Z*. (2013). Inactivation of serum response factor contributes to decrease vascular muscular tone and arterial stiffness in mice., Circulation Research. 112(7), 1035-1045*

3. Lagrange J, Li Z, Fassot C, Bourhim M, Louis H, Nguyen Dinh Cat A, Parlakian A, Wahl D, Lacolley P, Jaisser F, Regnault V. (2014). Endothelial mineralocorticoid receptor activation enhances endothelial protein C receptor and decreases vascular thrombosis in mice., FASEB Journal. 28(5), 1062-2072

1. Boufenzer A, Lemarié J, Simon T, Derive M, Bouazza Y, Tran N, Maskali F, Groubatch F, Bonnin P, Bastien C, Bruneval P, Marie PY, Cohen R, Danchin N, Silvestre JS, Ait-Oufella H, Gibot S. (2015). TREM-1 Mediates Inflammatory Injury and Cardiac Remodeling Following Myocardial Infarction., Circulation Research. 116(11), 1772-1782

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Popovic B, Zannad F, Louis H, Clerc-Urmès I, Lakomy C, Gibot S, Denis CV, Lacolley P, Regnault V*. (2019). Endothelial-driven increase in plasma thrombin generation characterising a new hypercoagulable phenotype in acute heart failure., International Journal of Cardiology. 274(Jan 1), 195-201*

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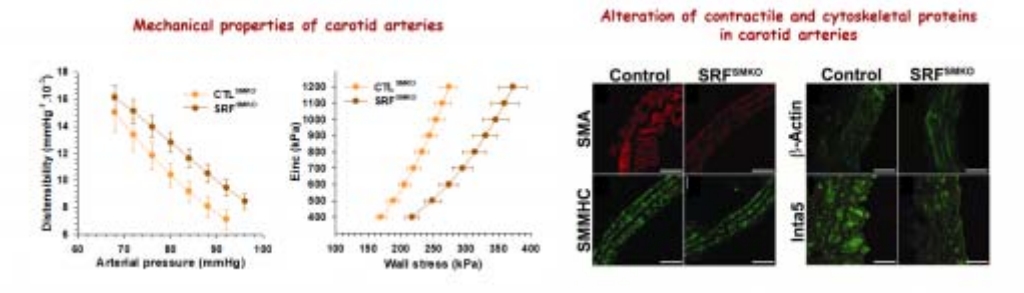
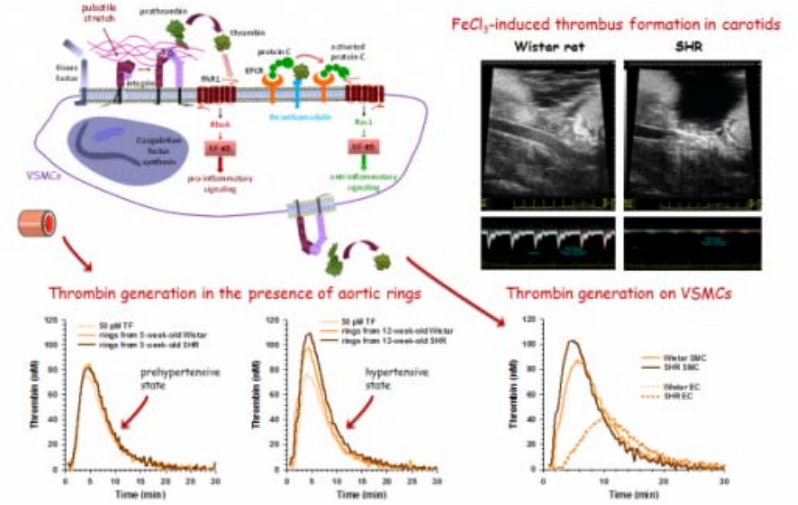
SRF-related decreases in contractile proteins and cell-ECM attachment increase arterial elasticity



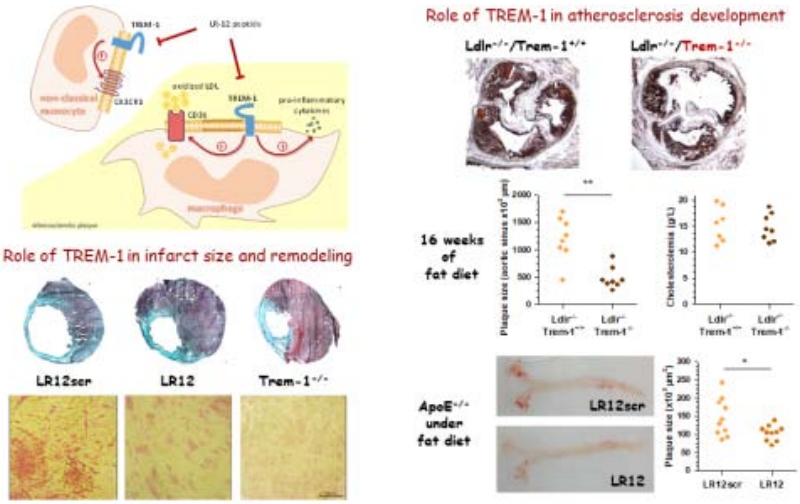
Left: mechanical properties of carotid arteries from control (CTLSMKO) and smooth muscle-specific knockout of serum response factor (SRFSMKO mice); distensibility-arterial pressure (AP) curves and incremental elastic modulus (Einc)-wall stress (WS) curves. Right: Alteration of contractile and cytoskeletal proteins. Carotid sections stained with antibodies against smooth muscle alpha-actin (SMA; red) and myosin heavy chain (SM-MHC), beta-actin, alpha5 integrin (green).

Prothrombotic phenotype of spontaneously hypertensive rat arteries



Top right: FeCl3-induced thrombus formation in carotid arteries from 12-week-old spontaneously hypertensive rats (SHR) or Wistar rats. Bottom left: Thrombin generation curves in a Wistar platelet-free plasma pool triggered with 50 pmol/L tissue factor (TF) or with 2 mm rings from thoracic aortas of 5-week-old or 12-week-old SHR or Wistar. Bottom right: Thrombin generation curves at the surfaces of vascular smooth muscle cells (VSMCs) or endothelial cells (ECs) from 12-week-old SHR or Wistar.

TREM-1 mediates inflammatory injury in myocardial infarction and atherosclerosis



Left: Inhibition of TREM-1 reduces infarct size and cardiac fibrosis. Right: Trem-1 deficiency in the bone marrow is associated with a decrease in lesion development and plaque size after a fat diet. Genetic invalidation of TREM-1 also induces a reduction of plaque size without modification in cholesterol concentration.

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Thierry COUFFINHAL

Biology of Cardiovascular Diseases

University of Bordeaux
Inserm UMR1034
Thierry COUFFINHAL
Pessac

Our team combine tools of genetics, in vivo and in vitro experiments and imagery to characterize and follow in time and space the role of target genes in the vascular and thrombosis function.

Key facts

Team

• Researchers : 11
• Technicians : 7
• Postdoc fellows : 1
• PhD Students : 7

Translational approaches

• Patents : 4
• Clinical research grants : 1
• Industry partnerships : 0

International research links

• FLIEGEL Larry (Canada) - WEHBE Katia (UK)
• MRAICHE Fatima (Qatar) - JOSEFSSON Emma (Australie) - BECHER Harald (UK)
• MARHL Marko (Slovénie) - STARK Konstantin (Allemagne)

Keywords

• Vascular biology
• Endothelial function
• Cardiovascular diseases
• Animal models
• Experimental animal models
• Vessel imaging
• Vascular cell culture
• Molecular and cellular biology

Biological Resources

• IMAGING: White field and fluorescent microscopy; Confocal microscopy; Time lapse microscopy; Rapid film imaging; Perfusion imaging (laser Doppler); Xray tomography; Infrared imaging
• IN VITRO: Cell culture; In vitro models; Biochemistry; Molecular Biology; Histology; Analysis
• CLINICS: Pharmacology
• IN VIVO: Transgenic mice; Mouse experimental models; Measurement of physiologic cardiovascular parameters; Thrombosis; Pig experimental models

Research Brief :

Clinical and basic research demonstrates that the endothelium plays a crucial role in mediating homeostasis and is involved in virtually every disease, either as a primary determinant of pathophysiology or as a victim of collateral damage. The endothelium is involved in the maintenance of normal organs and vascular structure and function. It may be thought as an organ by itself. Following its abnormalities in function would provide a tremendous opportunity to inform about the status of the disease progression. As it is widely distributed and easily accessible, it may be regarded as critical target in the fight against some cardiovascular ischemic diseases.
Our project aims to improve endothelium knowledge and how endothelium interacts with its microenvironment. We are interested in understanding endothelial machinery in the control of vessel maintenance and function in different pathological settings:
- Role of endothelial dysfunction in heart failure with preserved ejection fraction
- Role of endothelial dysfunction in critical hind limb ischemia
- Endothelial cells, blood-brain barrier dysfunction in cerebrovascular disease
- Retinopathy and vascular lesions
- Role of endothelial cells in thrombosis ? example of myeloproliferative neoplasms
Wnt/Frizzled, Hedgehog and JAK2 signaling pathways are specifically studied in endothelial dysfunction.

• **Methodologies Used :**

Molecular and cellular biology
Cell culture: vascular cell proliferation, directional migration, cell velocity, videomicroscopy, 2-D and 3-D, adhesion, NETs, angiogenesis models, hypoxia models; Platelets, megacaryopiesis
Biochemistry
Vessel imaging: microscanner (microCt), confocal microscopy, 3D image reconstruction
Experimental animal models: conditional knock-out mouse models, model of hindlimb ischemia, infarctus and ischemia reperfusion, oxygen induced retinopathy, corneal angiogenesis, Thrombosis models

Publications

Sewduth Raj Nayan, Jaspard-Vinassa Béatrice, Peghaire Claire, Guillabert-Gourgues Aude, Franzl Nathalie, Larrieu-Lahargue Frédéric, Moreau Catherine, Fruttiger M., Dufourcq Pascale, Couffinhal Thierry and Duplaa Cécile (2014). The ubiquitin ligase PDZRN3 is required for vascular morphogenesis through Wnt/planar cell polarity signalling, Nature Communications. 5(4832),

Guillabert-Gourgues Aude, Jaspard-Vinassa Béatrice, Bats Marie-Lise, Sewduth Raj Nayan, Franzl Nathalie, Peghaire Claire, Jeanningros Sylvie, Moreau Catherine, Roux Etienne, Larrieu-Lahargue Frédéric, Dufourcq Pascale, Couffinhal Thierry and Duplaa Cécile (2016). Kif26b controls endothelial cell polarity through the Dishevelled/Daam1-dependent planar cell polarity-signaling pathway, Molecular Biology of the Cell. 27(3), 941-953

Peghaire Claire, Bats Marie-Lise, Sewduth Raj Nayan, Jeanningros Sylvie, Jaspard-Vinassa Béatrice, Couffinhal Thierry, Duplaa Cécile and Dufourcq Pascale (2016). Fzd7 (Frizzled-7) Expressed by Endothelial Cells Controls Blood Vessel Formation Through Wnt/beta-Catenin Canonical Signaling, Arteriosclerosis, Thrombosis, and Vascular Biology. 36(), 2369-2380

R. Markovic, J. Peltan, M. Gosak, D. Horvat, B. Zalik, B. Seguy, R. Chauvel, G. Malandain, T. Couffinhal, C. Duplaa, M. Marhl, and E. Roux (2017). Planar Cell Polarity Genes Frizzled4 and Frizzled6 Exert Patterning Influence on Arterial Vessel Morphogenesis, PLoS One. (12),

R.N. Sewduth, H. Kovacic, B. Jaspard-Vinassa, V. Jecko, T. Wavasseur, N. Fritsch, M. Pernot, S. Jeanningros, E. Roux, P. Dufourcq, T. Couffinhal, and C. Duplaa (2017). Pdzrn3 Destabilizes Endothelial Cell-Cell Junctions through a Pkc?-Containing Polarity Complex to Increase Vascular Permeability, Science Signaling. (10), 464

C. Caradu, Guy A., C. James, A. Reynaud, A.P. Gadeau, and M. A. Renault (2018). Endogenous Sonic Hedgehog Limits Inflammation and Angiogenesis in the Ischaemic Skeletal Muscle of Mice, Cardiovascular Research. (114), 759

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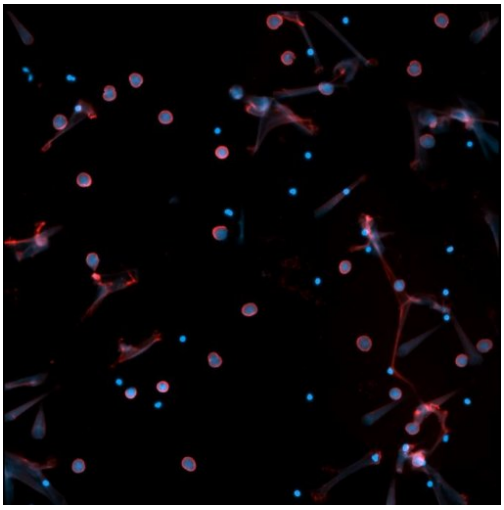
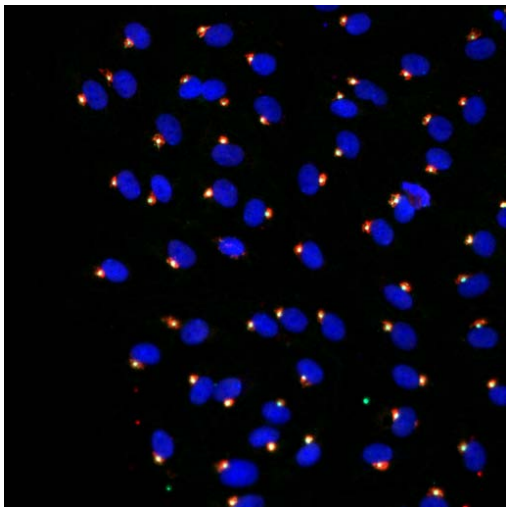
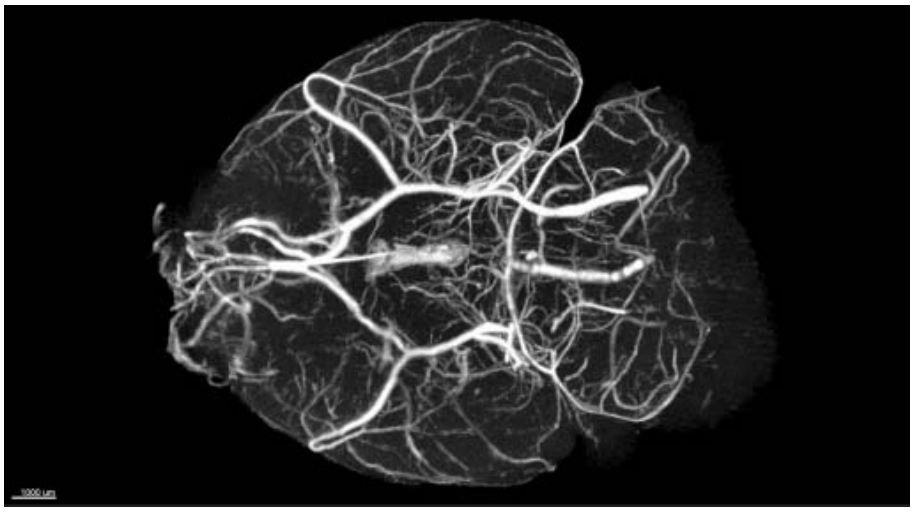
Neutrophil extracellular traps in patients with JAK2V617F positive myeloproliferative neoplasms



Endothelial polarization



3D visualisation of mouse cerebral vascularisation (microscanner)



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Key facts

Team

• Researchers : 32
• Technicians : 8
• Postdoc fellows : 3
• PhD Students : 36

Translational approaches

• Patents : 2
• Clinical research grants : 12
• Industry partnerships : 2

International research links

• Belgique
• Angleterre
• Etats Unis

Keywords

• cardiovascular calcification
• uraemia
• calcified aortic valve disease
• pulse pressure
• bone remodelling
• molecular biology
• cardiovascular exploration
• bone cell evaluation
• animal model of chronic kidney disease

Biological Resources

• primary cell culture
• secondary cell culture
• wild type and knock-out mice
• biological samples (animal and human)

Said Kamel

Pathophysiological mechanisms and consequences of cardiovascular calcifications: role of cardiovascular and bone remodelling

Université d' Amiens
(Université de Picardie - Jules Verne)
Said Kamel
Amiens

Direct collaboration between bone and vascular experts in same research group.

Research Brief :

Cardiovascular calcifications (CVC) are frequently encountered in the general population. They are associated with a high cardiovascular risk. They are observed with a much greater prevalence in patients with chronic kidney disease (CKD), with diabetes and also in patients with inflammatory diseases such as rheumatoid arthritis. The work done during last few years have allowed us to go along several important research pathways. We are pursuing our work following several of these research lines, in particular the role of the calcium-sensing receptor and that of the uremic toxins, the hemodynamic consequences of CVC, and the identification of novel markers able to predict these soft-tissue calcifications. We are currently evaluating the role of pro-inflammatory mediators in the pathogenesis of CVC, by using experimental models and performing clinical investigations. Our research will focus on the development of innovating therapeutic strategies.
The consequences of our research efforts, based on cell culture models, animal models and human investigation, should be a better understanding of the molecular mechanisms which are responsible for CVC. In addition, our research work should permit an easier detection and more adequate follow-up of the calcification as well as the identification of novel therapeutic targets, with the final goal to improve the care of patients with CVC, in the presence or absence of CKD, who carry a major cardiovascular risk.

• **Methodologies Used :**

Cell culture, cell migration assays (Boyden?s Chamber), molecular biology including MicroRNA
In vitro mineralization assays, osteoclast differentiation
Cranial window technique, isolated cerebral micro-vessel preparation
Echocardiography, pulse wave velocity, cardiac hemodynamics
Ex vivo vascular exploration, histomorphometry

Publications

Maizel J, Six I, Slama M, Tribouilloy C, Sevestre H, Poirot S, Giummelly P, Atkinson J, Choukroun G, Andrejak M, Kamel S, Mazière JC, Massy ZA (2009). Mechanisms of aortic and cardiac dysfunction in uremic mice with aortic calcification., Circulation. 119(2), 306-13

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Hénaut L, Boudot C, Massy ZA, Lopez-Fernandez I, Dupont S, Mary A, Drüeke TB, Kamel S, Brazier M, Mentaverri R (2014). Calcimimetics increase CaSR expression and reduce mineralization in vascular smooth muscle cells: mechanisms of action., Cardiovascular research. 101(2), 256-65

Mary A, Hénaut L, Boudot C, Six I, Brazier M, Massy ZA, Drüeke TB, Kamel S, Mentaverri R. (2015). Calcitriol prevents in vitro vascular smooth muscle cell mineralization by regulating calcium-sensing receptor expression., Endocrinology. 156(6), 1965-74

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Stinghen AE, Massy ZA, Vlassara H, Striker GE, Boullier A (2016). Uremic Toxicity of Advanced Glycation End Products in CKD., J Am Soc Nephrol. 27(2), 354-70

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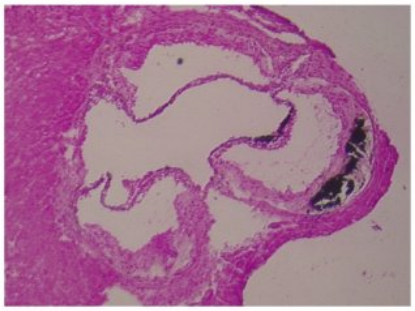
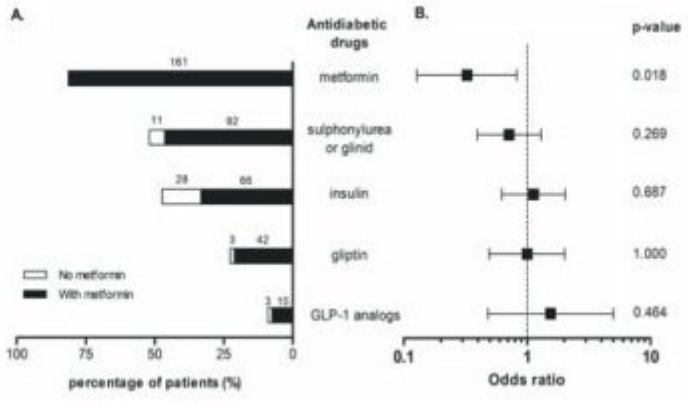
Calcified aortic valve



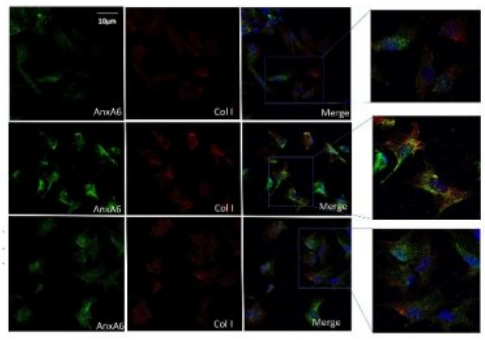
Calcified aortic valve stained with von Kossa in a model of chronic kidney disease Apo E-/- mice .

Association between metformin and vascular calcification in type 2 diabetic patients



Association of antidiabetic drugs with below-knee arterial calcification. A. The histogram represents the frequency of each antidiabetic drug. The black bars indicate patients treated by metformin alone or in combination with other antidiabetic drugs. The white bars indicate patients treated by other antidiabetic drugs without metformin. B. Univariate logistic regression with specific focus on pharmacological antidiabetic therapy

Calcifying matrix vesicles produced by vascular smooth muscle cells.



Interaction between matrix vesicles produced by vascular sooth muscle cells and type I collagen.
Immunofluorescence was assayed using Alexa555-labeled type I collagen (Col I) and Alexa488-labeled Annexin A6 (AnxA6) antibodies. Non permeabilized MOVAS-1 cells were cultured in the absence (Ctrl) or presence of 4 mM phosphate (Pi) for 8 days without or with an inhibitor of vascular calcification. scale: 10 ?m. Boxes highlight the inset region (x3)

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Research teams with secondary association to PMN Institute

Key facts

Team

• Researchers : 5
• Technicians : 1
• Postdoc fellows : 2
• PhD Students : 4

Translational approaches

• Patents : 0
• Clinical research grants : 2
• Industry partnerships : 6

International research links

• USA , China, Spain

Keywords

• Viral cardiac infection
• Inflammation
• Persistence
• Physiopathology
• CVB3 induced myocarditis in mice model
• Human cardiac cell infection

Biological Resources

• Cardiac tissue collection from patients with acute or chronic cardiomyoapathies

LAURENT ANDREOLETTI

Cardiovir

Université de Reims
Champagne-Ardenne
Université EA4684
LAURENT ANDREOLETTI
REIMS

The research is original at the national and international levels, both in the fields of heart viral diseases and enterovirus infections. In France, there are only two research groups involved in enterovirus persistent infections and with its will and effort to study these infections in humans.

Research Brief :

Human enteroviruses (EVs), and specifically Coxsakievirus B (CVB), are a common cause of acute cardiac infection and myocarditis in children and young adults. In 10% of the cases, the acute infection evolves to persistence, inducing a chronic myocarditis. This pathology will lead in 9% of the patient to a dilated cardiomyopathy (DCM 7 cases/100 000 inhabitants), which is the second leading cause of cardiac transplantation. The involvement of these forms in DCM is supported by the detection of viral RNA and VP1 capsid protein in 35% of the cardiac samples of end stage patient suffering from idiopathic myocarditis. Molecular mechanisms triggering the switch from the acute to the chronic myocarditis and DCM are still unknown, therefore limiting the development of specific therapeutic strategies against EV-induced chronic heart diseases. A better understanding of the molecular mechanisms implicated in EV persistence of viral forms in human cardiac tissues and could stimulate the development of new therapeutic strategies in acute and chronic cardiac infections, such as DCM, caused by EV.

• **Methodologies Used :**

We used for the first time a new technology allowing broad viral detection in clinical samples that couples
broad-range PCR amplification to electrospray ionization-time of flight mass spectrometry analysis (PCRMS).
We developed NGS approaches to quantify major and minor persistent viral population in heart tissues.
We developed an original CVB3 induced chronic myocarditis in DBA/2J mice model.

Publications

Lévêque N, Renois F, Talmud D, Nguyen Y, Lesaffre F, Boulagnon C, Bruneval P, Fornes P, Andréoletti L (2012). Quantitative genomic and antigenomic enterovirus RNA detection in explanted heart tissue samples from patients with end-stage idiopathic dilated cardiomyopathy., J Clin Microbiol. 50(10), 3378-80

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Ashrafpoor G, Andréoletti L, Bruneval P, Macron L, Azarine A, Lepillier A, Danchin N, Mousseaux E, Redheuil A. (2013). Fulminant human herpesvirus 6 myocarditis in an immunocompetent adult: role of cardiac magnetic resonance in a multidisciplinary approach., Circulation.. 128(23), e445-7

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Wehbe M, Huguenin A, Lévêque N, Semler BL, Hamze M, Andreoletti L, Bouin A. (2016). Construction of a subgenomic CV-B3 replicon expressing emerald green fluorescent protein to assess viral replication of a cardiotropic enterovirus strain in cultured human cells, J Virol Methods.. 230(3), 1-6

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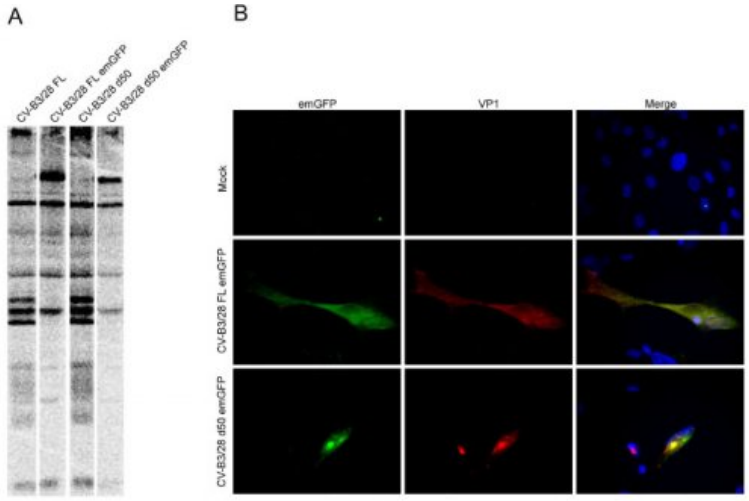
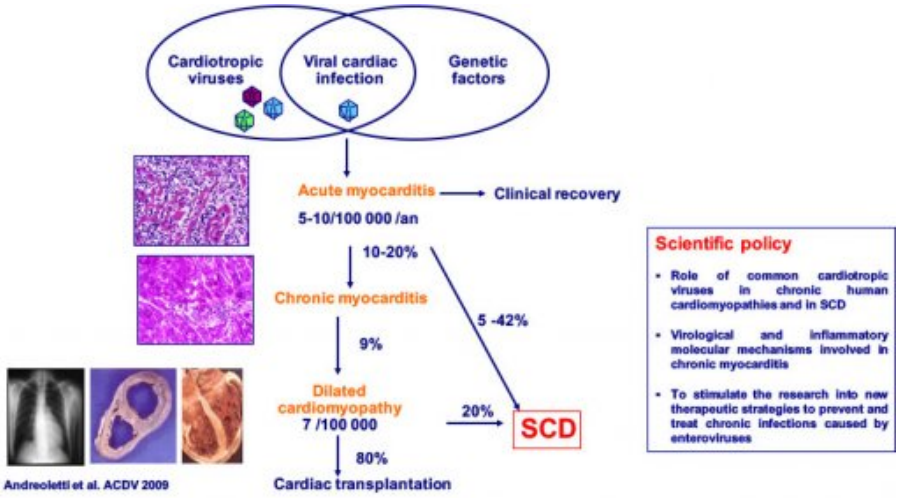
Expression of viral proteins of 5' deleted viral forms



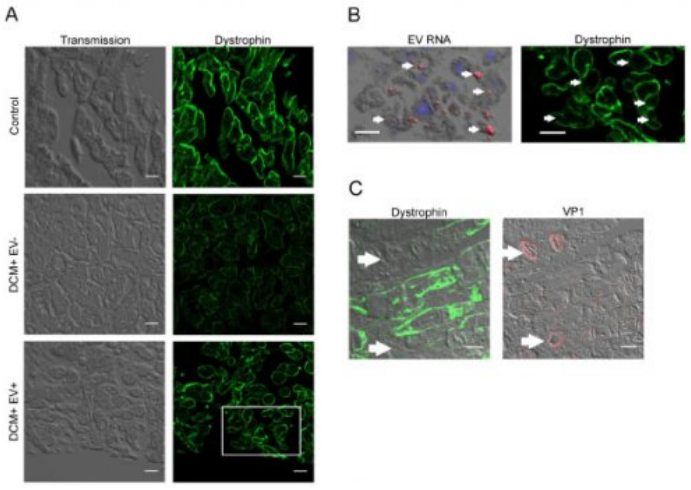
A. In vitro translation assay of CV-B3 replicons B. Transfection of FL and deleted viral RNA carrying emGFP into HCM. Cells were fixed 24H and immunofluorescent assays were performed. Blue: Nucleus, Red: VP1, Green: emGFP.

Pathophysiology of viral cardiac infection



Andreoletti et al. ACDV 2009

Impact of EV B persistence on dystrophin



A. Immunofluorescent staining of dystrophin in the heart tissue sections of infected DCM patients (DCM+ EV+), uninfected EV DCM patients (DCM+ EV-) and controls (DCM- EV-). Bar scale=50?m. The white rectangle is displayed in B. B. Serial sections of cardiac tissues of infected DCM patients (DCM+ EV+) were analyzed by in situ hybridization of the viral RNA (left, blue: nucleus, red: RNA) and immunofluorescent staining of dystrophin (right, green).

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Key facts

Team

- Researchers : 4
- Technicians : 4
- Postdoc fellows : 3
- PhD Students : 0

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- Europe (Norway, Spain, Sweden, the Netherlands)
- USA, others (Israel, UK)

Keywords

- extracellular matrix
- nuclear envelope
- Lamin A/C
- collagen VI
- muscular dystrophy
- animal models
- Cell Biology
- molecular genetics
- confocal microscopy
- virus-based gene therapy

Biological Resources

- Mouse models of LMNA- and COL6-related disorders, Zebrafish models (morphants)
- Patient and mouse fibroblasts and myogenic cells
- DNA and fluids (serum/plasma)
- RNA extracted from cultured cells or tissues
- Biobank: AFM-Myobank
- Patient registry: OPALE, Observatory of Patients Affected with Laminopathies or Emerinopathies

Gisèle Bonne

Genetics and pathophysiology of neuromuscular disorders linked to the extracellular matrix and to the nucleus

Sorbonne Université
Inserm U974
Bertrand Fontaine
Paris

Our team regroups scientists and clinicians with complementary backgrounds that enable our translational research projects for our neuromuscular diseases of interest

Research Brief :

Our team focuses on two groups of neuromuscular disorders: myopathies due to defective myomatrix (collagen VI and other components of the extracellular matrix) and to defects of the myonucleus (Emery-Dreifuss muscular dystrophy and other striated muscle laminopathies due to mutations in the lamin A/C gene or genes encoding components of nuclear membrane). These myopathies share some clinical features, notably prominent contractures, and constitute differential diagnoses.

These disorders are highly heterogeneous, clinically and genetically, and to date no treatment is available. Our previous work led us to identify various genetic alterations and to develop tools (cellular and animal models) that are crucial for deciphering pathomechanisms and unveiling therapeutic targets.

Our current research axes are 1) Definition of genetic and clinical spectrum and delineation of natural history of these NMDs, 2) Development of new tools to validate genetic variants identified through NGS (next generation sequencing), 3) Deciphering pathomechanisms that affect skeletal and/or cardiac muscle, with the overall goal of identifying and assessing therapeutic options for these disorders. Our work is carried out on biological material derived from patients (DNA, RNA, serum/plasma, cultured cells, or muscle biopsies), and on animal models developed in the team (mouse, zebrafish).

- **Methodologies Used :**

Immunohistology / immunocytology
Real time Quantitative PCR
Western blotting / slot blotting
Proximity ligation assays
Co-immunoprecipitations
Culture of human/mouse primary and immortalized cells (fibroblasts, myogenic cells)
Live cell imaging
Transient transfections (plasmids)/ AAV and lentivirus transduction
Molecular biology (cloning)
NGS (Whole Exome and Whole Genome Sequencing)/ ChIP-seq / RNA-seq
Muscle tissue histology
Animal model characterization (mobility, force measurement, cardiac function exploration...)

Publications

Ramanoudjame L, Rocancourt C, Lainé J, Klein A, Joassard L, Gartioux C, Fleury M, Lyphout L, Kabashi E, Ciura S, Cousin X, Allamand V (2015). Two novel COLVI long chains in zebrafish that are essential for muscle development, Hum Mol Genet. 24(23), 6624-6639

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Bolduc V, Foley AR, Solomon-Degefa H, Sarathy A, Donkervoort S, Hu Y, Chen GS, Sizov K, Nalls M, Zhou H, Aguti S, Cummings BB, Lek M, Tukiainen T, Marshall JL, Regev O, Marek-Yagel D, Sarkozy A, Butterfield RJ, Jou C, Jimenez-Mallebrera C, Li Y, Gartioux C, Mamchaoui K, Allamand V, Gualandi F, Ferlini A, Hanssen E; COL6A1 Intron 11 Study Group, Wilton SD, Lamandé SR, MacArthur DG, Wagener R, Muntoni F, Bönnemann CG (2019). A recurrent COL6A1 pseudoexon insertion causes muscular dystrophy and is effectively targeted by splice-correction therapies, Journal of Clinical Investigation Insight. 4(6), e124403

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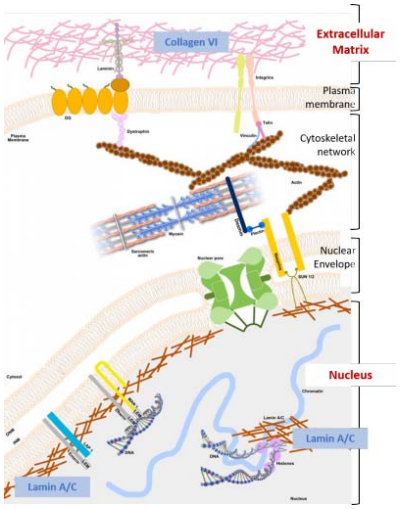
Hathazi D, Cox D*, D'Amico A, Tasca G, Charlton R, Carlier RY, Baumann J, Kollipara L, Zahedi RP, Feldmann I, Deleuze JF, Torella A, Cohn R, Robinson E, Ricci F, Jungbluth H, Fattori F, Boland A, O'Connor E, Horvath R, Barresi R, Lochmüller H, Urtizberea A, Jacquemont ML, Nelson I, Swan L, Bonne G#, Roos A# (2021). NPP5K and SIL1 associated pathologies with overlapping clinical phenotypes converge through dysregulation of PHGDH, Brain. (), awab133*

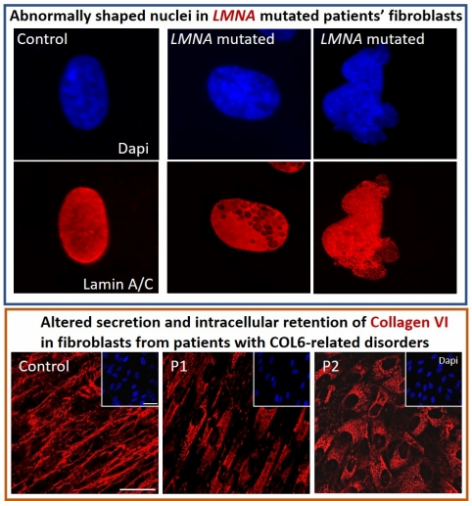
Ben Yaou R, Yun P*, Dabaj I*, Norato G*, Donkervoort S, Xiong H, Nascimento A,Maggi L, Sarkozy A, Monges S, Bertoli M, Komaki H, Mayer M, Mercuri E, Zanoteli E, Castiglioni C, Marini-Bettolo C, D'Amico A, Deconinck N, Desguerre I, Erazo-Torricelli R, Gurgel-Giannetti J, Ishiyama A, Kleinsteuber K, Lagrue E, Laugel V, Mercier S, Messina S, Politano L, Ryan M, Sabouraud P, Schara U, Siciliano G,Vercelli L, Voit T, Yoon G, Alvarez R, Muntoni F, Pierson TM, Gómez-Andrés D, Foley AR, Quijano-Roy S£, Bönnemann CG£, Bonne G£. (2021). International Retrospective Natural History Study of LMNA-related Congenital Muscular Dystrophy, Brain Communication. 3(3), fcab075*

Figure 1 Team G Bonne



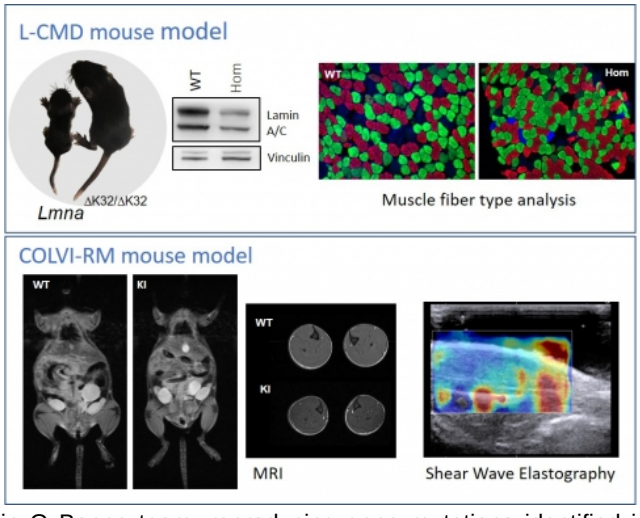
Schematic presentation of the cytoskeletal network linking the extracellular matrix and the nucleus of the striated muscle cells

Figure 2 Team G Bonne



Cellular abnormalities observed in primary fibroblasts of patients presenting with laminopathies or Collagen VI related myopathies

Figure 3 Team G Bonne



Known-in mouse models developed in G Bonne team, reproducing gene mutations identified in patients presenting with LMNA related muscular dystrophy (L-CMD) or Collagen VI related myopathies (COLVI-RM).

Bonne Gisèle - gisele.bonne@inserm.fr - https://recherche-myologie.fr/research/labs/bonne-lab/?lang=en

Hemostasis

Key facts

Team

• Researchers : 13
• Technicians : 14
• Postdoc fellows : 8
• PhD Students : 11

Translational approaches

• Patents : 7
• Clinical research grants : 0
• Industry partnerships : 10

International research links

• Israel (N. Korin)
• Italy (A. Balduini)
• USA (Pr M Poncz; K. Ravid)

Keywords

• Platelet
• Megakaryocytes
• Transfusion
• Thrombosis
• Fluorescence microscopy
• Flow cytometry
• Electron microscopy
• Reversible protein phosphorylation

Biological Resources

• Development of in vitro models to study platelets under flow
• In vivo models of arterial thrombosis
• Stroke models
• in vivo and in vitro models to study megakaryopoiesis
• Biochemistry and Molecular Biology
• in vivo models to study blood transfusion

Pierre Mangin

Biology and pharmacology of blood platelets : hemostasis, thrombosis, transfusion

Université de Strasbourg
Inserm U1255
Pierre Mangin
Strasbourg

Our lab has accumulated 30 years of expertise in the field of platelet biology. This allows us to address unanswered questions regarding the mechanisms involved in platelet production and the multiple functions of platelets through the development of state-of-the-art models and technologies.

Research Brief :

Platelets play a major physiological role in stopping bleeding (hemostasis) and, in pathology, in the occurrence and extension of arterial thrombosis (myocardial infarction, stroke and peripheral arteriopathy). Defective platelet production and function are the cause of serious bleeding disorders. In addition to their involvement in hemostasis and thrombosis, platelets have multiple roles and participate in complex processes, including vascular inflammation, tissue repair, angiogenesis, atherosclerosis, innate and adaptive immunity and embryonic development. Aberrant megakaryocyte development and function gives rise to myeloproliferative neoplasms, thrombocytosis, myelofibrosis and osteoclerosis. For more than 30 years, our research unit has been studying blood platelets in all aspects of their biology, genetics, pharmacology, and clinical and transfusion implications. Our approaches are both fundamental and applied to biomedical issues.
The group is structured around two interdependent teams that focus on platelet production mechanisms and defects, and their role in hemostasis and thrombosis and transfusion, respectively. The unit draws on multidisciplinary expertise in molecular and cellular biology, signal transduction, electron and confocal microscopy, animal models, and a translational and clinical approach.

• **Methodologies Used :**

Research undertaken in our unit is multi- and inter-disciplinary in nature and includes a cutting-edge hemostasis laboratory, experimental thrombosis models, flow cytometry, biochemistry and molecular biology, and animal facility. We have an electron microscopy platform, with a scanning electron microscope and a transmission electron microscope. We also have fluorescence microscopes (inverted epifluorescence microscopes, confocal microscope and a bi-photon microscope). We have a flow cytometry platform composed of two analysis flow cytometer and a cell sorter.

Publications

Bornert A, Boscher J, Pertuy F, Eckly A, Stegner D, Strassel C, Gachet C, Lanza F, Léon C (2021). Cytoskeletal-based mechanisms differently regulate in vivo and in vitro proplatelet formation, Haematologica. 106(5), 1368-1380

Kimmerlin Q, Dupuis A, Bodakuntla S, Weber C, Heim V, Henriot V, Moog S, Eckly A, Guéguen P, Ferec C, Gachet C, Janke C, Lanza F. (2022). Mutations in the most divergent alpha-tubulin isotype, alpha8-tubulin, cause defective platelet biogenesis., J Thromb Haemost. 20(2), 461-469

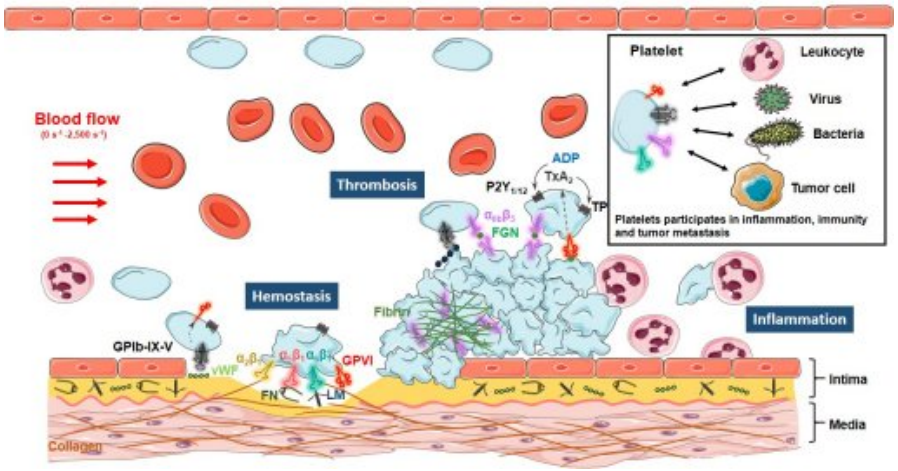
Yakusheva AA, Butov KR, Bykov GA, Závodszky G, Eckly A, Ataullakhanov FI, Gachet C, Panteleev MA, Mangin PH. (2022). Traumatic vessel injuries initiating hemostasis generate high shear conditions, Blood Advances. 6(16), 4834-4846

Couvidou A, Angénieux C, Ruch L, Mangin PH, Gachet C, Maître B (2022). Marginal zone B cells are responsible for the production of alloantibodies following platelet transfusion in mice, Blood Advances. doi: 10.1182/bloodadvances.20220(),

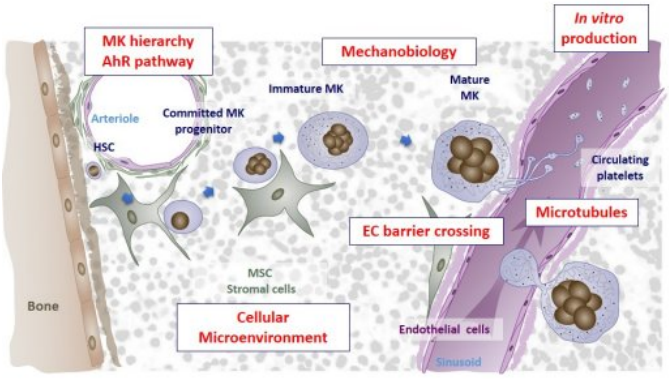
Mazharian A, Maître B, Bornert A, Hennequin D, Lourenco-Rodrigues M, Geer MJ, Smith CW, Heising S, Walter M, Montel F, Walker LSK, de la Salle H, Watson SP, Gachet C, Senis YA. (2023). Treatment of congenital thrombocytopenia and decreased collagen reactivity in G6b-B-deficient mice, Blood Advances. 7(1), 46-59

Tacquard A, Mouriaux C, Delabranche X, Bourdon C, Eckly A, Magnenat S, Sattler L, Gachet C, Mertes PM, Hechler B, Mangin PH (2023). Platelet dysfunction and thrombus instability in flow conditions in patients with severe COVID-19, J Thromb Haemost. 221(), 137-148

Mangin Pierre - pierre.mangin@efs.sante.fr - 0388212525 - http://www.u1255.inserm.fr/



Following vascular injury, platelets form a hemostatic plug that stops bleeding. A similar process occurs in a diseased vessel leading to the formation of a thrombus that can become occlusive and cause serious ischemic diseases such as myocardial infarction or stroke. Platelets are also involved in non-hemostatic processes such as inflammation, immunity and tumour metastasis.



Team 2 projects focus on the mechanisms of platelet biogenesis related to the engagement of megakaryocytes (MKs) from HSCs, the role of the cellular microenvironment and biomechanical constraints leading to the production of mature MKs, their interaction with the sinusoidal endothelium and the release of MK fragments into the circulation, the assembly of the tubulin cytoskeleton during platelet release, and the application of this knowledge to the production of platelets in culture.

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Key facts

Team

- Researchers : 17
- Technicians : 7
- Postdoc fellows : 1
- PhD Students : 6

Translational approaches

- Patents : 4
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- RESSTORE H2020 project (Spain, Czech Republic, Scotland, Finland)

Keywords

- Haemostasis
- thrombo-inflammation
- neurovascular disease
- neurovascular repair
- Biochemistry and cell biology
- Immuno-cyto/histochemistry
- in vivo imaging
- clinical research

Marie-Christine Bouton

Haemostasis, Thrombo-Inflammation and Neurovascular Repair

Université de Paris
Inserm U1148
Didier Letourneur
Paris

Our team combines expertise and knowledge in different fields that are at the crossroads of several clinical specialities (Haemostasis, Cardiology, Neurology, Pneumology)

Research Brief :

The projects of the team are focused on hemostasis, thrombosis and vascular injury, but are also involved in developing therapeutic strategies for cerebral ischemia at the acute and at the chronic phase, as well as in ICU patients. We combine biochemical and cellular approaches, in vivo experimental models and clinical researches for translational application.
Recently, we have demonstrated that:
- Protease Nexin-1 is a serine protease inhibitor with an important protective role in tissues
- GPVI is a platelet receptor with a central role in the repairing functions of platelets
- There are tight interactions between actors of hemostasis/thrombosis and of the immune system during stroke
- Immunomodulation and cell therapy might help to improve post-stroke functional recovery
- Neutrophil extracellular traps interfere with thrombolysis

Our major common research themes are:
Coagulation disorders (haemophilia, thrombophilia...)
Thrombo-inflammation (Platelets/ Leucocytes/ proteases & antiproteases of coagulation)
Vascular and cerebral injury (stroke, aneurysms)
Cerebral plasticity
The search for prognostic markers of functional outcome in stroke and neuro-ICU patients

• Methodologies Used :

Biochemistry
Cell Biology
Human samples
State of the art animal models
In vivo imaging

Publications

Ducroux C, Di Meglio L, Loyau S, Delbosc S, Boisseau W, Deschildre C, Ben Maacha M, Blanc R, Redjem H, Ciccio G, Smajda S, Fahed R, Michel JB, Piotin M, Salomon L, Mazighi M, Ho-Tin-Noe B, Desilles JP. (2018). Thrombus Neutrophil Extracellular Traps Content Impair tPA-Induced Thrombolysis in Acute Ischemic Stroke, Stroke. 49(3), 754-7

Aymonnier K, Kawecki C, Venisse L, Boulaftali Y, Christophe OD, Lenting PJ, Arocas V, de Raucourt E, Denis CV, Bouton MC. (2019). Targeting protease nexin-1, a natural anticoagulant serpin, to control bleeding and improve hemostasis in hemophilia, Blood. 134(19), 1632-44

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Bourrienne MC, Loyau S, Faille D, de Raucourt E, de Mazancourt P, Ho-Tin-Noé B, Gabison E, Ajzenberg N. (2020). Functional Fibrinolysis Assays Reveal Different Mechanisms underlying Plasminogen Dysfunction in Ligneous Conjunctivitis, Thromb. Haemost.. 120(5), 758-67

Cogo A, Mangin G, Maïer B, Callebert J, Mazighi M, Chabriat H, Launay JM, Huberfeld G, Kubis N. (2021). Increased serum QUIN/KYNA is a reliable biomarker of post-stroke cognitive decline., Mol. Neurodegener.. 16(1), doi: 10.1186/s13024-020-00421-4.

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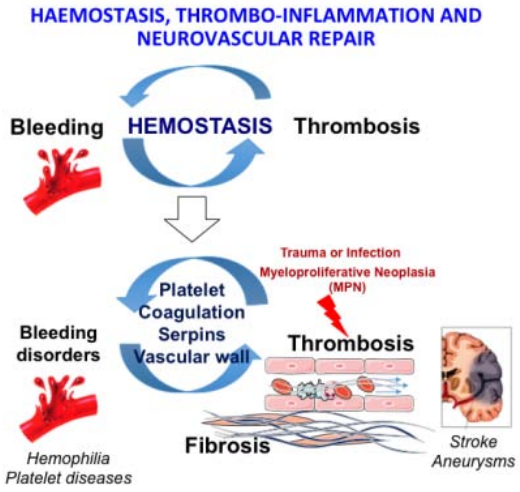
Team: Haemostasis-Thrombo-Inflammation and Neurovascular Repair



PN-1 and Haemophilia

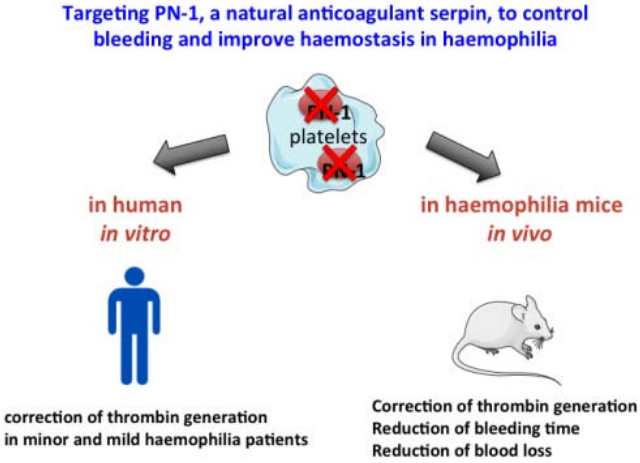
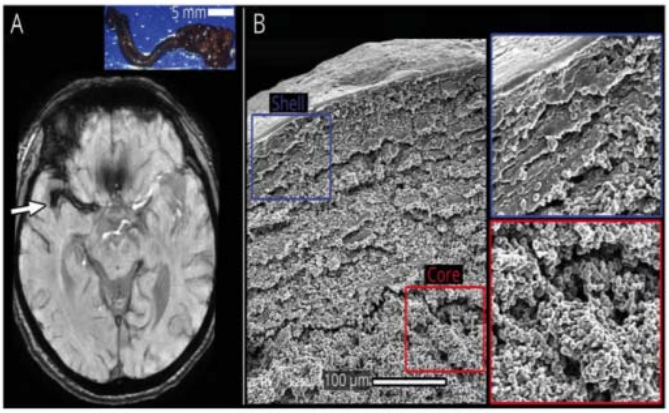


Image of a thrombus recovered from a patient after endovascular thrombectomy



Transversal cross-section of a thrombus shows the presence of a dense compacted peripheral layer forming a continuous shell (blue) encapsulating the thrombus core (red).

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DENIS Cécile

Hemostasis-Inflammation-Thrombosis

Université Paris-Saclay
Inserm UMR1176
Denis Cécile
Le Kremlin-Bicêtre

Key facts

Team

- Researchers : 17
- Technicians : 10
- Postdoc fellows : 2
- PhD Students : 6

Translational approaches

- Patents : 3
- Clinical research grants : 0
- Industry partnerships : 5

International research links

- Canada
- Germany
- Italy

Keywords

- Calcium
- Coagulation
- Platelets
- Sepsis
- Bleeding disorders
- Murine models
- Biochemistry

Biological Resources

- Von Willebrand disease mouse models
- Macrophage specific LRP1-deficient mice
- Hemophilia A murine model
- Inducible Factor X-deficient mice
- Filamin A knockin mice
- Protein S mice

Our Unit strength resides in the integrative approach applied to the study of hemostatic proteins with techniques ranging from enzymology to the use of dedicated murine models and patients samples.

Research Brief :

The research portfolio of the team is tailored around the patho-physiological aspects of haemostasis. On one hand we aim at studying the pathogenesis of hemorrhagic diseases, such as von Willebrand disease, haemophila and platelet disorders. Using dedicated and multiple models, Unit researchers are working on deciphering the underlying pathophysiological mechanisms involved in these pathologies, optimizing diagnosis and proposing targeted biotherapies. From a fundamental point of view, the role of a number of coagulation proteins in biological processes beyond hemostasis is also being investigated. On the other hand, we aim at studying the reciprocal interactions between coagulation and inflammation in the pathogenesis of vascular diseases, including severe sepsis but also ischemia/reperfusion injuries. Cellular effects of natural anti-coagulant proteins are also being investigated with a particular focus on protein Z-dependent protease inhibitor. In addition, the role of the calcium ATPase SERCA3 in hemostasis/vascular biology is also under investigation

- **Methodologies Used :**

In vivo thrombosis models in mice
Platelet function analysis
Culture of CD34+ cells
Bleeding assays in mice (tail clip assay, tail vien transection)
Surface Plasmon Resonance (Octet)
Coagulation assays/ Thrombin Generation Time
Hydrodynamic injection
Stable cell transfection
Immunofluorescence staining (Classic or Duo-link)
Perfusion assays in flow
ELISA
Production and purification of recombinant proteins
Nanobodies
NETs

Publications

Feng M, Elaïb Z, Borgel D, Denis CV, Adam F, Bryckaert M, Rosa JP, Bobe R. (2020). NAADP/SERCA3-Dependent Ca2+ Stores Pathway Specifically Controls Early Autocrine ADP Secretion Potentiating Platelet Activation, Circulation. 127(7), e166-e183

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Barbon E, Aymé G, Mohamadi A, Ottavi J-F, Kawecki C, Casari C, Verhenne S, Marmier S, van Wittemberghe L, Charles S, Collaud F, Denis CV, Christophe OD, Mingozzi F, Lenting PJ (2020). Single-domain antibodies targeting antithrombin reduce bleeding in hemophilic mice with or without inhibitors, EMBO Mol Med. 12(4), e11298

Denis CV, Susen S, Lenting PJ (2021). von Willebrand disease: what does the future hold?, Blood. 137(), 2299-2306

45) Sedzro JC, Adam F, Auditeau C, Bianchini E, De Carvalho A, Peyron I, Daramé S, Gandrille S, Thomassen S, Hackeng TM, Christophe OD, Lenting PJ, Denis CV, Borgel D, Saller F (2022). Antithrombotic potential of a single-domain antibody enhancing the activated protein C-cofactor activity of protein S, J Thromb Haemost. 20(), 1653-1664

36) Magnani A, Semeraro M, Adam F, Booth C, Dupré L, Morris EC, Gabrion A, Roudaut C, Borgel D, Toubert A, Clave E, Abdo C, Gorochov G, Petermann R, Guiot M, Miyara M, Moshous D, Magrin E, Denis A, Suarez F, Lagresle C, Roche AM, Everett J, Trinquand A, Guisset M, Bayford JX, Hacein-Bey-Abina S,Kauskot A, Elfeky R, Rivat C, Abbas S, Gaspar HB, Macintyre E, Picard C, Bushman FD, Galy A, Fischer A, Six E, Thrasher AJ, Cavazzana M (2022). Long-term safety and efficacy of lentiviral hematopoietic stem/progenitor cell gene therapy for Wiskott-Aldrich syndrome., Nature Medicine. 28(), 71-80

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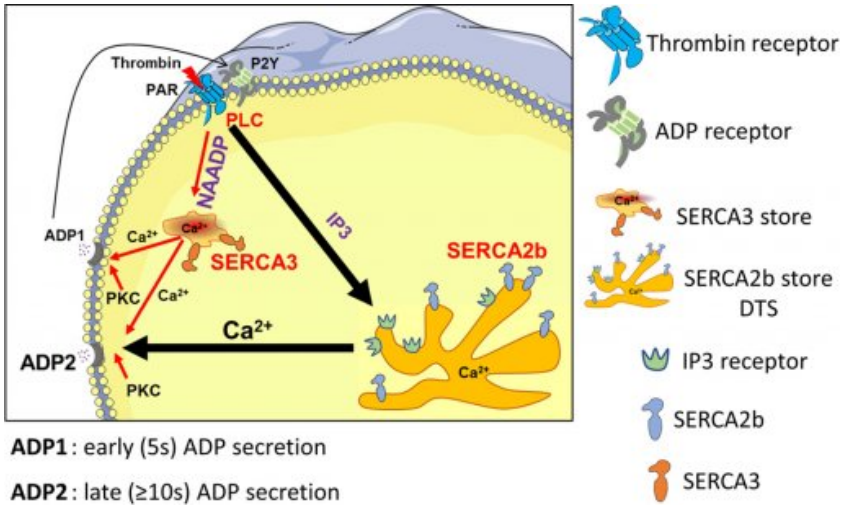
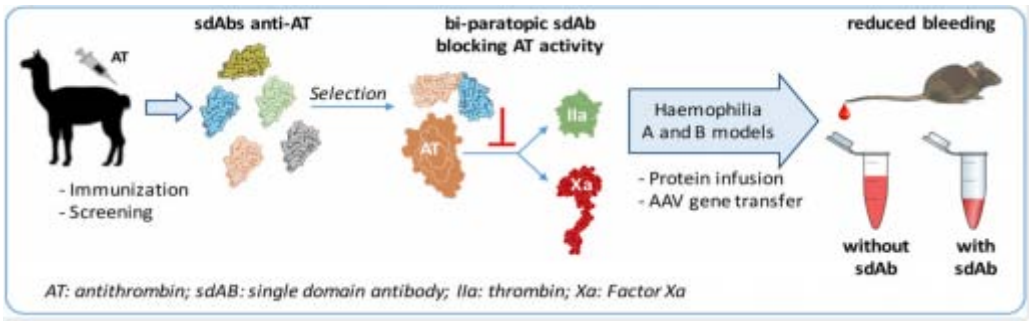
Description of a new pathway contributing to platelet activation



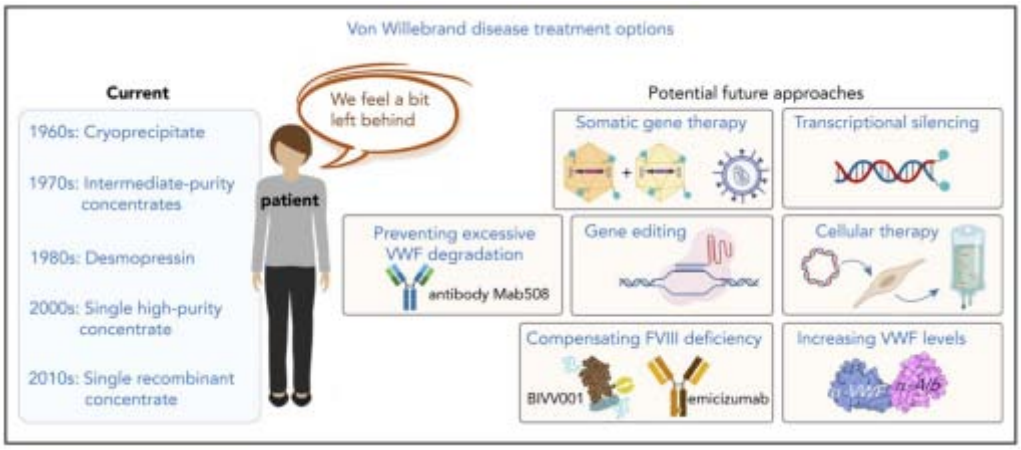
ADP1 : early (5s) ADP secretion

ADP2 : late (≥10s) ADP secretion

Targeted inhibition of antithrombin anticoagulant effect by nanobodies



Von Willebrand disease: present and future treatments



Cécile DENIS - cecile.denis@inserm.fr - http://www.umrs1176.u-psud.fr

Pascale Gaussem

Innovative Therapies in Haemostasis IThEM

Faculté de Pharmacie de Paris Université de Paris
Inserm UMR-S1140 CHU Paris
Pascale Gaussem
Paris

UMR_S1140 is recognized for its expertise in haemostasis, in management of antithrombotic treatments and in development of innovative biotherapies (in vitro vascular cell production).

Key facts

Team

- Researchers : 11
- Technicians : 6
- Postdoc fellows : 0
- PhD Students : 9

Translational approaches

- Patents : 3
- Clinical research grants : 7
- Industry partnerships : 5

International research links

- USA, Netherlands, Italy, China, Mexico, Poland, Greece, Germany, Canada, UK, Switzerland, belgium, Spain

Keywords

- signalling
- platelets
- antithrombotic agents
- vasculogenesis
- endothelium
- cell culture
- genetics
- preclinical model
- thrombosis
- biochemistry

Biological Resources

- human and animals tissus (biopsy)
- human and animal peripheral blood (rat, mouse, rabbit)
- human and animals adult stem cells (rat, mouse, rabbit)
- cohorts : Venous thrombosis (FARIVE), pulmonary fibrosis (COFI), COVID-19 (SARCODO)
- DNA and RNA banks from cardiovascular disease
- human cord blood

Research Brief :

The main mission of UMR_S1140 is to develop new therapeutic strategies in haemostasis and cardiovascular diseases through the improvement of knowledge in the field of molecular mechanisms of haemostasis and vasculogenesis, and of management of antithrombotic drugs to notably decrease drug-related adverse events, with strong clinical application potential.
Our scientific objectives are:
i) to understand the role of adult stem cells with vasculogenic properties in blood vessel formation in physiological conditions and in lung and cardiovascular diseases, and to analyse the haemocompatibility in mechanical circulatory/respiratory support (Theme 1),
ii) to analyse new mechanisms involved in the regulation of platelet functions and to conduct a transversal program on antithrombotic agents from the molecular basis of coagulation to animal models and clinical studies in targeted populations (Theme 2).

- **Methodologies Used :**

Preclinical models of angiogenesis, thrombosis, bleeding, and intravital microscopy
Cell biology: cell culture in 2D and 3D scaffold (primary (endothelial), stem cells(endothelial progenitors, megacaryocytes,mesenchymal), cell transfection, in vitro angiogenesis assays, flow experiments, immunocytochemistry, production of recombinant proteins
Molecular biology, RT-qPCR, Flow cytometry, biochemistry (WB, ELISA, signalling)
Immunohistochemistry, confocal microscopy...

Publications

DECOUTURE B, DREANO E, BELLEVILLE-ROLLAND T, KUCI O, DIZIER D, BAZAA A, COQUERAN B, LOMPRE AM, DENIS CV, HULOT JS, BACHELOT-LOZA C, GAUSSEM P (2015). Impaired platelet activation and cAMP homeostasis in MRP4-deficient mice, blood. 126(15), 1823

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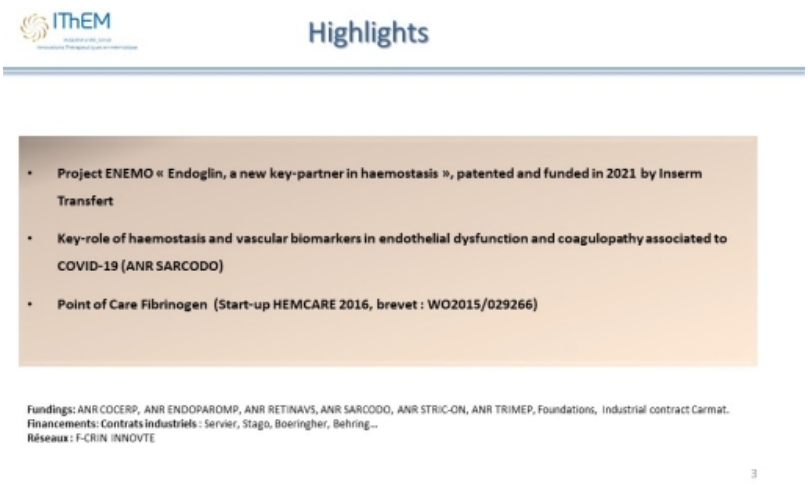
DÉTRICHÉ G, GENDRON N, PHILIPPE A, GRUEST M, BILLOIR P, ROSSI E, GUERIN CL, LOKAJCZYK A, BRABANT S, PRIÉ D, MIRAULT T, SMADJA DM (2022). Gonadotropins as novel active partners in vascular diseases: insight from angiogenic properties and thrombotic potential of endothelial colony-forming cells, J Thromb Haemost. 20(1), 230

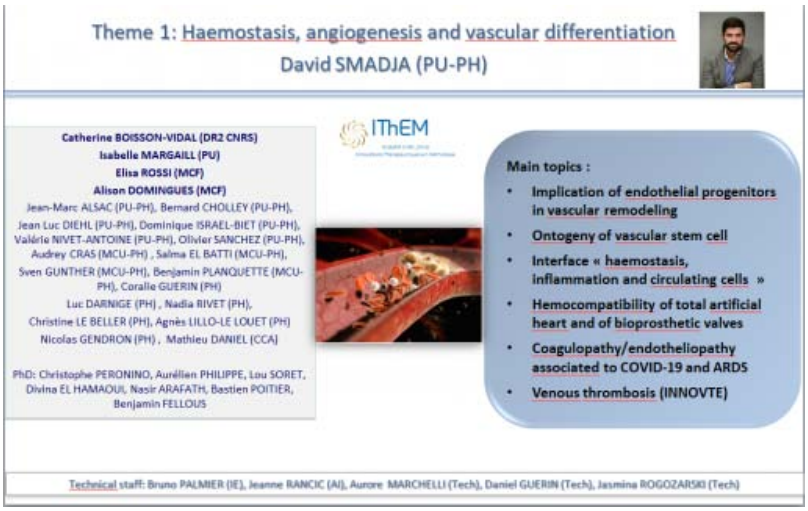
FOULON-PINTO G, LAFUENTE-LAFUENTE C, JOURDI G, LE GUEN J, TALL F, PUYMIRAT E, DELRUE M, RIVIERE L, KETZ F, GOUIN-THIBAULT I, MULLIER F, GAUSSEM P, PAUTAS P, LECOMPTE T, CURIS E, SIGURET V (2023). Assessment of Direct oral Anticoagulants in GEriatrics (Adage) study: rivaroxaban/apixaban concentrations and thrombin generation profiles in NVAF very elderly patients, Thromb Haemostas. (),

Gaussem Pascale - pascale.gaussem@u-paris.fr - +33153739939 - umrs1140@pharmacie.parisdescartes.fr / http://www.ithem.fr

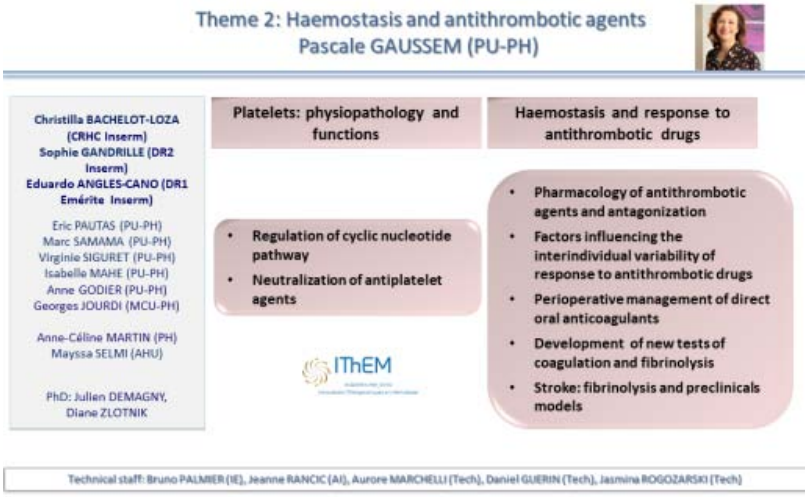
UMR-S1140 highlights



Work force and research of Theme 1



Work force and research of Theme 2



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Research teams with secondary association to PMN Institute

Muriel Priault

Protein instability and molecular aging

Université de Bordeaux
CNRS UMR5095
Isabelle Sagot
Bordeaux

We discovered that the sequential deamidation of Bcl-xL qualifies as a biomarker of aging, and we transfer this finding to applied science to screen anti-aging compounds and as a marker for pathology.

Key facts

Team

- Researchers : 3
- Technicians : 1
- Postdoc fellows : 0
- PhD Students : 2

Translational approaches

- Patents : 2
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- molecular aging
- protein deamidation
- Bcl-2 family proteins
- protein interaction
- aging biomarker
- production of recombinant proteins
- protein separation by chromatography
- protein detection
- functional characterization
- membrane protein reconstitution

Biological Resources

- membrane protein reconstitution
- cell culture

Research Brief :

The "Protein Instability and Molecular aging" team works on protein deamidation, a post-translational modification widely regarded as a molecular clock. Our aim is to determine how and when this reaction occurs, and what the functional consequences are. We ask these questions at the scale of isolated proteins, but also in cultured cells (with 2D and 3D models) and at the level of whole organisms. We further transfer the knowledge earned from this basic science to applied science : our goals are to identify new anti-aging compounds and to correlate protein deamidation to pathology to improve health-span.

- **Methodologies Used :**

NA

Publications

Beaumatin F, El Dhaybi M, Bobo C, Verdier M, Priault M. (17). Bcl-xL deamidation and cancer: Charting the fame trajectories of legitimate child and hidden siblings., Biochim Biophys Acta Mol Cell Res. 1864(10), 1734-1745

Beaumatin F, El Dhaybi M, Lasserre JP, Salin B, Moyer MP, Verdier M, Manon S, Priault M. (2016). N52 monodeamidated Bcl?xL shows impaired oncogenic properties in vivo and in vitro, Oncotarget. 7(13), 17129-43

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Priault M (2022). Intrinsic instability of proteins: Deamidation, METHODS. 200(), 1-2

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Boudier-Lemosquet A, Mahler A, Bobo C, Dufossée M, Priault M (2022). Introducing protein deamidation: Landmark discoveries, societal outreach, and tentative priming workflow to address deamidation., METHODS. 200(), 3-14

Priault Muriel - muriel.priault@ibgc.cnrs.fr - +33 556999038

Pneumology

Key facts

Team

- Researchers : 9
- Technicians : 1
- Postdoc fellows : 0
- PhD Students : 4

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- Germany Universitätsklinikum Carl Gustav Carus, équipe du Pr Hummel USA
- USA University of Michigan, Department of Biomedical Engineering (Pr Grotberg)

Keywords

- Biomechanics
- Respiratory Distress
- Mucociliary Clearance
- ENT Diseases
- Upper Airways
- Mechanical Ventilation
- Modeling

Bruno Louis Marcel Filoche

Biomechanics & Respiratory Apparatus

Université Paris-Est Créteil
INSERM UMR955 CNRS EMR7000
Jorge Boczkowski
Créteil

Our team develops a multidisciplinary research at the interface between biomechanics, bioengineering, and biomedical sciences. Our program is dedicated at further deciphering the physiological and pathophysiological mechanisms of acute and chronic respiratory failure and at designing more efficient

Research Brief :

We focus our research on the new tools for ventilation, on the biomechanical response of the airway epithelium to the aggression, and on the use of the nasal epithelium as new pathway to administrate treatment.
Optimizing mechanical ventilation requires measuring, monitoring, and refining the physiological and clinical interpretation of the global mechanical parameters. This approach is one hand performed on bench and through physical/simulation models, and on the other hand through in vivo investigations at the bedside with the aim of defining new protective ventilatory modes.
In the airways, interactions between the airway wall (the organ) and the airway flow (the environment) play a crucial role. We aim to determine the interdependent mechanisms of mucus, fluid, particle motions cilia beating and gas transport (from mouth to alveoli) in realistic airway geometries, notably in obstructive geometries and in physio-pathological situations.
We also want to further decipher the interaction between cellular function and the three kinds of aggression/stimulation (mechanical, inflammatory, or virulent) that can be encountered from upper airways to acinar ducts and alveoli. It is postulated that cellular function response to stimulation might be at the origin of functional deficiencies expressed at larger scales.
Our aim is also to evaluate the role of the neonatal Fc receptor for the transcystosis of monoclonal antibody in nasal epithelial cell.

- **Methodologies Used :**

Cells culture: air-liquid interface model of primary culture of human nasal epithelial cells
Magnetic bead Twisting Cytometry
Atomic Force Microscopy
High speed video-microscopy
Numerical simulation

Publications

M. Filoche, C. F. Tai and J. B. Grotberg (2015). Three-dimensional model of surfactant replacement therapy, Proc Natl Acad Sci U S A. 112(30), 9287-9292

M. Bottier, S. Blanchon, G. Pelle, E. Bequignon, D. Isabey, A. Coste, E. Escudier, J. B. Grotberg, J. F. Papon, M. Filoche and B. Louis (2017). . A new index for characterizing micro-bead motion in a flow induced by ciliary beating: Part I, experimental analysis, PLoS Comput Biol. 13(7), e1005605

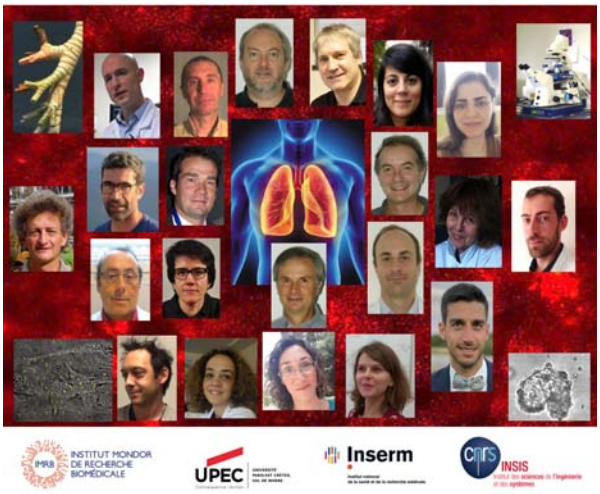
E. Bequignon, C. Dhommee, C. Angely, L. Thomas, M. Bottier, E. Escudier, D. Isabey, A. Coste, B. Louis, J. F. Papon and V. Gouilleux-Gruart (2019). FcRn-Dependent Transcytosis of Monoclonal Antibody in Human Nasal Epithelial Cells In Vitro: A Prerequisite for a New Delivery Route for Therapy?, Int J Mol Sci. 20(6), 1379. doi: 10.3390/ijms20061379

S. Blanchon, M. Legendre, M. Bottier, A. Tamalet, G. Montantin, N. Collot, C. Faucon, F. Dastot, B. Copin, A. Clement, M. Filoche, A. Coste, S. Amselem, E. Escudier, J. F. Papon and B. Louis (2019). Deep phenotyping, including quantitative ciliary beating parameters, and extensive genotyping in primary ciliary dyskinesia, J Med Genet. 57(4), 237-244

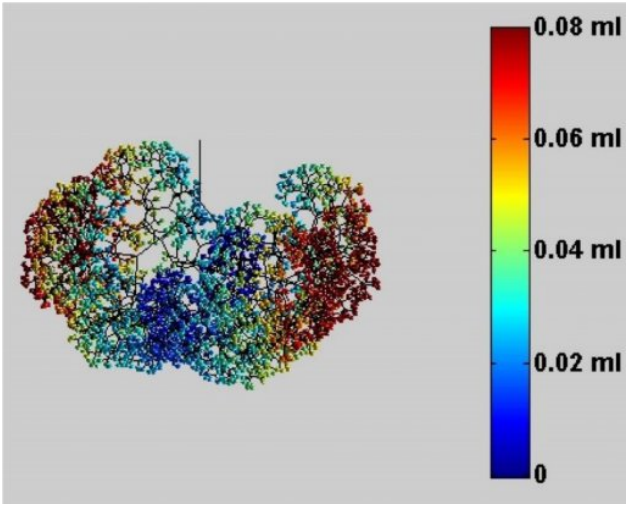
A. Kazemi, B. Louis, D. Isabey, G. F. Nieman, L. A. Gatto, J. Satalin, S. Baker, J. B. Grotberg and M. Filoche (2019). Surfactant delivery in rat lungs: Comparing 3D geometrical simulation model with experimental instillation, PLoS Comput Biol. 15(10), e1007408

E. Bequignon, D. Mangin, J. Becaud, J. Pasquier, C. Angely, M. Bottier, E. Escudier, D. Isabey, M. Filoche, B. Louis, J. F. Papon and A. Coste (2020). Pathogenesis of chronic rhinosinusitis with nasal polyps: role of IL-6 in airway epithelial cell dysfunction, J Transl Med. 18(1), 136. doi: 10.1186/s12967-020-023

Team

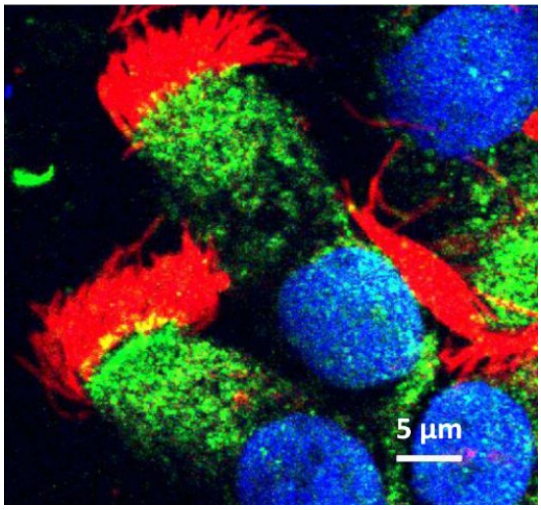


Simulation



Surfactant replacement therapy

Expression of FvRn in human nasal epithelial cells



FcRn is shown in green, cilia in red and nucleus in blue

Louis Bruno - bruno.louis@inserm.fr - https://www.imrb.inserm.fr/en/teams/b-louis-2/

INSTITUT MONDOR DE RECHERCHE BIOMÉDICALE

Sophie Lanone

GEIC2O: Gene-environment interactions in Cystic fibrosis, Chronic Obstructive Pulmonary Disease and Other (rare) respiratory diseases

UPEC
Inserm UMR955
Jorge Boczkowski
Créteil

A unique approach based on the pluridisciplinarity of the team, bringing a broad scientific expertise from genetics to lung (electro)physiology, allowing to conduct a research aimed to understand the interaction of genets and environment in the course of lung diseases.

Key facts

Team

- Researchers : 23
- Technicians : 6
- Postdoc fellows : 3
- PhD Students : 9

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- Canada
- Germany
- Japan

Keywords

- COPD
- Cystic fibrosis
- Environmental agressions
- Genetics
- Senescence
- Preclinical models
- (Primary) cell culture
- Lung function
- Human samples
- Electrophysiology

Biological Resources

- Atg5-LysMCre mice
- COPD patients lung fibroblasts
- RespiRare - Reference centre for rare lung repiratory diseases

Research Brief :

The general scientific objective of GEIC2O team is to understand the interplay between genetic and environmental factors in the development of lung diseases throughout the life (namely from children to adults). We particularly focus on lung diseases of non-genetic (Chronic Obstructive Pulmonary Disease or COPD) and genetic (Cystic Fibrosis and surfactant disorders) origins. The large pluridisciplinarity of GEIC2O team staff comprising MD (lung specialists - adult and pediatricians, occupational medicine, geneticists, ear/nose/throat specialists, and lung pathologist) as well as PhD (in cellular and molecular biology, biochemistry, genetic, bioinformatics, electrophysiology and respiratory physiology) allows us to develop a comprehensive scientific approach ranging from in vitro experimental work to preclinical models and patient cohorts. Overall, our research is developed through four main axes: 1/ Molecular bases of cigarette smoke-induced COPD; 2/ Genetic and cellular bases of CF and surfactant disorders; 3/ Resolution of inflammation in lung diseases, and 4/ Environmental aggressions and course of lung diseases.

- **Methodologies Used :**

Human samples (lung tissue, blood, bronchoalveolar lavage, cells...)
Cell culture (primary, cell lines - human and mice)
Development of preclinical models (cigarette smoke exposure, nanoparticle exposure, exposure to complex realistic atmospheres...)
Lung function evaluation
Electrophysiology, ionic transport
Target pathways/genes of interest: senescence, autophagy, resolution of inflammation, CFTR, surfactant
Synchrotron-based X-ray microfluorescence

Publications

Hinzpeter A, Aissat A, de Becdelièvre A, Bieth E, Sondo E, Martin N, Costes B, Costa C, Goossens M, Galietta LJ, Girodon E, Fanen P (2013). Alternative splicing of in-frame exon associated with premature termination codons: implications for readthrough therapies., Hum Mutat. 34(2), 287

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Paul E, Franco-Montoya ML, Paineau E, Angeletti B, Vibhushan S, Ridoux A, Tiendrebeogo A, Salome M, Hesse B, Vantelon D, Rose J, Canouï-Poitrine F, Boczkowski J, Lanone S, Delacourt C, Pairon JC. (2017). Pulmonary exposure to metallic nanomaterials during pregnancy irreversibly impairs lung development of the offspring., Nanotoxicology. 11(4), 48

Andujar P, Courbon D, Bizard E, Marcos E, Adnot S, Boyer L, Demoly P, Jarvis D, Neukirch C, Pin I, Thabut G, Boczkowski J, Leynaert B. (2018). Smoking, telomere length and lung function decline: a longitudinal population-based study., Thorax. 73(), 283

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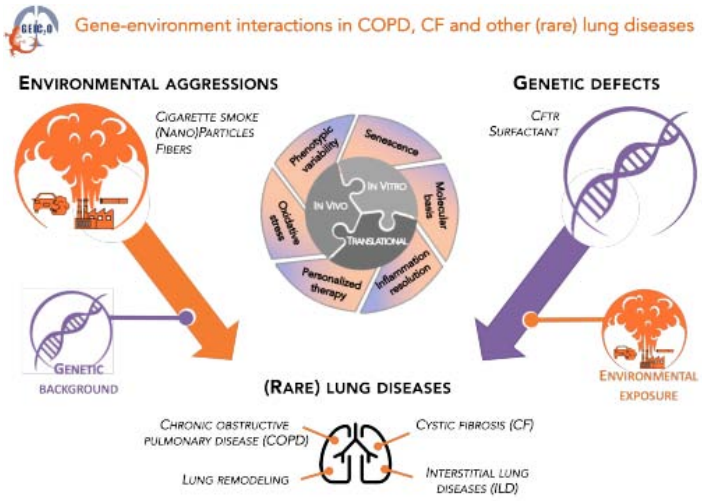
Audureau É, Simon-Deckers A, Franco-Montoya ML, Annangi B, Kermanizadeh A, Boczkowski J, Lanone S (2018). Substantial modification of the gene expression profile following exposure of macrophages to welding-related nanoparticles., Sci. Rep.. 4(8), 8554

Lanone Sophie - sophie.lanone@inserm.fr - http://www.imrb.inserm.fr/equipes/s-lanone/

Global approach



Global approach developed by the team to study the gene-environment interactions in lung diseases

Lanone Sophie - sophie.lanone@inserm.fr - http://www.imrb.inserm.fr/equipes/s-lanone/

Key facts

Team

• Researchers : 12
• Technicians : 2
• Postdoc fellows : 2
• PhD Students : 8

Translational approaches

• Patents : 2
• Clinical research grants : 0
• Industry partnerships : 4

Keywords

• asthma pathophysiology
• Airway smooth muscle
• clinical research
• cell biology
• molecular biology
• imaging

Biological Resources

• animal models of asthma and COPD
• Cohorts of patients
• human lung tissue

Patrick Berger

Bronchial remodeling

Université de Bordeaux
Inserm U1045
Patrick Berger
Bordeaux

The project of the team associates human and animal studies in a multidisciplinary approach (physiologists, chest physicians, radiologists, physicists, pharmacologists, and paediatricians) with strong interconnection between the team and the clinical investigation center in the hospital

Research Brief :

Asthma and chronic obstructive pulmonary disease (COPD) are very frequent inflammatory diseases that are characterized by different patterns of bronchial remodelling. However, characteristics and localization of the increased in Bronchial Smooth Muscle (BSM) mass are different. In COPD, there is a BSM cell hypertrophy which is only present in distal bronchi whereas in asthma, there are both BSM cell hypertrophy and hyperplasia within the entire bronchial tree. Anyhow, BSM remodelling has been associated with a poor prognosis, high morbidity, and deterioration of lung function. As a consequence BSM remodelling should be a target of innovative treatments.

The general aim of this project is therefore to understand, evaluate and treat bronchial remodelling. The specific aims are to further unravel the mechanisms of bronchial remodelling in both asthma and COPD as well as to develop new non invasive tools to assess bronchial remodelling in vivo.

• Methodologies Used :

For this purpose, the research project will combine clinical, functional, radiological data obtained in vivo with histological, functional, cellular, and molecular data obtained in vitro.

Publications

Girodet PO, Dournes G, Thumerel M, Begueret H, Dos Santos P, Ozier A, Dupin I, Trian T, Montaudon M, Laurent F, Marthan R, Berger P. (2015). A Double-Blind, Placebo-Controlled Trial of Gallopamil for Severe Asthma., Am J Respir Crit Care Med. 191(8), 876-883

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Dournes G, Grodzki D, Macey J, Girodet PO, Fayon M, Chateil JF, Montaudon M, Berger P, Laurent F. (2015). Quiet sub-millimetric MRI of the lung is feasible using PETRA sequence at 1.5 T: a technical note., Radiology. 276(1), 258-265

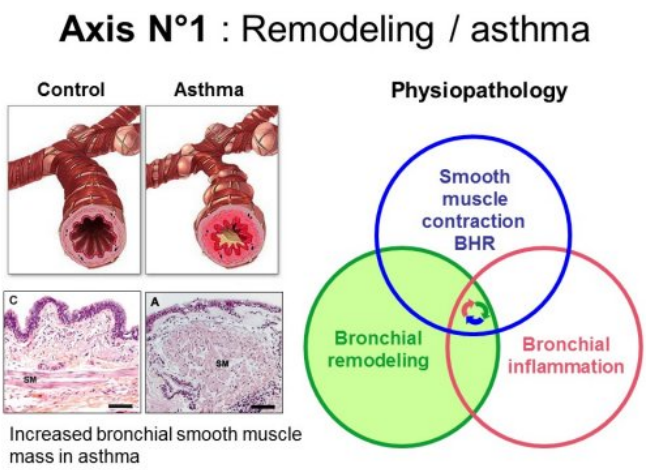
Dupin I, Allard B, Ozier A, Maurat E, Ousova O, Delbrel E, Trian T, Bui HN, Dromer C, Guisset O, Blanchard E, Hilbert G, Vargas F, Thumerel M, Marthan R, Girodet PO, Berger P. (2016). Blood fibrocytes are recruited during acute exacerbations of chronic obstructive pulmonary disease through a CXCR4 dependent pathway., J Allergy Clin Immunol. 137(4), 1036-1042

Trian T, Allard B, Ozier A*, Dupin I, Carvalho G, Ousova O, Maurat E, Thumerel M, Begueret H, Girodet PO, Marthan R, Berger P. (2016). Selective dysfunction of p53 for mitochondrial biogenesis induces cellular proliferation in asthmatic bronchial smooth muscle., J Allergy Clin Immunol. 137(6), 1717-1726*

Girodet PO, Allard B, Thumerel M, Begueret H, Dupin I, Ousova O, Maurat E, Ozier A, Trian T, Marthan R, Berger P. (2016). Bronchial smooth muscle remodeling in non-severe asthma., Am J Respir Crit Care Med. 193(6), 627-633

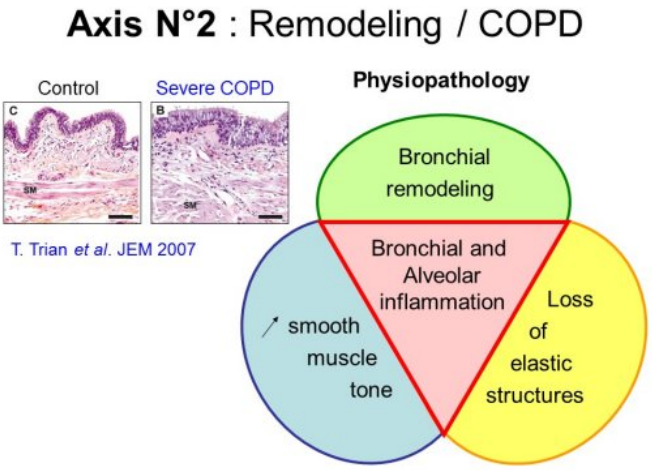
Berger Patrick - patrick.berger@u-bordeaux.fr - https://crctb.u-bordeaux.fr

Axis 1



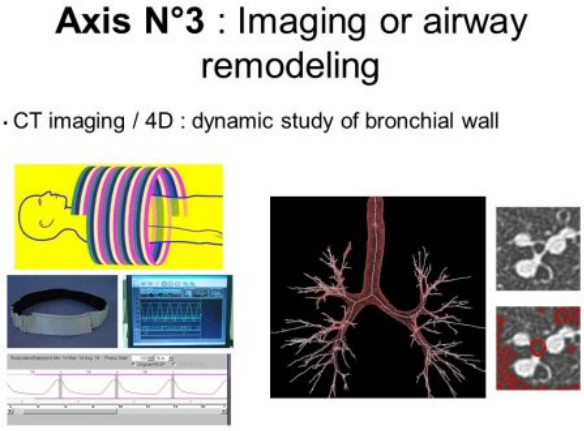
Bronchial remodeling in asthma

Axis 2



Bronchial remodeling in COPD

Axis 3



Imaging of bronchial remodeling

Berger Patrick - patrick.berger@u-bordeaux.fr - https://crctb.u-bordeaux.fr

Key facts

Team

• Researchers : 11
• Technicians : 3
• Postdoc fellows : 3
• PhD Students : 3

Translational approaches

• Patents : 3
• Clinical research grants : 0
• Industry partnerships : 1

International research links

• Department of cellular and molecular medicine - Department of pediatrics - University of Ottawa - Canada - Pr B. Thébaud
• Laboratory of cell physiology - Brussels - Belgium - Pr P. Gailly
• Cardiovascular research institute - Department of Cardiology - New York - USA - Pr L. Hadri and Dr M. Bisserier

Keywords

• Pulmonary hypertension
• Calcium signalling
• Vascular remodelling
• Broncho-Pulmonary Dysplasia
• Airborne pollution
• Patch-clamp
• Chronic hyperoxia
• Chronic hypoxia
• Fluorescent imaging
• Transgenic mice

Biological Resources

• Connexin 43 +/- transgenic mice
• biobank of fetal and adult pulmonary arterial smooth muscle cells
• Rat model of severe pulmonary hypertension (combined treatment of chronic hypoxia and monocrotaline)
• Various animal models of pulmonary hypertension (a single injection of monocrotaline or SUGEN + hypoxia protocol)
• Rats and mice with chronic hypoxic pulmonary hypertension (with the use of a hypobaric chamber)
• Newborn rats with pulmonary hypertension associated with bronchopulmonary dysplasia (14 days of hyperoxia)

Christelle Guibert

Pathophysiology of pulmonary circulation

Université de Bordeaux
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Patrick Berger
Pessac

Our team works on a real interface between cardio-vascular and pulmonary diseases in adult and infants and is composed of multidisciplinary researchers with various trainings (scientists, physicians, pharmacists). Our aims are to perform translational research with clinical trial when relevant.

Research Brief :

The main scientific scope of the team relates to biology of the pulmonary circulation. We focus our research on (1) pulmonary hypertension (PH) in adults and neonates (cellular and molecular mechanisms associated to vascular remodelling and reactivity as well as pharmacological treatments) and (2) impact of environmental factors (airborne pollution and hyperoxia). Our studies are based on animal models including transgenic animals as well as human pulmonary arteries. By addressing vascular pathophysiology on pulmonary circulation, our team works on a real interface between cardio-vascular and pulmonary diseases. Our team is composed of multidisciplinary researchers with various trainings (scientists, physicians, pharmacists).

Specific objectives of the team are the following:
1. To address the role of Stretch-activated channels (SAC) and intercellular communications (connexins) in PH
2. To use an animal model of bronchopulmonary dysplasia associated to PH in newborn and to address the role of SAC and intercellular communications in connection with theme 1
3. To address the impact of particulate pollution on the pulmonary circulation
4. To address right ventricular cardiac function in PH

• **Methodologies Used :**

Biological material and main methodologies used:
(1) Freshly isolated vascular cells, cultured cells and tissue (pulmonary arteries) for molecular biology (PCR, qPCR), cellular biology (electron microscopy, Western Blot, siRNA, tests for migration, proliferation and apoptosis), immunohistochemistry, patch-clamp and fluorescent imaging (calcium, reactive oxygen species (ROS))
(2) Vessels (arterial rings, pressurized and cannulated small vessels) from animal models and human tissue (reactivity, electron paramagnetic resonance for measurement of ROS)
(3) Animal models of pulmonary hypertension and/or transgenic animals for in vivo and in vitro experiments
(4) Human tissue (pulmonary arteries and/or lung from adult and fetus)

Publications

Freund-Michel V, Cardoso Dos Santos M, Guignabert C, Montani D, Phan C, Coste F, Tu L, Dubois M, Girerd B, Courtois A, Humbert M, Savineau JP, Marthan R, Muller B. (2015). Role of Nerve Growth Factor in Development and Persistence of Experimental Pulmonary Hypertension., American Journal of Respiratory and Critical Care Medicine. 192(3), 342-355

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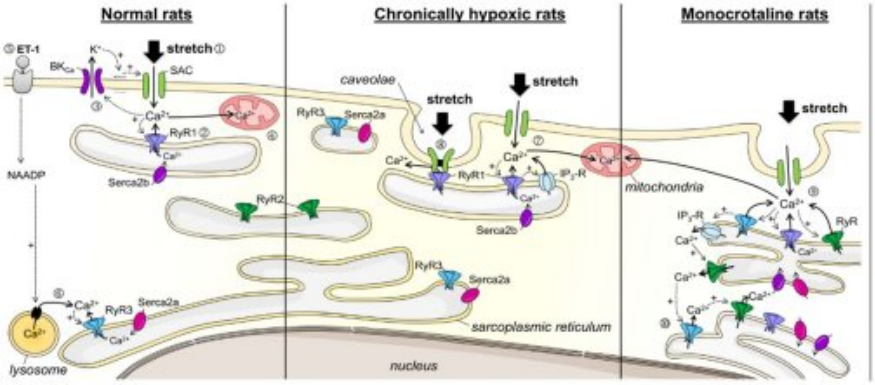
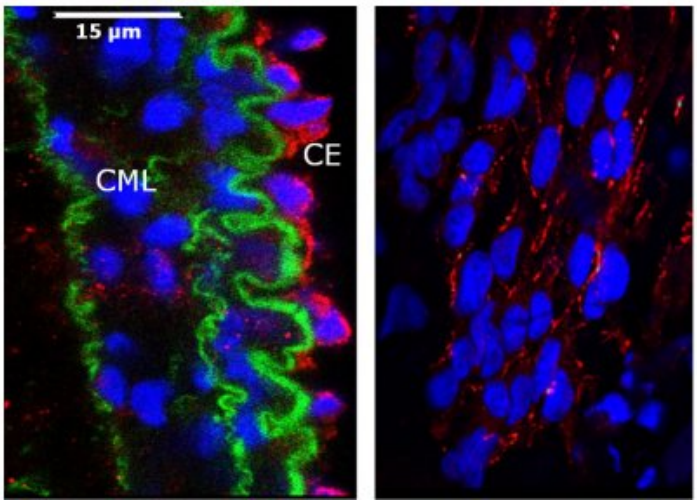
Summary of signalling pathways associated to stretch in pulmonary arterial smooth muscle cells.



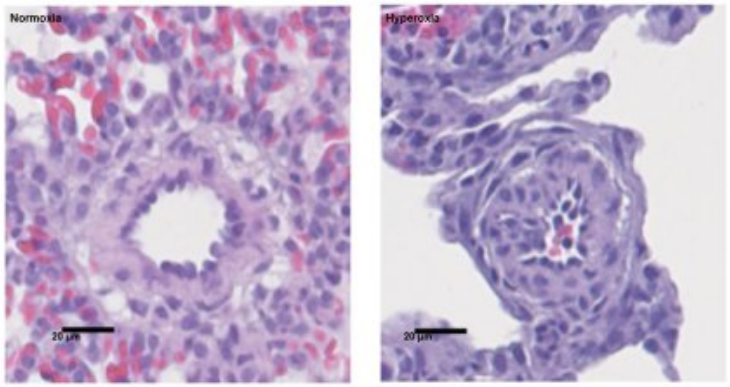
Signalling pathways in normal rats (left), rats suffering from chronically hypoxic pulmonary hypertension (middle) and rats suffering from pulmonary arterial hypertension induced by monocrotaline (right) (from Gilbert G. et al., Cardiovasc Res, 2014).

Connexin 43 immunofluorescent labelling (red).



Connexin 43 labelling is shown on a pulmonary arterial cross section (left) and on the endothelial side of an opened vessel (right). Nuclei are labelled in blue and autofluorescence of external and internal elastic lamina are in green. Labellings were observed with a confocal microscope (Nikon TE2000). CML, smooth muscle cells, CE, endothelial cells. Scale bar is 15 µm.

Remodelling of intrapulmonary arteries (IPA) from newborn rats following 15 days of hyperoxia.



Left picture is an IPA from newborn rat breathing air (21 % O2) and right picture is an IPA from newborn rat breathing 90 % O2 during 14 days. Scale bar is 20 µm.

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Key facts

Team

- Researchers : 12
- Technicians : 2
- Postdoc fellows : 1
- PhD Students : 10

Translational approaches

- Patents : 6
- Clinical research grants : 10
- Industry partnerships : 10

Keywords

- Pulmonary hypertension
- Vascular remodeling
- Endothelial dysfunction
- Vascular inflammation
- Therapeutic targets and Pronostic biomarkers
- Preclinical PH models
- RNA sequencing and other \"omics\" techniques
- Catheterisation
- Primary cultures of Human cells
- Confocal imaging

Biological Resources

- International chronic thromboembolic pulmonary hypertenison (CTEPH) registry
- Tissue bank and biobank on PH and CTEPH
- French Pulmonary Hypertension (PH) registry
- Preclinical rodent models of PH: chronic hypoxia (CHx), monocrotaline (MCT), Sugen/hypoxia (SuHx)
- Primary cultures of Human pulmonary vascular cells (ECs, PA-SMCs, pericytes)

Christophe GUIGNABERT
Marc HUMBERT

Endothelial cell dysfunction & Therapeutic innovation

Université Paris-Saclay
Inserm UMR_S 999
Marc HUMBERT
Le Kremlin-Bicêtre

Our research Team benefits from an environment of excellence: ERN LUNG (European Reference Network on respiratory diseases); RHU DESTINATION 2024; RHU Bioart Lung; LIA Inserm-Technion-Univ Paris-Saclay; National Referral Centre (CNR) for PH; Institut Paris-Saclay en Santé et Innovation Thérapeutique

Research Brief :

The main scope of the Research Team "ENDOTHELIAL DYSFUNCTION & THERAPEUTIC INNOVATION" relates to the pathophysiology and clinical management oh pulmonary hypertension (PH). Deciphering of the pathophysiology of lung vascular remodelling and identification of new molecular targets to alleviate and ultimately cure PH are the general objectives of our team. Our Team aims at a better understanding of the pathophysiology of PH. The cellular/molecular mechanisms and the immunopathology of pulmonary vascular remodelling in PH is the main focus of this research team. Thanks to a large tissue bank and biobank we have access to a unique pool of human biological material from well-phenotyped patients. Based on a 20-year expertise in the field, our members also promotes clinical research in PH with an emphasis on registries, patient management (include hemodynamic assessment) and development of novel medical and surgical approaches.

The Team is divided in two groups one with an emphasis on the role of endothelial cell (EC) dysfunction and cell-cell miscommunications in the PH onset and progression, the other one on patients' clinical management from risk factor to diagnosis and treatment and on innovative surgery and bio-artificial lung. In particular, Group 1 is pursuing a strategy of focusing our research activities around the question how pulmonary ECs interact with their environment, and to use this knowledge to control EC function and phenotype.

- **Methodologies Used :**

Our Research Team has always prioritized cross-fertilization between our Pathophysiology Group and our Innovative Therapy Group. Importantly, our Team mix basic researchers with medical and surgical healthcare providers, all involved in translational research with a common aim to improve patients care and outcome and provide better education to our students with optimal research facilities and access to well-phenotyped biological samples. Discovering novel PH models, novel therapeutic targets and biomarkers as well as novel patient management options is our ambition, leading to publications and patents whenever possible.

Publications

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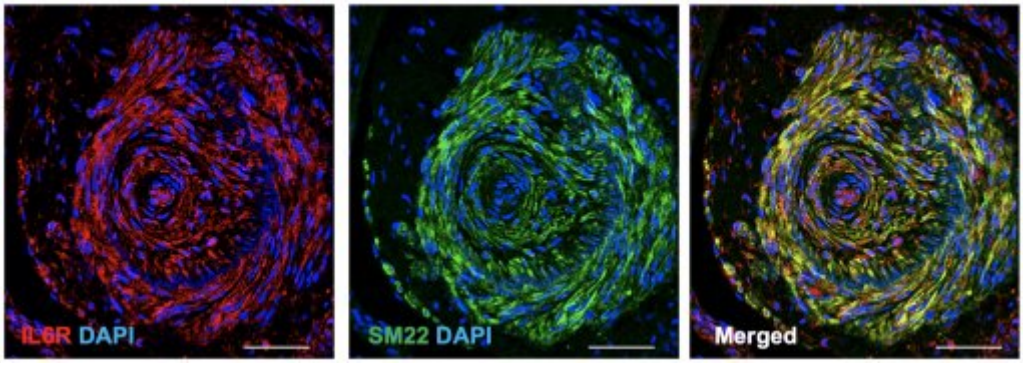
Ectopic upregulation of membrane-bound IL6R drives vascular remodeling in PAH:



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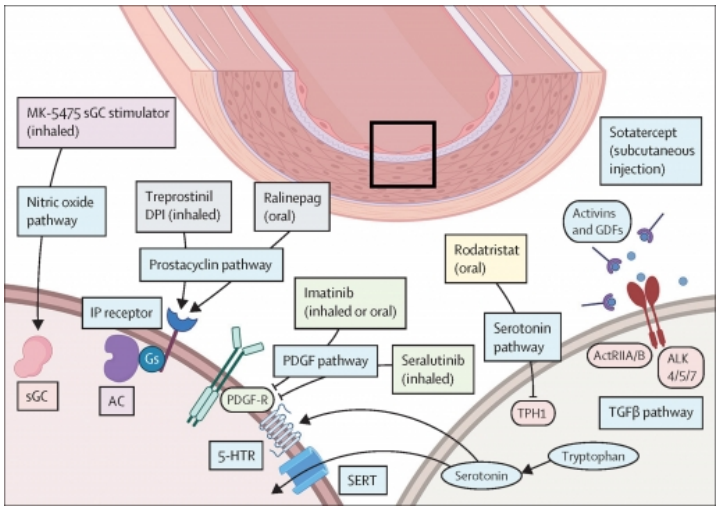
The evolving landscape of pulmonary arterial hypertension clinical trials:



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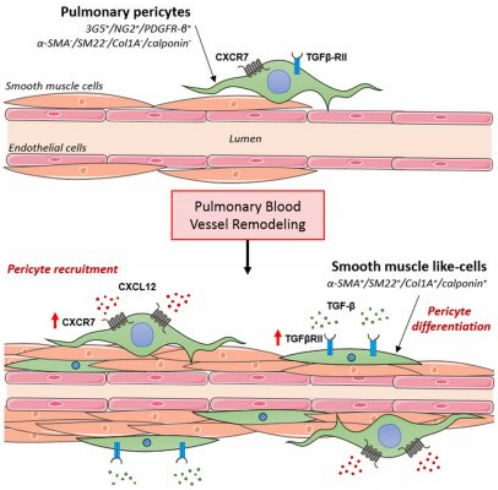

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Key facts

Team

• Researchers : 4
• Technicians : 2
• Postdoc fellows : 1
• PhD Students : 1

Translational approaches

• Patents : 2451467
• Clinical research grants : 0
• Industry partnerships : 0

International research links

• Great Britain, United States, Canada, Germany

Keywords

• immunity inflammation lung infection bacteria virus nanoparticles adenovirus
• PCR ; nanoparticles ;FACS ;cell culture ; in vivo lung experimental procedures

Jean-Michel Sallenave

Innate Immunity and anti-infective pulmonary defenses

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Bruno Crestani
PARIS

We are interested in the molecular and cellular mechanisms involved in pathogen (eg viruses such as Influenza, bacteria such as Pseudomonas aeruginosa) recognition and in the response to environmental and manufactured agents (i.e nanoparticles).

Research Brief :

It is now accepted that lung mucosal tissue confer important properties to the immune system, both at homeostasis and during infectious situations. At the mucosal surface, epithelial cells and alveolar macrophages interact, eg through surfactant, regulatory cytokines and antimicrobial molecules, to ensure a non-inflammatory regulatory and tolerogenic phenotype. After infection, this brake is released, and these cells participate in the network to organize pro-inflammatory responses and adaptive immunity to contain microbial aggression and to insure return to haemostasis. Our group is particularly interested in the innate mechanisms of defense and its dysregulation, which could explain the pathophysiology of lung chronic and acute inflammatory disorders.
Our main models of study focus on two aspects :
A) a therapeutic one, which aims to understand the basic mechanisms of host reponses against:
1) Pseudomonas aeruginosa infections, an opportunistic pathogen in nosocomial infections, as well as in cystic fibrosis and in exacerbations of chronic obstructive pulmonary diseases (COPD).
2) Lung infections by Influenza virus, a pathogen responsible for acute infections leading to seasonal flu or pandemic episodes, but also present during exacerbations in asthma, cystic fibrosis, COPD or lung fibrosis.
B) a prophylactic one, which aims to increase immune responses against these pathogens, by choosing adjuvant formulations able to break the mucosal tolerogenic milieu.

• **Methodologies Used :**

-PCR
-cell culture
-FACS
-ELISA
-PAGE analysis and Western Blot
-in vivo injections and instillation techniques (lung)
-immunological techniques

Publications

Motta JP, Magne L, Descamps D, Rolland C, Squarzoni-Dale C, Rousset P, Martin L, Cenac N, Balloy V, Huerre M, Fröhlich LF, Jenne D, Wartelle J, Belaaouaj A, Mas E, Vinel JP, Alric L, Chignard M, Vergnolle N, Sallenave JM (2011). Modifying the protease, antiprotease pattern by elafin overexpression protects mice from colitis., Gastroenterology. 140(4), 1272-82

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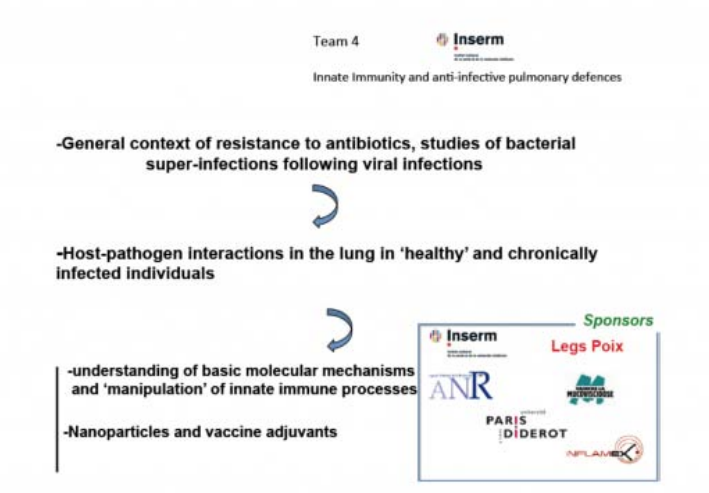
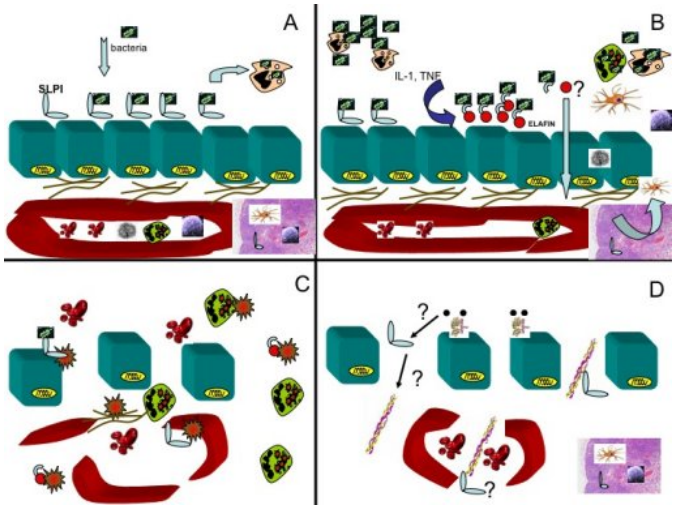
Team research interests



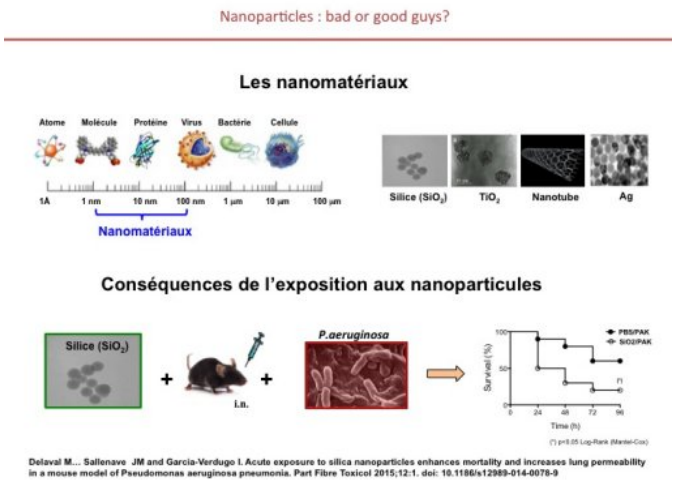
General themes and research interests of our team

Antimicrobial expression and functions at the lung mucosal interface



A)The lung alveolar-capillary barrier at haemostasis : antimicrobial molecules (AMMs, SLPI, elafin) are protective against infections and provide a tolerogenic phenotype at local lymph nodes. B)During infection, AMM expression increases in epithelial cells and generate chemotactic signals for inflammatory cells C)When the alveolar-capillary barrier is disrupted, AMM can protect tissue destruction with their anti-protease activity. D)AMMs are also important for tissue repair.

Nanoparticles as modulators of lung infections



Nanoparticles can influence/modulate lung responses towards infections. Our team is deciphering the molecular and cellular mechanisms by which nanoparticles (silica, silver...) can modulate the lung responses against bacteria (Pseudomonas aeruginosa...) and viral (Influenza) infectious agents.

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Key facts

Team

- Researchers : 2
- Technicians : 1
- Postdoc fellows : 0
- PhD Students : 3

Translational approaches

- Patents : 0
- Clinical research grants : 3
- Industry partnerships : 3

International research links

- Germany
- Greece
- Ireland

Keywords

- fibrosis
- fibroblast
- immune response
- lung cancer
- genetics
- animal models
- single cell analysis
- proteomics

Biological Resources

- animal models of pulmonary fibrosis (bleomycin, AdTGF)
- Biobank of lung tissue and lung fibroblasts from patients and controls, with and without telomere related gene mutation
- Biobank of DNA for Rheumatoid arthritis patients with and without interstitial lung disease, and familial pulmonary fibrosis

Bruno Crestani

Lung inflammation and Fibrosis

Université Paris Cité
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Understanding lung fibrosis through translational science

Research Brief :

Our project is focused on elucidating the mechanisms involved in the development of pulmonary fibrosis (PF) and identifying new therapeutic targets. Our disease model is Idiopathic PF (IPF), a rare chronic fibrotic pulmonary disease of unknown etiology, while Rheumatoid arthritis-associated interstitial lung disease (RA-ILD) is a model of auto-immune-induced PF. Our aim is to assess 1) the role of the pathological cross-talk between epithelial cells and lung fibroblast in the initiation and maintenance of the fibrotic process. We identified PRRX1 as a key mesenchymal transcription factor whose expression is restricted to fibroblastic lineages and upregulated in IPF. We will identify Prrx1 subpopulations by lineage tracing and characterize their role in lung fibrosis. We also characterize the role of lung adipocyte in lung fibrosis; 2) the control of the fibrotic process by the immune cells, focusing on the role of immune checkpoints and the role of MAIT cells; 3) the mechanisms behind the unusual prevalence of lung cancer in patients with lung fibrosis, focusing on the genes/signaling pathways associated with carcinogenesis, and deciphering how the fibrotic environment drives tumor growth in the experimental model of lung cancer in mice with lung fibrosis; and 4) the role of genetics in lung fibrosis development and progression, in familial pulmonary fibrosis, and in rheumatoid arthritis.

- **Methodologies Used :**

organoids; precision cut lung slices; bleomycin induced lung fibrosis; lung fibroblasts in primary culture

Publications

Kannengiesser C, Borie R, Ménard C, Réocreux M, Nitschké P, Gazal S, Mal H, Taillé C, Cadranel J, Nunes H, Valeyre D, Cordier JF, Callebaut I, Boileau C, Cottin V, Grandchamp B, Revy P, Crestani B. (2015). Heterozygous RTEL1 mutations are associated with familial pulmonary fibrosis., Eur Respir J. 46(), 474-485

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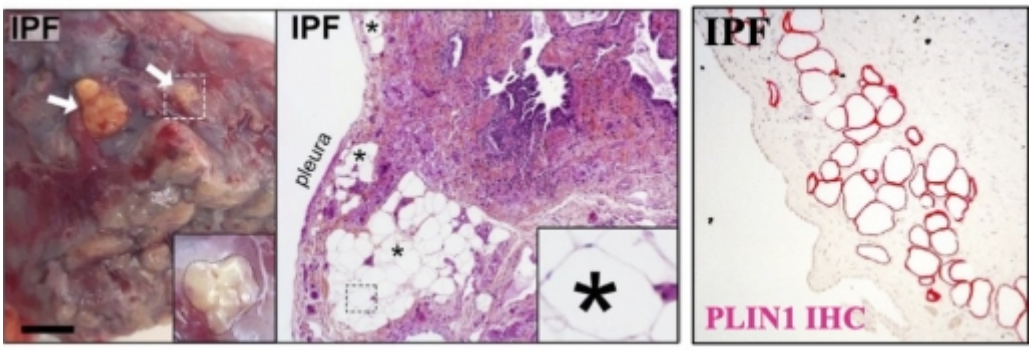
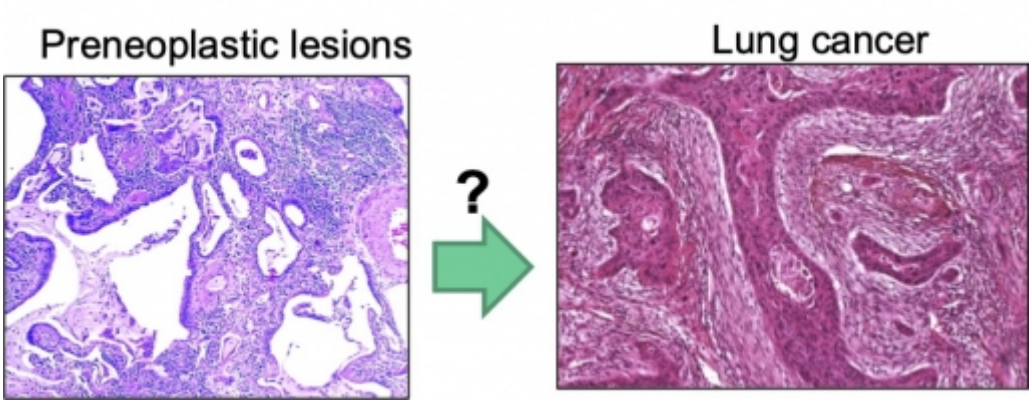
Presence of adipocytes in the distal parenchyma of IPF patients



Preneoplastic lesions and associated microenvironment in IPF



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Bernard Mari

Non coding genome & lung disorders

Université de Nice - Sophia Antipolis
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Sophia-Antipolis

Key facts

Team

- Researchers : 5
- Technicians : 2
- Postdoc fellows : 0
- PhD Students : 3

Translational approaches

- Patents : 1
- Clinical research grants : 0
- Industry partnerships : 3

International research links

- Germany, Belgium, USA

Keywords

- Fibrosis
- Cancer
- Lung
- Non-coding RNA
- Hypoxia
- Functional Genomics
- Gene Editing
- Biochemistry
- Bioinformatics

Developing RNA therapeutics and biomarkers for lung diseases

Research Brief :

Our team explores the potential function of several non-coding RNAs whose expression is deregulated in several lung disorders. Controlling the expression of some of these RNAs may likely provide important opportunities for the development of powerful new therapeutic strategies. Our research uses functional genomics methods including single-cell transcriptomics and CRISPR-based screens. It is strongly associated to the Pulmonology department of the Nice CHU (Pr. C-H Marquette & Dr S. Leroy) and is affiliated to the hospital-university federation (FHU) OncoAge. Our research mainly focuses on two axes :

- Exploration of non coding RNAs (miRNAs & LncRNAs) as therapeutic targets and prognosis biomarkers in idiopathic pulmonary fibrosis (IPF).

- Identification of non-coding RNAs associated with lung cancer aggressiveness, in particular in adaptation to a hypoxic environment.

- **Methodologies Used :**

Functional genomics - Molecular Biology - CRISPR/Cas9 - Bioinformatics - Biochemistry - Animal models

Publications

Pottier, N., Cauffiez, C., Perrais, M., Barbry, P., and Mari, B (2014). FibromiRs: translating molecular discoveries into new anti-fibrotic drugs, Trends Pharmacol Sci. 35(), 119

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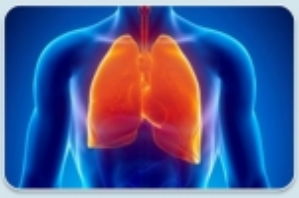
Team Non Coding Genome & Lung Disorders



Fundamental Aspects:
Deciphering ncRNAs target gene networks and mode of action

Clinical Aspects:
Developing RNA therapeutics and prognosis tools

- Fibrosis
- Cancer

Main questions:

- ncRNAs associated with tumor aggressiveness (hypoxic adaptation) and drug resistance (chemo-and targeted therapy)
- ncRNAs involved in the regulation of fibrogenic pathways and in the plasticity of mesenchymal cells

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Mustapha Si-Tahar

Respiratory Infection & Immunity

Université de Tours
Inserm UMR1100
Mustapha Si-Tahar
Tours

Understanding and targeting innate immune cells-pathogens interactions during respiratory infections

Key facts

Team

• Researchers : 6
• Technicians : 3
• Postdoc fellows : 1
• PhD Students : 3

Translational approaches

• Patents : 2
• Clinical research grants : 1
• Industry partnerships : 1

International research links

• Belgium
• Germany
• Canada

Keywords

• Pseudomonas aeruginosa
• Influenza
• Immunoregulation
• Lung infection
• Immunometabolism
• Animal models of lung infection
• Cell culture
• Flow cytometry
• Omics

Biological Resources

• Culture of primary human lung epithelial cells
• Collection of expectorations from patients with cystic fibrosis (in collaboration with the Pulmonology Department, Tours university hospital).
• Collection of respiratory fluids from patients under mechanical ventilation (in collaboration with the medical-surgical intensive care department, Tours university hospital).
• Collection of sera from patients with serious community-acquired lung diseases: in the process of being collected (400 patients expected out of the 1200 in the CAPE COD therapeutic trial).
• Collection of bacterial strains: Either isolated from expectorations from cystic fibrosis patients or from biofilms on the endotracheal tubes of intensive care patients (Staphylococcus aureus and Pseudomonas aeruginosa)

Research Brief :

Despite advances in diagnosis, management and treatment, acute respiratory infections (ARI) remain one of the main causes of death due to infection. One possible explanation is that the host defence response may be inappropriate in term of intensity and duration and thus may contribute to a worsening of the patient's condition.
Therefore, we consider paramount to gain insight into the molecular and cellular mechanisms involved in the interaction between pathogens and the respiratory mucosa by:

i) Characterizing the role of novel mediators such as immunometabolites as well as new key players) of the innate immune response (i.e. Regulatory neutrophils and unconventional T cells) during lung infections

ii) Developing innovative anti-infectious interventions which could pave the way to valuable alternatives strategies for clinicians.
To achieve this, we will capitalise on the knowledge and know-how developed over recent years by the entire team in the fields of anti-infective immunity and microbiology.

• **Methodologies Used :**

- Animal models of respiratory infections and exacerbations (e.g. influenza virus and bacterial infections)
- Culture and characterization of respiratory pathogens
- Analysis of immunometabolism in fluids of animal models (bronchoalveolar lavages, blood,) as well as in ventilated patients (tracheal aspirates,)
- Detailed analysis of innate immune response during respiratory infection (both in mouse models and in humans)
- Clinical studies in patients with acute pneumonia and cystic fibrosis

Publications

Guillon A, Jouan Y, Brea D, Gueugnon F, Dalloneau E, Baranek T, Henry C, Morello E, Renauld JC, Pichavant M, Gosset P, Courty Y, Diot P, Si-Tahar M (2015). Neutrophil proteases alter the interleukin-22-receptor-dependent lung antimicrobial defence, Eur Respir J. 46(3), 771

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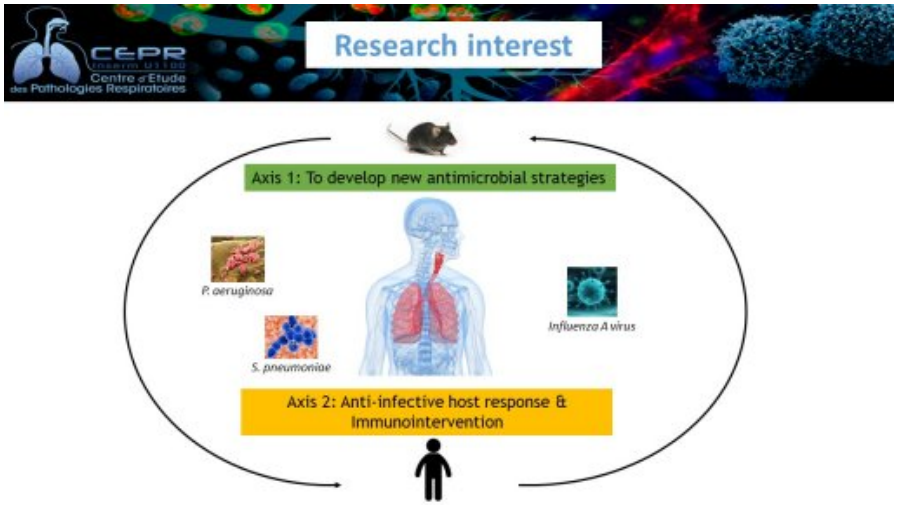
Research interest



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Gilles Lalmanach

Proteolytic mechanisms in inflammation

Université François
Rabelais Tours
Inserm UMR1100
Mustapha Si-Tahar
Tours

Key facts

Team

• Researchers : 10
• Technicians : 2
• Postdoc fellows : 0
• PhD Students : 5

Translational approaches

• Patents : 2
• Clinical research grants : 2
• Industry partnerships : 2

International research links

• Voir le lien: https://cepr.inserm.univ-tours.fr/equipes-/equipe-inserm-2-br-g-lalmanach/collaborations-internationales/

Keywords

• Lung
• Protease
• Protease inhibitor
• inflammation
• COPD, Fibrosis
• Enzymology
• Protein Chemistry
• Cell Biology
• Signaling pathways

Biological Resources

• Annotated collections of frozen lung tissues and derivatives
• Collection of sputa from patients with COPD (GOLD1 to GOLD4)
• Anima model of COPD (+/- exacerbation)

Unique expertise in France in the field of proteolysis. At the crossroads of fundamental/basic sciences and translational clinical approaches.

Research Brief :

Major research axes developed within the team are:

1- Role of pulmonary proteases in inflammatory pathologies:
(a) Regulation of the protease-antiprotease balance in idiopathic pulmonary fibrosis (IPF) and chronic obstructive pulmonary disease (COPD)
(b) Proteolytic regulation of proteins/peptides involved in the innate immunity
(c) Structure-function relationships of neutrophil serine proteases (NSPs), macrophage cysteine cathepsins and kallikrein-related proteinases
(d) Role of proteases in the epithelial?mesenchymal transition (EMT) and in the epithelial integrity
(e) Role of proteases in BM and ECM remodeling

2 - Control of the proteolytic activity in inflammatory pulmonary pathologies
(a) Targeting of NSPs and cysteine cathepsins
(b) Design of pseudopeptidic and biosynthetic analogs of protease inhibitors
(c) Imaging of proteolysis: activity-based probes

• **Methodologies Used :**

- Biochemical analyses (enzymology, peptide design, etc ...)
- Cellular analyses (signaling pathways, etc...)
- Biological analyses (biopsies, tissues, various biological fluids)
- Animal models of human pathologies

Publications

I. E. Valverde, F. Lecaille, G. Lalmanach, V. Aucagne & A. F. Delmas (2012). A biologically active bis-triazolo analogue of cystatin A through successive peptidomimetic alkyne/azide ligations., Angew. Chem. Int. Ed. (),

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Team "Proteolytic mechanisms in inflammation"

Team "Proteolytic mechanisms in inflammation"CEPR/Inserm U100/University of Tours (January 2018)

CIIL
CENTER FOR INFECTION & IMMUNITY OF LILLE

Anne Tsicopoulos

Pulmonary Immunity

Université du Droit et de la
Santé Lille 2, Université de Lille
Inserm, CNRS, Institut Pasteur de Lille, CHRU de Lille U1019, UMR 9017
Jean Dubuisson
Lille

Key facts

Team

• Researchers : 16
• Technicians : 2
• Postdoc fellows : 1
• PhD Students : 2

Translational approaches

• Patents : 3
• Clinical research grants : 5
• Industry partnerships : 2

International research links

• Canada
• USA

Keywords

• Asthma, ARDS, endothelial cells, lymphoid cells
• human cell biology, animal models

Biological Resources

• animal models of asthma and Acute Lung Injury and genetically modified animals
• cohort of asthmatic patients (COBRA)

We evaluate the immunobiology of asthma, by deciphering the mechanisms involving lymphoid and endothelial cells as targets of different environmental determinants involved in the severity of asthma (infections, pollutants, metabolism) and a new molecule endocan as biomarker of ARDS.

Research Brief :

Among respiratory diseases, allergic asthma and pulmonary infections represent major problems of public health. These diseases affect millions of people, are in constant increase and are a major cause of morbidity and mortality. Although considerable therapeutic progress has been made over the last 20 years, there is still no treatment able to modify the natural course of chronic respiratory diseases. These diseases share common key target cells involved in their pathogenesis: the endothelial cells (EC) as a barrier allowing the recruitment of inflammatory cells in the tissues, and the lymphoid cells, as major actors of the immune response to environmental challenges. Our goal is to evaluate how these cells and their mediators can orchestrate the host inflammatory reaction and tissue remodeling in response to allergens, bacteria or stress and to characterize some of the mechanisms involved in the immune response associated with these respiratory diseases in order to highlight potential therapeutic strategies.
The project focus on the mechanisms involved in the regulation of pulmonary immunity by endothelial cells in sepsis and asthma and by lymphoid cells in severe asthma including T cells and Innate Lymphoid Cells (ILC).

• **Methodologies Used :**

Cell biology
Flow cytometry
cell imaging
animal models of diseases
genetically modified animals
genomics
Histology, immunohistochemistry

Publications

Ait Yahia S, Azzaoui I, Everaere L, Vorng H, Chenivesse C, Marquillies P, Duez C, Delacre M, Grandjean T, Balsamelli J, Fanton d'Andon M, Fan Y, Ple C, Werts C, Boneca IG, Wallaert B, Chamaillard M, Tsicopoulos A (2014). CCL17 production by dendritic cells is required for NOD1-mediated exacerbation of allergic asthma, Am J Respir Crit Care Med. 189(8):899-908(),

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Key facts

Team

• Researchers : 27
• Technicians : 9
• Postdoc fellows : 1
• PhD Students : 6

Translational approaches

• Patents : 2
• Clinical research grants : 1
• Industry partnerships : 3

International research links

• Europe, Singapour, United States, Canada

Keywords

• Airway epithelium biology
• Respiratory diseases (CF, COPD, Carcinoma)
• Epithelial-mesenchymal transition
• Epithelium remodeling
• Bacteriology
• Cell imaging
• Cell biology
• Cell culture

Biological Resources

• Human tissues from lungs and nose
• Cohorts of CF and COPD patients
• Biocollection of airway epithelial cells and lung tissues
• In vitro/in vivo models of epithelium regeneration and epithelial cell migration
• Primary cultures of airway epithelial cells
• Clinical bacterial strains

Myriam Polette

Pulmonary Pathologies and Cell Plasticity (P3Cell)

Université de Reims
Champagne-Ardenne
Inserm UMR-S 1250
Myriam POLETTE
Reims

Combine biological and clinical approaches to identify predictive or severity-associated biomarkers of respiratory diseases and to test novel therapeutic strategies to restore a functional airway epithelium

Research Brief :

Respiratory epithelial cell plasticity plays a crucial role in inflammatory diseases such as chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF) as well as in cancers regarding to metastatic progression of Non-Small-Cell Lung Carcinoma (NSCLC). Epithelial cell transdifferentiation characterizes chronic inflammatory respiratory pathologies: epithelium remodeling (basal and secretory cells hyperplasia, squamous cell metaplasia, lack of terminal mucociliary differentiation) interferes with epithelial functional integrity repair. The inflammation and/ or the infection impact the airway epithelium remodeling often leading to severe and irreversible respiratory insufficiency. In addition, the alteration of epithelial regeneration may promote metaplasia or preneoplastic lesions. In this context, epithelial-mesenchymal transition (EMT)-associated dedifferentiation is involved in the tumor progression of NSCLC. We identified two research axes to investigate cell plasticity: epithelial transdifferentiation in the remodeling of the airway epithelium in CF and COPD and epithelial dedifferentiation in the tumor progression of NSCLC. The two main objectives are (1) to characterize biomarkers associated with the severity of the pathology or reveal new phenotypical subclasses of patients for a better care and (2) to highlight those functionally involved to propose innovative therapeutic strategies.

• **Methodologies Used :**

Cell models
Cell and molecular biology
Infection models
Microscopy (Video, confocal, calcium signaling,...)
Histology and immunohistochemistry

Publications

Audrey Joannes, Simon Grelet, Laurent Duca, Christine Gilles, Claire Kileztky, Veronique Dalstein, Philippe Birembaut, Myriam Polette, Beatrice Nawrocki-Raby (2014). Fhit Regulates EMT Targets through an EGFR/Src/ERK/Slug Signaling Axis in Human Bronchial Cells, Molecular Cancer Research. 12(5), 775-83

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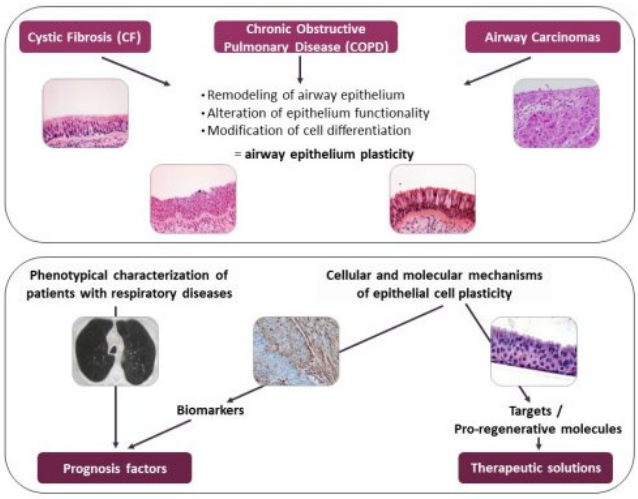
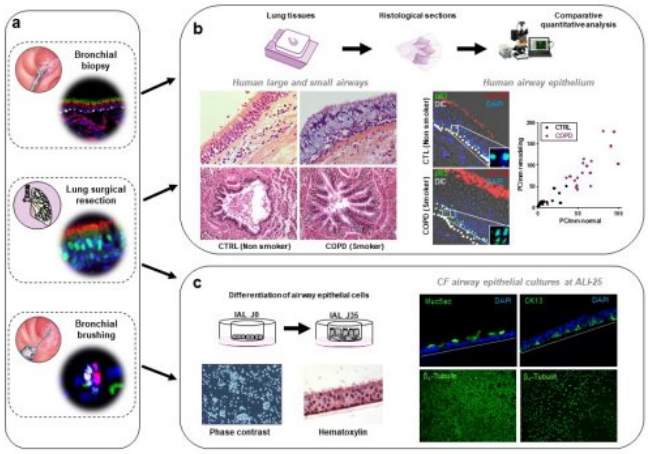
Research strategies

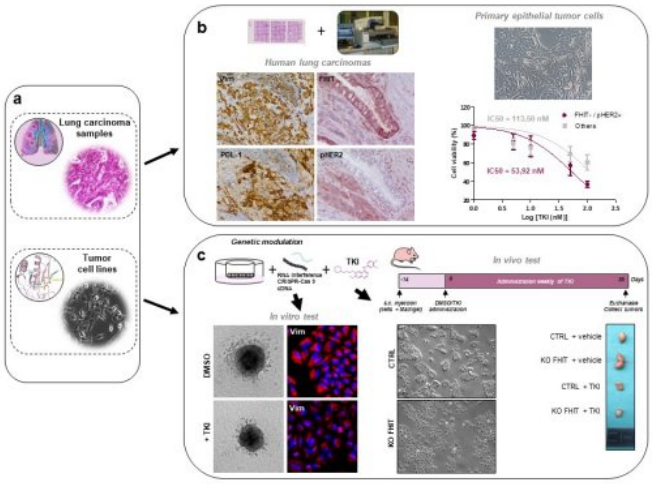


Airway epithelium remodeling and ciliogenesis alteration in CF and COPD



a. Modalities of collection for human lung specimen. b. Lung tissues and bronchial biopsies are formalin-fixed paraffin-embedded to analyze histo-morphologic parameters and identify novel markers. c. Isolated cells from brushes and airway tissues are cultivated in air-liquid interface (ALI) conditions to study epithelial cell differentiation in respiratory diseases and homeostasis.

Predictive biomarkers for targeted therapy in NSCLC



a. Strategy to study the relationship between cell phenotype and sensitivity to targeted therapy in lung cancer. Identification of biomarkers in lung carcinoma by immunohistochemistry. NSCLC patients-derived cells are cultivated to evaluate their sensitivity against therapeutic drugs. c. Analyses of genetically modified tumor cell lines to establish tumor phenotypes as predictive biomarkers for targeted therapy.

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Arnaud Bourdin

Respiratory diseases and the environment

Université Montpellier
Inserm U1046 CNRS UMR9214
Alain Lacampagne
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Gather expertise in all areas involved in COPD onset and progression from air to muscles through lungs, heart, vessels and more

Key facts

Team

- Researchers : 21
- Technicians : 4
- Postdoc fellows : 0
- PhD Students : 8

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- Chronic airway diseases
- Skeletal muscle
- Non-coding RNA
- Epigenetics
- Telerehabilitation
- Airway epithelium
- Satellite cells
- AON antisense
- DNA methylation profiling

Biological Resources

- Biobanking (biopsies, human serum, ALI cultures, iPS, animals, COBRA cohort)
- 3D epihelium reconstituted from human samples

Research Brief :

The quality of the air we breathe has a major impact on our health, particularly on the pulmonary system, with consequences for the cardiovascular and muscular systems. In a context of multiple, complex and changing environmental exposures, the objective of our team is to understand why some are protected and others develop respiratory failure. Through clinical and fundamental studies on animal and cellular models, we study the physiological, molecular and epigenetic mechanisms responsible for alterations in heart-lung interactions and in the development of muscular and vascular comorbidities for respiratory pathologies in response to specific exhibitions.

- **Methodologies Used :**

Air Liquid Interface Cultures, iPSC, cellular models, animal models, molecular Biology, Pyrosequencing (Pyromark)

Publications

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GRED GENETIQUE REPRODUCTION & DEVELOPPEMENT

Vincent Sapin Loïc Blanchon

Translational approach to epithelial injury and repair

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CNRS UMR6293 Inserm 1103
Krzysztof JAGLA
Clermont-ferrand

Key facts

Team

• Researchers : 12
• Technicians : 2
• Postdoc fellows : 2
• PhD Students : 6

Translational approaches

• Patents : 0
• Clinical research grants : 1
• Industry partnerships : 2

International research links

• USA (Tennessee, New-York, California, Texas)
• CANADA (Quebec)

Keywords

• Lung and fetal membranes
• ARDS
• PROM
• Pathophysiology
• RAGE
• Molecular biology
• Cellular Biology
• Animal models
• Clinical research

Biological Resources

• Cirspr CAS9 cells for RAGE and
NLRP
• Fetal membrane cohots and explants
• Mice model for ARDS
• RAGE -/- mice
• Primary and immortalized cells

Team working on lung and fetal membrane epithelial injury and repair by using translational approaches.

Research Brief :

Following exo- and endogenous attacks, the attainment of the epithelial barrier integrity is an element found in human pathologies. The ability to repair such an epithelial attack conditions the evolution of these clinical events. Located at the intersections of many metabolic and inflammatory processes, the receptor for advanced glycation endproducts (RAGE) and its pathway could be of primary importance in this situation. The team has begun to demonstrate it on models of epithelial amniotic and pulmonary aggression encountered in 2 frequent pathologies (premature rupture of amniotic membranes (PROM) and acute respiratory distress syndrome (ARDS). Considering the complexity of the possible "RAGE ligand/isoform" combinations associated with the pathological activation of this pathway, it's essential to identify the importance of these different combinations and to determine if new ligands could be involved in PROM and ARDS. Using pharmacological and molecular approaches, we will identified abnormally modulated pathways that could be associated with the arising of both pathologies. Then, as the interaction of the epithelium with the cells of its near environment is a strong determinant of such aggression, the project aims to demonstrate the importance of RAGE pathway in cellular communications. Finally, availability of a mouse KO for RAGE will also allow us to study, in vivo, such impacts. Our results must permit to obtain diagnostic, prognostic and therapeutic advances.

• **Methodologies Used :**

- Cloning
- Cell tranfection
- Promotology studies and reporter gene
- Microscopy
- Western-blot
- qPCR
- Multiplex assay
- Elisa
- Crispr CAS9

Publications

Audard J, Godet T, Blondonnet R, Joffredo JB, Paquette B, Belville C, Lavergne M, Gross C, Pasteur J, Bouvier D, Blanchon L, Sapin V, Pereira B, Constantin JM, Jabaudon M (2016). Inhibition of the Receptor for Advanced Glycation End-Products in Acute Respiratory Distress Syndrome: A Randomised Laboratory Trial in Piglets., Scientific reports. 9(1), 9227

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Zhai R , Blondonnet R, Ebrahimi E, Belville C, Audard J, Gross C, Choltus H, Henrioux F, Constantin JM , Pereira B, Blanchon L, Sapin V, Jabaudon M (2020). The receptor for advanced glycation end-products enhances lung epithelial wound repair: An in vitro study, Exp. Cell. Res.. 391(2), 112030

Choltus H, Lavergne M, Belville C, Gallot D, Minet-Quinard R, Durif J, Blanchon L, Sapin V (2020). Occurrence of a RAGE-Mediated Inflammatory Response in Human Fetal Membranes, Front. Physiol.. 11(581),

Lavergne M, Belville C, Choltus H, Gross C, Minet-Quinard R, Gallot D, Sapin V, Blanchon L (2020). Human Amnion Epithelial Cells (AECs) Respond to the FSL-1 Lipopeptide by Engaging the NLRP7 Inflammasome, Front. Immunol.. 11(1645),

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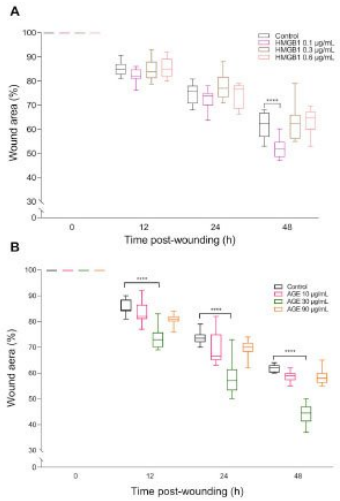
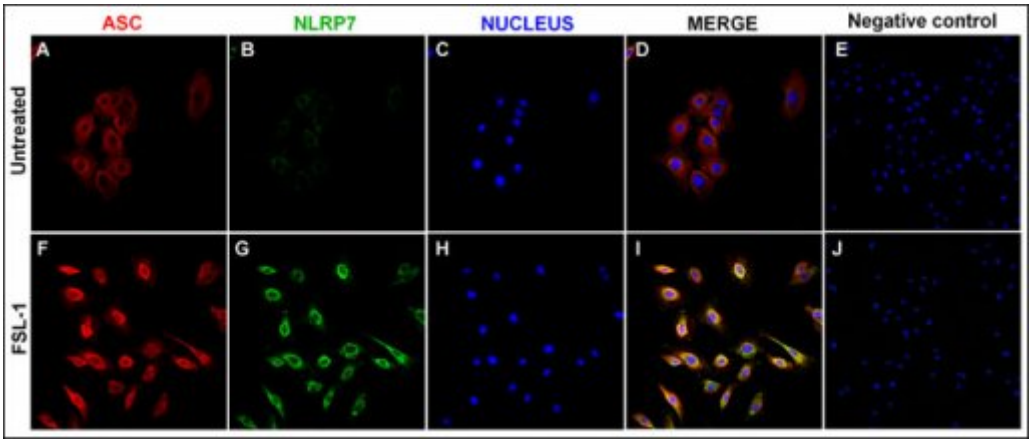
Dose response effect of HMGB1 and AGEs on the wound healing of lung A549 cells



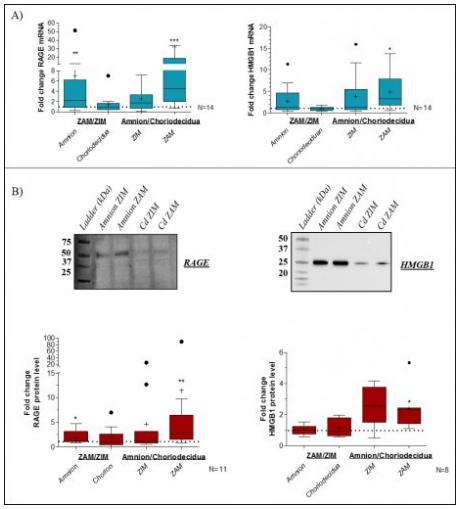
A and B] Wound healing was assessed up to 48H using a scratch assay of A549 cells treated with culture medium (control) of with different concentrations of HMGB1 and AGE.

NLRP7 and ACS colocalize in response to FSL-1 in AEC.



Immunofluorescence assay of AEC treated (F-J) or not (A-E) with 250ng/mL of FSL-1 during 20 hours. ASC proteins were stained in red (A, F), NLRP7 proteins in green (B, G) and nucleus in blue with the Hoescht staining (C, H). Merge pictures are seen in D and I. Negative controls, corresponding to secondary antibodies incubation without primary antibodies

Quantification of RAGE and HMGB1 expression in human fetal membranes at term in the ZIM and ZAM.



RAGE and HMGB1 expression were quantified by RT-qPCR (A) and western blot (B) on the amnion and choriodecidua (Cd) at term in the ZIM (Zone of intact morphology) and ZAM (Zone of Altered Morphology). To highlight an area (ZAM versus ZIM) or tissue effect (Amnion versus Choriodecidua), ZIM was reported to ZAM, or Amnion to Choriodecidua. * means p

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Dermatology

Catherine Moali

Metalloproteinases and tissue remodeling

Université Claude Bernard
Lyon I
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Dominique Sigaudo-Roussel
Lyon

We want to exploit therapeutic targets from the collagen biosynthesis machinery based on our detailed analysis of their activities and mechanisms of action. Our research can find applications in skin wound healing and all tissue repair processes.

Key facts

Team

- Researchers : 2
- Technicians : 1
- Postdoc fellows : 1
- PhD Students : 2

Translational approaches

- Patents : 1
- Clinical research grants : 1
- Industry partnerships : 4

International research links

- Germany
- UK

Keywords

- Fibrosis
- Collagen
- Proteolysis
- Tissue Repair
- Skin
- Biochemistry
- Proteomics
- Cell Biology
- Animal models

Biological Resources

- heart, skin and cornea primary cells
- biobank of human left ventricule samples shared with CHU Dijon

Research Brief :

Our group focusses on a subfamily of metalloproteinases, known as the BMP-1/tolloid-like proteinases (BTPs), which were first described for their important role in collagen fibrillogenesis. Indeed, by cleaving the C-terminal propeptides of collagens I, II and III, BTPs trigger collagen fibril formation. They also control the proteolytic maturation of several extracellular matrix proteins and regulate the activity of several growth factors (TGF-?, BMP-2/4/11, GDF8, IGF) with the capacity to synchronize matrix assembly with growth factor activation in order to promote tissue morphogenesis and remodeling. Therefore, they play an essential role in development, bone remodeling and tissue repair. It is also important to note that these proteinases are part of a complex network involving regulatory proteins and other proteinases which can potentially cleave the same substrates, leading to interesting mechanisms of synergy, inhibition or competition.

Our main objective is to better understand the functions of the BTPs and of their main partners (substrates, regulatory proteins, associated proteinases) in the context of tissue repair, in order to propose novel therapeutic strategies to be applied to human diseases such as fibrosis, chronic wounds or corneal scarring. To achieve this, we use a combination of complementary approaches including biochemistry, structural biology, enzyme assays, proteomics, cell biology and animal models.

- **Methodologies Used :**

- Biochemistry and structural biology
- Proteomics
- Cell Biology
- Animal models
- Analysis of patient samples

Publications

David Pulido 1 , Urvashi Sharma 2 , Sandrine Vadon-Le Goff 3 , Sadaf-Ahmahni Hussain 1 , Sarah Cordes 1 , Natacha Mariano 3 , Emmanuel Bettler 3 , Catherine Moali 3 , Nushin Aghajari 2 , Erhard Hohenester 4 , David J S Hulmes (2018). Structural Basis for the Acceleration of Procollagen Processing by Procollagen C-Proteinase Enhancer-1, Structure. 26(10), 1384

Maya Talantikite 1 , Pascaline Lécorché 2 , Fabrice Beau 2 , Odile Damour 1 3 , Christoph Becker-Pauly 4 , Wen-Bin Ho 5 , Vincent Dive 2 , Sandrine Vadon-Le Goff 1 , Catherine Moali (2018). Inhibitors of BMP-1/tolloid-like proteinases: efficacy, selectivity and cellular toxicity, FEBS Open Bio. 8(12), 2011

Stefanie Elisabeth Heumüller 1 , Maya Talantikite 2 , Manon Napoli 2 , Jean Armengaud 3 , Matthias Mörgelin 4 , Ursula Hartmann 1 , Gerhard Sengle 1 5 6 7 , Mats Paulsson 1 5 6 8 , Catherine Moali 9 , Raimund Wagener (2019). C-terminal proteolysis of the collagen VI ?3 chain by BMP-1 and proprotein convertase(s) releases endotrophin in fragments of different sizes, The Journal of Biological Chemistry. 294(37), 13769

Cyril Anastasi 1 , Patricia Rousselle 1 , Maya Talantikite 1 , Agnès Tessier 1 , Caroline Cluzel 1 , Alice Bachmann 1 , Natacha Mariano 1 , Mélissa Dussoyer 1 , Lindsay B Alcaraz 2 , Laëtitia Fortin 1 , Alexandre Aubert 1 , Frédéric Delolme 1 3 , Naïma El Kholti 1 , Jean Armengaud 4 , Pierre Fournié 5 6 , Céline Auxenfans 1 7 , Ulrich Valcourt 1 2 , Sandrine Vadon-Le Goff, Catherine Moali (2020). BMP-1 disrupts cell adhesion and enhances TGF-? activation through cleavage of the matricellular protein thrombospondin-1, Science Signaling. 13(639), eaba3880

Priscillia Lagoutte, Emmanuel Bettler, Sandrine Vadon-Le Goff, Catherine Moali (2021). Procollagen C-proteinase enhancer-1 (PCPE-1), a potential biomarker and therapeutic target for fibrosis, Matrix Biology Plus. 11(), 100062

Priscillia Lagoutte, Alexandra Oudot, Mélissa Dussoyer, Victor Goncalves, Mélanie Guillemin, Olivier Bouchot, David Vandroux, Pierre-Simon Bellaye, Catherine Moali, Sandrine Vadon-Le Goff (2021). Procollagen C-Proteinase Enhancer 1 (PCPE-1) is a marker of myocardial fibrosis and impaired cardiac function in a murine model of pressure overload, BioRxiv. (),

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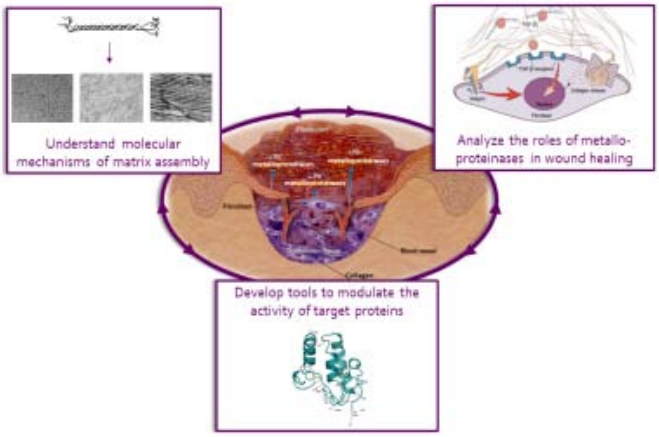
Summary of our main research axes.



We study the molecular mechanisms (both proteolytic and non proteolytic) of extracellular matrix assembly and the role of various metalloproteinases and their regulatory proteins in wound healing and tissue repair. In addition, we develop synthetic and protein inhibitors of the most promising therapeutic targets identified in above studies. Pictures adapted from Singer et al. N. Engl. J. Med. 1999, Schultz et al. Wound Repair Regen. 2009 and Binz et al. Nat. Biotechnol. 2004.

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Diabetes

Corinne Leloup

Brain nutrient sensing and energy homeostasis

Université de Dijon
(Université de Bourgogne)
CNRS UMR 6265 INRA UMR1324
Loïc Briand
Dijon

Combination of multiple in vivo and in vitro studies to explore the detection of nutrient in the brain. (animal models) Multiple approaches (Prefquest to Gustatory evoked potentials) to study preferences and gustatory detection in metabolic pathologies with eating disorders. (Human beings)

Key facts

Team

• Researchers : 5
• Technicians : 4
• Postdoc fellows : 0
• PhD Students : 1

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 1

International research links

• Suisse
• Etats-Unis

Keywords

• hypothalamic glucose sensing
• obesity and diabetes
• mitochondria, fission, ROS signaling
• food intake and nervous control of energy metabolism
• astrocytes, glial networks
• Human studies on feeding behaviour
• preferences, liking/wanting, taste exploration
• Human metabolic disorders/eating disorders
• electrophysiological studies (on brain in vivo; ex-vivo; on freshly isolated islets)
• mitochondrial exploration (oxygraphy)
• freshly isolated hypothalamic cells and pancreatic islets/Ca+ imaging
• stereotaxy for brain injection
• hyperinsulinemic euglycemic clamp
• Gustatory evoked potentials

Biological Resources

• in vivo/vitro hypothalamic models to study obesity and diabetes
• Human beings for metabolic pathologies associated with eating disorders

Research Brief :

The brain participates in energy homeostasis by regulating both energy intake and metabolism. The hypothalamus in particular monitors nervous, hormonal and metabolic signals and integrates them to elicit adaptive responses. The hypothalamus is sensitive to glucose whose blood level is tightly regulated and has profound effects on some hypothalamic neurons. These hypothalamic glucose changes then participate in food intake and numerous peripheral controls, for instance insulin secretion or hepatic glucose production. Our research focuses on hypothalamic glucose sensing mechanisms, especially the detection of increased blood glucose levels, and gustatory detection in Humans and the relationships between these detections and energy homeostasis. In particular, our studies are aimed at 1) deciphering cellular and molecular mechanisms involved in hypothalamic glucose sensing (especially those of mitochondria, the role of the astroglial networks), 2) determining its importance both in physiology and pathology (obesity, diabetes) on food intake and nervous control of peripheral organs , 3) exploring similarities of the glucose sensing mechanism with the pancreatic beta-cell, and finally 4) identifying changes in gustatory nutrient sensing and preferences in metabolic human pathologies associated with changes in food intake.

• **Methodologies Used :**

Stereotaxic brain injections:drugs, viral particles or siRNA
Food intake and metabolic characterizations (functional tests for physiology exploration: refeeding, hyperinsulinemic/ eu(hypo)glycemic clamps, glucose and insuline tolerance tests, targeting the brain through carotid injection), preference/aversion and electrophysiological gustatory study through evoked potentials recording (Humans)
Mitochondrial exploration: oxygraphy (OXPHOS studies), ROS production, antioxidant defences, redox metabolism
Patch clamp recordings on acute hypothalamic brain slices and in vivo electrophysiological recordings
Ca2+ imaging on hypothalamic freshly dissociated cells
Single cell RT-PCR, qPCR, immunohistochemistry

Publications

Colombani AL, Carneiro L, Benani A, Galinier A, Jaillard T, Duparc T, Offer G, Lorsignol A, Magnan C, Casteilla L, Pénicaud L, Leloup C (2009). Enhanced hypothalamic glucose sensing in obesity: alteration of redox signaling, Diabetes. 58(10), 2189-97

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Kim JH, Meyers MS, Khuder SS, Abdallah SL, Muturi HT, Russo L, Tate CR, Hevener AL, Najjar SM, Leloup C, Mauvais-Jarvis F (2014). Tissue-selective estrogen complexes with bazedoxifene prevent metabolic dysfunction in female mice., Molecular Metabolism. 3(2), 2014

Allard C, Carneiro L, Grall S, Cline BH, Fioramonti X, Chrétien C, Baba-Aissa F, Giaume C, Pénicaud L, Leloup C (2014). Hypothalamic astroglial connexins are required for brain glucose sensing-induced insulin secretion, Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 34(2), 339-46

Jacquin-Piques A, Mouillot T, Gigot V, Meillon S, Leloup C, Penicaud L, Brondel L (2016). Preference for Sucrose Solutions Modulates Taste Cortical Activity in Humans, Chemical Senses. 41(7), 591-9

Chrétien C, Fenech C, Liénard F, Grall S, Chevalier C, Chaudy S, Brenachot X, Berges R, Louche K, Stark R, Nédélec E, Laderrière A, Andrews ZB, Benani A, Flockerzi V, Gascuel J, Hartmann J, Moro C, Birnbaumer L, Leloup C, Pénicaud L, Fioramonti X (2017). Transient Receptor Potential Canonical 3 (TRPC3) Channels Are Required for Hypothalamic Glucose Detection and Energy Homeostasis, Diabetes. 66(2), 314-324

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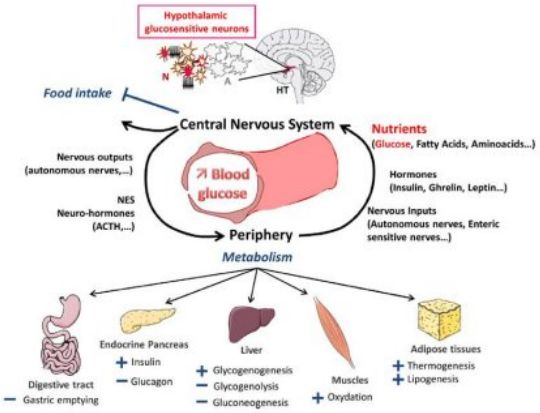
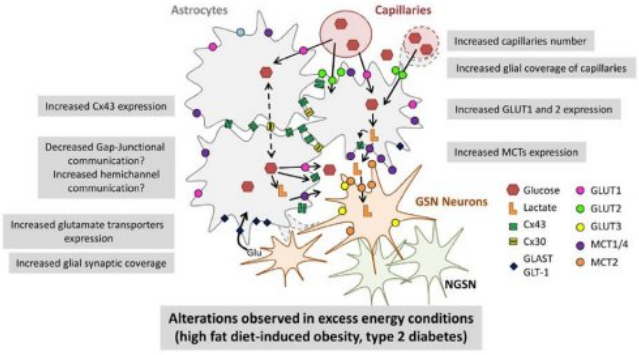
physiological responses after hypothalamic glucose detection



Major actors of hypothalamic glucose detection- Alterations in obese, diabetic models



GSN: glucosensitive neurons

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Mireille Cormont
Jean-François Tanti

Cellular and Molecular Pathophysiology of Obesity and Diabetes

Université Côte d'Azur
Inserm U1065
Patrick Auberger
NICE

Our team performs studies from molecular to cells and animal level in order to have an integrative view of the dysfunction of adipose tissue and metabolism linked to obesity and diabetes

Key facts

Team

• Researchers : 6
• Technicians : 0
• Postdoc fellows : 0
• PhD Students : 5

Translational approaches

• Patents : 1
• Clinical research grants : 0
• Industry partnerships : 1

International research links

• Italia
• Czech Republic
• Sweden

Keywords

• obesity
• diabetes
• insulin resistance
• adipose tissue
• signaling
• glucose transport
• trafficking
• Inflammation
• real-time RT-qPCR
• cell imaging
• 3D adipose tisssue imaging
• adipocyte transfection
• primary adipocyte culture
• primary mouse hepatocyte culture
• Western blot
• animal metabolism
• glucose and lipid metabolism in cells and organs

Biological Resources

• antibodies
• model of obese mice
• primary adipocytes
• primary macrophages

Research Brief :

Our team aims to identify cellular and molecular mechanisms that link the pathological remodelling and dysfunction of adipose tissue in obesity to the development of insulin resistance, a central metabolic abnormality in the pathogenesis of type 2 diabetes and metabolic syndrome. By combining multidisciplinary approaches, our research is organized in three highly integrated core programs: 1) the identification of how metabolic stresses contribute to adipose tissue dysfunction and insulin resistance; 2) the study of the impact of altered endosomal trafficking on metabolic dysfunction and insulin resistance in adipose tissue and the liver; and 3) the identification of novel signalling pathways which could mitigate the pathological expansion of adipose tissue.Our research has contributed to significant advances in the identification of new mechanisms involved in insulin resistance, allowing us to propose new targets to fight insulin resistance and decrease the risk of developing type 2 diabetes.

• **Methodologies Used :**

Primary human adipocytes in culture
Cell signaling and gene expression quantification
Metabolic studies in isolated adipocytes and muscles and in animals
Cellular imaging of protein trafficking
3D adipose tissue imaging by 3DISCO technic
Animal models of obesity and diabetes (KO mice, High-Fat diet and genetically obese mice)

Publications

Vergoni B, Cornejo PJ*, Gilleron J, Djedaini M, Ceppo F, Jacquel A, Bouget G, Ginet C, Gonzalez T, Maillet J, Dhennin V, Verbanck M, Auberger P, Froguel P, Tanti JF*, Cormont M*. (2016). DNA Damage and the Activation of the p53 Pathway Mediate Alterations in Metabolic and Secretory Functions of Adipocytes, Diabetes. 65(10), 3062-74*

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Key facts

Team

- Researchers : 5
- Technicians : 6
- Postdoc fellows : 1
- PhD Students : 5

Translational approaches

- Patents : 4
- Clinical research grants : 3
- Industry partnerships : 5

International research links

- Belgium, Italy, Germany, Switzerland, Sweden, Finland, UK
- Australia, USA

Keywords

- Diabetes
- Obesity
- MAIT-NKT cell
- Treg cell
- Genetics
- Epitopes
- Pancreatic islet
- Humanized mice
- Immunometabolism

Biological Resources

- PBMC of diabetic patients
- Cohorts of diabetes patients
- Transgenic mice

Agnès Lehuen

Immunology of diabetes

Université de Paris
Inserm U1016 CNRS UMR8104
Florence Niedergang
Paris

We are studying innate and adaptative immune cells and genetics in diabetes and obesity.

Research Brief :

We are investigating immune cell cross-talks and genetics in type 1 and type 2 diabetes (T1D, T2D) and obesity, with focus on adaptive and innate immune cells. Our projects may provide targets for understanding disease mechanisms, discovering biomarker and developing innovative therapeutic strategies. Specific aims: 1) To determine the role of innate-like T cells in the regulation of T1D. Natural Killer T (NKT) and MAIT cells are non-conventional T cells that act as sensors of metabolic abnormalities and can regulate both innate and adaptive immunity, and are efficient in the prevention of T1D. 2) To determine the role of innate-like T cells in T2D, obesity and non-alcoholic liver steatosis. In T2D and obese patients MAIT cells produce high levels of inflammatory cytokines in the adipose tissue. MAIT cells are profibrogenic in the liver of nonalcoholic steatohepatitis (NASH)-related cirrhotic patients. In obese mice, MAIT cells are pro-inflammatory and modify the structure and the homeostasis of adipose tissue and ileum. 3) To analyse 'humanized' mouse models mimicking human T1D and to understand co-stimulatory pathways, to launch clinical trials exploring vaccination strategies with beta-cell antigens aimed at restoring immune tolerance. 4) To determine genetic factors involved in the diversity of juvenile-onset diabetes, ranging from multifactorial T1D to monogenic forms of diabetes whose clinical presentation may be atypical or not.

- **Methodologies Used :**

Cytometry including Cytek
Functional assays using mouse models
Cellular assays
RNA-Sequencing
RT-PCR analysis
Genotyping and sequencing, including GWAS, WES, WGS and Sanger sequencing
Statistical genetics, bioinformatics analyses

Publications

Rouxel O., J. Da silva*, L. Beaudoin*, I. Nel, C. Tard, L. Cagninacci, B. Kiaf, M. Oshima, M. Diedisheim, M. Salou, A. Corbett, J. Rossjohn, J. McCluskey, R. Scharfmann, M. Battaglia, M. Polak, O. Lantz, J. Beltrand, and A. Lehuen (2017). Cytotoxic and regulatory role of mucosal-associated invariant T cells in type 1 diabetes, Nature Immunology. 18(12), 1321-1331*

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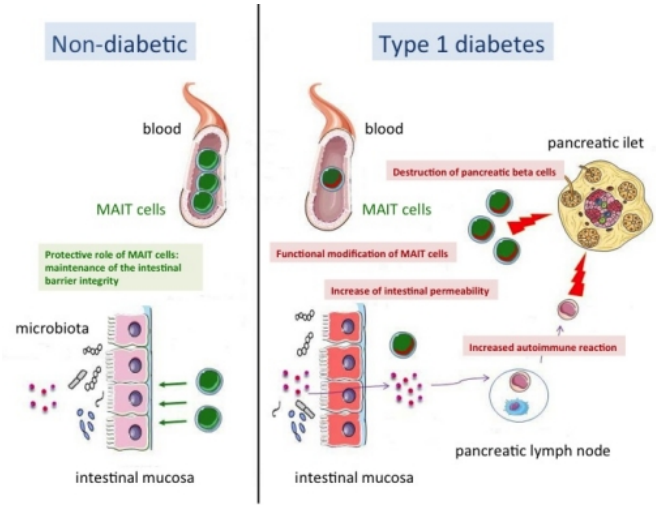
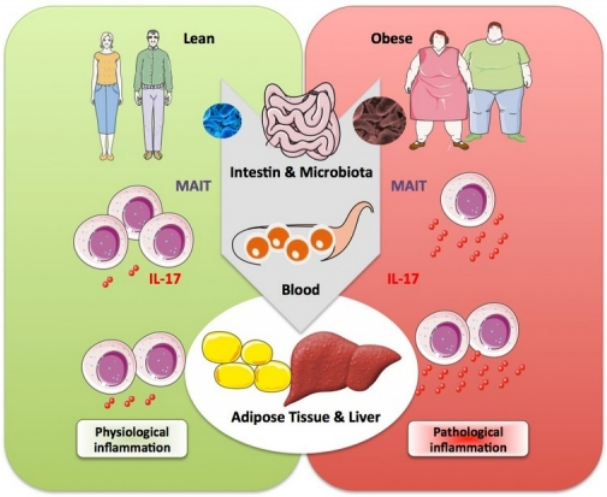
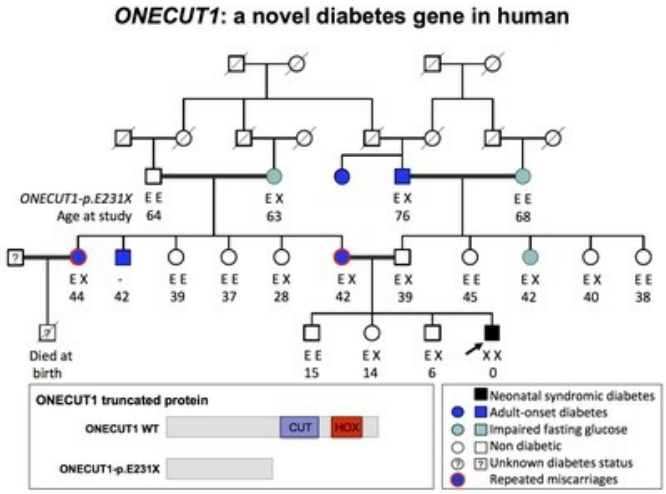
Role of MAIT cells in type 1 diabetes



Role of MAIT cells in obesity



Gene identification in diabetes



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Key facts

Team

- Researchers : 3
- Technicians : 3
- Postdoc fellows : 5
- PhD Students : 2

Translational approaches

- Patents : 3
- Clinical research grants : 3
- Industry partnerships : 8

International research links

- Denmark, Germany, Nederland, USA

Keywords

- Pancreas
- islets
- beta and alpha cells
- development
- function
- in vitro bioassays
- in vivo bioassays

Biological Resources

- Human beta cell lines
- Rodent bioassays for cell differentiation
- Protocols to prepare and analyze the function of cell populations derived from islets (alpha, beta and delta cell populations))

Raphaël Scharfmann

Control of pancreatic endocrine cell development

Université de Paris
Inserm U1016
Florence Niedergang
Paris

We have gained expertise in developing assays in reconstituted rodent and human models to define intercellular signals regulating pancreatic beta cell development and function in physiological and pathological (diabetes) conditions..

Research Brief :

Type-1 diabetes is caused by an autoimmune destruction of insulin producing beta cells resulting in insulin deficiency. Insulin therapy is unsatisfactory. Thus defining new strategies (cell or regenerative therapies) as basis to cure diabetic patients represents a major challenge. Beta cells develop from pancreatic progenitors that proliferate and next differentiate into functional insulin-producing cells. This is a complex process, each step being controlled by specific signals. Theoretically, beta cell mass can be enhanced by: i) activating the proliferation of pancreatic progenitors; ii) activating their differentiation into beta cells; iii) activating the proliferation of beta cells themselves. During the past years, we developed tools based on rodent models to search for signals controlling each step of beta cell development. We developed strategies to transfer to reconstituted human models, data generated in rodent models. We also developed the first available human beta cell lines (a premiere). We generated new results and hypotheses concerning signals controlling each step of pancreatic development. We also dissected specific forms of neonatal diabetes in Human, which permits to define new treatments for children with neonatal diabetes. We are currently continuing this work which is important on a cognitive point of view, but also to define new approaches to find a cure for diabetes.

- **Methodologies Used :**

Bioassays to define signals regulating beta cell development.
In vitro and in vivo bioassays.
Reconstituted rodent and human bioassays.
Methodologies to develop human beta cell lines.

Publications

Chandra V, Albagli-Curiel O, Hastoy B, Piccand J, Randriamampita C, Vaillant E, Cavé H, Busiah K, Froguel P, Vaxillaire M, Rorsman P, Polak M, Scharfmann R. (2014). RFX6 Regulates Insulin Secretion by Modulating Ca2+ Homeostasis in Human Beta Cells., Cell Reports. (),

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Characterization of sorted-cell populations from human fetal pancreata

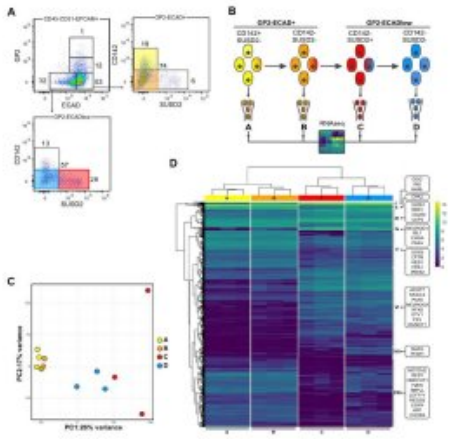

Figure 1: Characterization of sorted-cell populations from human fetal pancreata by RNAseq. This figure is a reproduction from Ramond C...Scharfmann R, Development 2018 (PMID: 30042179)

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Roberto Mallone Sylvaine You

DeARLab - Diabetes & Autoimmunity Research Laboratory

Université Paris Descartes
Paris 5
Inserm U1016
Florence Niedergang
Paris

Innovative technologies are developed to move towards 'immune staging' strategies that may offer novel diagnostic and therapeutic options for autoimmune diseases.

Key facts

Team

• Researchers : 3
• Technicians : 6
• Postdoc fellows : 4
• PhD Students : 4

Translational approaches

• Patents : 5
• Clinical research grants : 2
• Industry partnerships : 4

International research links

• Belgium
• Denmark
• USA

Keywords

• type 1 diabetes
• T cell
• beta cell
• antigen
• tolerance
• HLA tetramer
• Tolerogenic vaccines
• T-cell cloning
• TCR sequencing / re-expression
• Cytotoxicity

Biological Resources

• ImMaDiab/BeAT1D cohort & biobank
• TRAKR cohort & biobank
• INNODIA cohort & biobank
• Autoimmune T-cell clones and related TCRs

Research Brief :

Type 1 diabetes (T1D) prevalence is steadily increasing in industrialized countries, with an incidence of 15 new diagnoses/100,000 inhabitants/year in France, which further increases of 3-4% every year. As it mainly affects children and young adults leading to lifelong treatments and frequent long-term complications (cardiovascular diseases, end-stage renal failure, blindness), it is a highly debilitating disease and an important voice of public health expense.

Type 1 diabetes (T1D) is an autoimmune disease caused by autoreactive T lymphocytes which destroy insulin-producing pancreatic islet beta-cells. Despite this knowledge, neither the diagnosis nor the therapy of T1D targets pathogenic T lymphocytes. Our research projects therefore aim at exploiting these T lymphocytes as disease biomarkers and as therapeutic targets to prevent beta-cell destruction, and at understanding the cross-talk between T lymphocytes and pancreatic beta cells.

The long-term objective is to develop an immune "staging" and intervention protocol in subjects at risk for T1D development, in order to detect and block beta-cell autoimmunity at an early stage. The strategies developed may lead to a paradigm shift in the approach to T1D by identifying and treating the immune disease early, before the appearance of its metabolic consequences. By targeting the mechanisms underlying disease development, such strategies would pave the way to T1D prevention and treatment.

• **Methodologies Used :**

* Human and mouse models
* Cell culturing and T-cell cloning
* Flow cytometry and HLA tetramers
* ELISpot

Publications

Culina S, Gupta N, Boisgard R, Afonso G, Gagnerault MC, Dimitrov J, Østerbye T, Justesen S, Luce S, Attias M, Kyewski B, Buus S, Wong FS, Lacroix-Desmazes S, Mallone R (2015). Materno-Fetal Transfer of Preproinsulin Through the Neonatal Fc Receptor Prevents Autoimmune Diabetes., Diabetes. 64(10), 3532-42

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Key facts

Team

- Researchers : 4
- Technicians : 5
- Postdoc fellows : 1
- PhD Students : 4

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- United States
- Europe

Keywords

- Circadian rhythm
- Nuclear receptors
- Metabolic and cardiovascular diseases
- Pharmacology
- Inflammation, immune disorders
- Metabolic phenotyping
- FACS
- 3D imaging of cleared tissue
- Molecular biology
- Cell lines and primary cell culture

Biological Resources

- Genetically-modified mouse models (tissue-specific KO/Tg models, AAV) (Crispr/Cas9)
- Ex vivo cultured human/mouse primary macrophages, endothelial cells, smooth muscle cells, satellite cells, isolated skeletal muscle muscle fibers, AAV/adenovirus-infected
- Human biopsies/samples (vascular tissue, liver, PBMCs, muscle)

Hélène Duez

Delineating the functIon of nUclear Receptors iN circAdian bioLogy (DIURNAL)

Lille
Inserm UMR1011 Institut Pasteur de Lille UMR1011
Bart Staels
LILLE

We study the cellular and molecular mechanisms that maintain circadian metabolic and immune homeostasis, the contribution of the nuclear receptors Rev-erba/b and RORa, among others, and their use as therapeutic targets to prevent/treat pathophysiological conditions linked to clock disruption

Research Brief :

The biological clock has long been known to play crucial roles in several aspects of physiology. For instance, it generates circadian rhythms in sleep patterns, blood pressure, the immune response, cell cycle and metabolism. Clock disruption, as seen in shiftwork, frequent jetlag, extended light exposure and feeding period, and social jetlag (different schedules between work days and days off), increases the risk of developing a myriad of pathologies including metabolic (obesity, type 2 diabetes, NASH), inflammatory and cardio-vascular (atherosclerosis, myocardial infarction) disorders. Focusing on Rev-erbs and RORs, our goal is to unravel the cellular and molecular mechanisms by which the clock impacts metabolism and inflammation in several patho-physiological contexts, particularly metabolic, cardio-vascular and muscle diseases. We also aim at determining whether and how pharmacological modulation of these nuclear receptors prevents clock disruption or restores circadian rhythmicity in genes/proteins/inflammatory mediators/metabolites and ameliorates these pathological conditions. Beside interactions developed with other teams of the unit, our team is engaged in local, national and international collaborations to complement our research expertise and extend our investigation into translational studies.

- **Methodologies Used :**

- Molecular biology (CRISPR, viruses, gene silencing, RNA and protein analysis, ChIP, etc)
- in vivo (Treadmill coupled to gas analysis, metabolic cages, etc) and in cellulo (Seahorse, Oroboros) metabolic phenotyping
- Imaging (immunofluorescence, histology, RNAscope, tissue clearing and whole-organ imaging, confocal, multiphoton and lightsheet microscopy, Muscle J for muscle analysis, Imaris for 3D-reconstruction)
- Cytometry and cell sorting (immunophenotyping, purified cell isolation)
- Cell culture: cell lines and primary human and murine cells
- In vivo experimentation (tissue-specific genetically modified mice, diet & light intervention, injury, inflammatory stress)

Publications

*Woldt E. *, Sebti Y. *, Solt L.A., Duhem C., Lancel S., Eeckhoute J., Hesselink M.K.C., Paquet C., Delhaye S., Shin Y., Kamenecka T.M., Schaart G., Lefebvre P., Nevière R., Burris T.P., Schrauwen P., Staels B., Duez H. (2013). Rev-erb-a modulates skeletal muscle oxidative capacity by regulating mitochondrial biogenesis and autophagy, Nature Medicine. 19(8), 1039-1046*

Lancel S, Hesselink MK, Woldt E, Rouillé Y, Dorchies E, Delhaye S, Duhem C, Thorel Q, Mayeuf-Louchart A, Pourcet B, Montel V, Schaart G, Breton N, Picquet F, Briand O, Salles JP, Duez H, Schrauwen P, Bastide B, Bailleul B, Staels B, Sebti Y (2018). 'Endospanin-2 enhances skeletal muscle energy metabolism and running endurance capacity, JCI Insight. 3(9), doi: 10.1172/jci.insight.98081

Pourcet B, Zecchin M*, Ferri L, Beauchamp J, Sitaula S, Billon C, Delhaye S, Vanhoutte J, Mayeuf-Louchart A, Thorel Q, Haas J, Eeckhoute J, Dombrowicz D, Duhem C, Boulinguiez A, Lancel S, Sebti Y, Burris T, Staels B and Duez H (2018). Nuclear Receptor Subfamily 1 Group D Member 1 (Rev-erb-a) Regulates Circadian Activity Of NLRP3 Inflammasome to Reduce the Severity of Fulminant Hepatitis in Mice, Gastroenterology. 154(5), 1449-1464.e20*

Montaigne David, Maréchal Xavier, Modine Thomas, Coisne Augustin, Mouton Stéphanie, Fayad Georges, Ninni Sandro, Klein Cédric, Ortmans Staniel, Seunes Claire, Potelle Charlotte, Berthier Alexandre, Gheeraert Celine, Piveteau Catherine, Deprez Rebecca, Eeckhoute Jérome, Duez Hélène, Lacroix Dominique, Deprez Benoit, Jegou Bruno, Koussa Mohamed, Edme Jean-Louis, Lefebvre Philippe, Staels Bart (2018). Day-time variation of peri-operative myocardial injury in cardiac surgery and its prevention by Rev-erba antagonism: a single-centre propensity-matched cohort study and a randomised study, The LANCET. 391(), 59-62

Mayeuf-Louchart A, Lancel S, Sebti Y, Pourcet B, Loyens A, Delhaye S, Duhem C, Beauchamp J, Ferri L, Thorel Q, Boulinguiez A, Zecchin M, Dubois-Chevalier J, Eeckhoute J, Vaughn LT, Roach PJ, Dani C, Pederson BA, Vincent SD, Staels B, Duez H (2019). Glycogen Dynamics Drives Lipid Droplet Biogenesis during Brown Adipocyte Differentiation, Cell Reports. 29(6), 1410-1418.e6.

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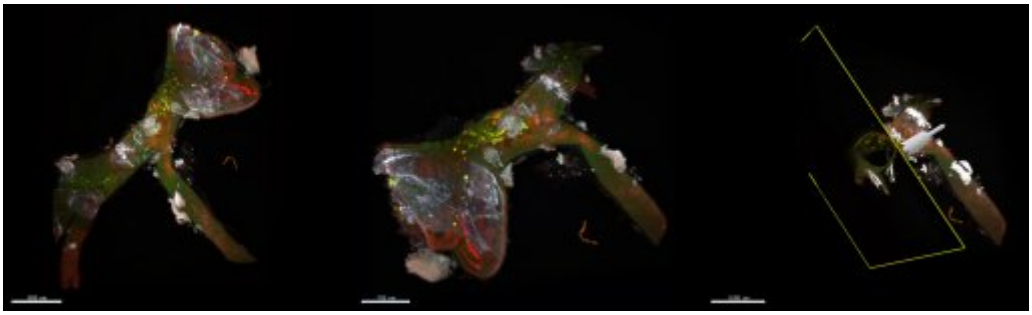
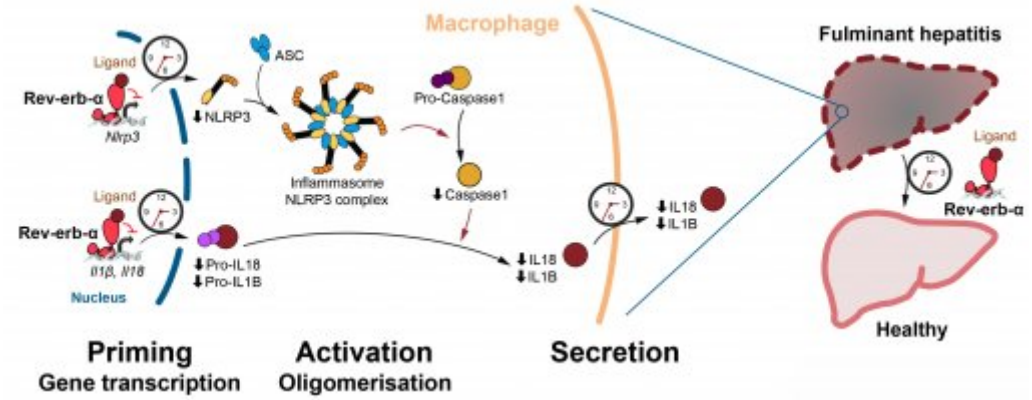
Whole tissue-cleared brachiocephalic artery in lightsheet microscopy



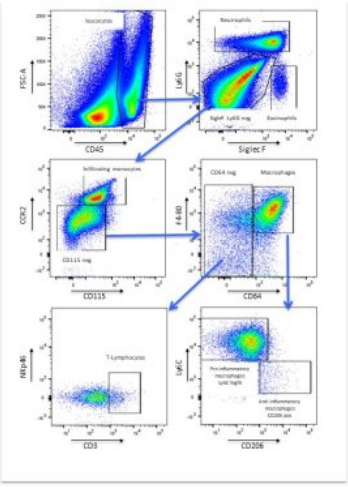
BCA were labelled for endothelial cells (VE-cadherin, white), macrophages (F4/80, red), cleared by 3DISCO and visualized by lightsheet microscopy. Autofluorescence of elastic fibers is shown in green. Intraplaque foam cells appear in yellow. Whole organ was reconstructed in 3D using Imaris software

Rev-erb-a controls NLRP3 inflammasome-mediated circadian immunity in fulminant hepatitis



Rev-erb-a controls the secretion of pro-inflammatory cytokines in mouse and human primary macrophages through rhythmic repression of the NLRP3 inflammasome pathway, identifying Rev-erb-a as a major player in the so-called circadian immunity and as a pharmacological target in NLRP3-driven diseases.

Immunophenotyping of skeletal muscle 24 hours after BaCl2 injury



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Key facts

Team

- Researchers : 2
- Technicians : 2
- Postdoc fellows : 3
- PhD Students : 4

Translational approaches

- Patents : 5
- Clinical research grants : 1
- Industry partnerships : 3

International research links

- Germany, Austria, Spain,
- Belgium, Sweden, Denmark
- USA, Canada,UK,

Keywords

- Reprogramming
- GABA
- Diabetes
- Pax4
- Arx
- Mouse
- Molecular Biology

Patrick Collombat

Diabetes Genetics

Université de Nice
Sophia-Antipolis
Inserm U1091
Besse Florence
Nice

We are regenerating pancreatic cells into insulin-producing beta-cells using multiple approaches and have also developed a startup (DiogenX)

Research Brief :

Our group is involved diabetes research. Both Type I Diabetes (insulinodependent) and Type II (non insulinodependent) diabetes ultimately result in the selective loss of insulin-producing beta-cells in the endocrine pancreas. The subsequent lack in insulin hormone induces a blood hyperglycemia that may be attenuated by daily injection of exogenous insulin hormone. Nevertheless, due to variations in glycemia, vascular damages, blindness, amputation or even death may occur.
We belong to a JDRF-funded consortium whose goal is to gain further insight into the mechanisms regulating the genesis of the mouse pancreas and apply this knowledge to improve the treatment of diabetes. Toward this aim, using the mouse as a model, we have identified two transcription factors, Arx and Pax4, playing a crucial role in the genesis of the different endocrine cell subtypes, including insulin-secreting beta-cells. Importantly, we showed that the forced expression of Pax4 in alpha-cells is sufficient to induce their continuous regeneration and conversion into cells displaying a beta-cell phenotype.
Aiming to eventually apply these finding to human, we searched for compounds able to induce similar processes. GABA was thus identified and found that it was able to induce alpha-cell-mediated beta-like cell neogenesis in the mouse. The beta-like cells thereby generated were functional and could reverse several times the consequences of chemically-induced diabetes in vivo.

- **Methodologies Used :**

- Mouse
- Immunohistochemistry
- Molecular Biology
- qPCR

Publications

Collombat P, Xu X, Ravassard P, Sosa-Pineda B, Dussaud S, Billestrup N, Madsen OD, Serup P, Heimberg H, Mansouri A (2009). The ectopic expression of Pax4 in the mouse pancreas converts progenitor cells into alpha and subsequently beta cells., Cell. 138(3), 449-62

Courtney M, Gjernes E, Druelle N, Ravaud C, Vieira A, Ben-Othman N, Pfeifer A, Avolio F, Leuckx G, Lacas-Gervais S, Burel-Vandenbos F, Ambrosetti D, Hecksher-Sorensen J, Ravassard P, Heimberg H, Mansouri A, Collombat P. (2013). The inactivation of Arx in pancreatic ?-cells triggers their neogenesis and conversion into functional ?-like cells., PLoS Genet. 9(10), e1003934

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GABA induces beta-like cell regeneration in mice rendered diabetics

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Gérard Gradwohl

Differentiation and pathophysiology of endocrine cells in the pancreas and intestine

Université de Strasbourg
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Frederic Dardel
Illkirch

Key facts

Team

- Researchers : 3
- Technicians : 2
- Postdoc fellows : 1
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- DENMARK/BELGIUM/USA

Keywords

- pancreas
- insulin
- cell fate
- diabetes
- transcription
- monogenic diseases
- enteroendocrine cells
- gut hormones
- mouse models
- human organoids
- human pluripotent stem cells

We made the seminal discovery that the transcription factor Neurogenin3 (Ngn3) was essential for pancreatic islet and enteroendocrine cell formation and uncovered the downstream endocrinogenic programs including genes required for the maintenance of beta cell identity.

Research Brief :

Understanding the mechanisms controlling the differentiation of stem cells into specialized cells is one of the current challenges in stem cell biology and regenerative medicine. Progress in this line of research is critical for the generation of therapeutic cells in vitro from pluripotent stem cells, in diseases such as Type-1 diabetes where insulin-producing beta-cells are destroyed. In this goal, we decipher the molecular and cellular mechanisms underlying the differentiation of pancreatic stem/progenitor cells into functional endocrine (islet) cells, including beta cells, during pancreas development both in mice and human. We focus on the role of signals and transcription factors in the control of cell fate choices and the acquisition of the generic and specific properties of the different endocrine cell types in the pancreas. We similarly study the differentiation and function of very closely related intestinal endocrine (enteroendocrine) cells which are scarce cells found in the intestinal epithelium secreting various hormones such as the gluco-incretins GLP1 and GIP controlling glycemic in concert with insulin. Our studies should provide novel insights into the regulation of cellular diversity in the pancreas and intestine as well as into the pathophysiology of endocrine failure in human monogenic diseases, including neonatal diabetes and enteric anendocrinosis.

- **Methodologies Used :**

human pluripotent stem cell derived pancreatic cultures.
human intestinal organoid cultures.
CRISPR/Cas9 gene editing.
Single cell transcriptomics, multiomics, systems biology.
mouse models for pancreatic and/or intestinal endocrine failure including models of human mutations

Publications

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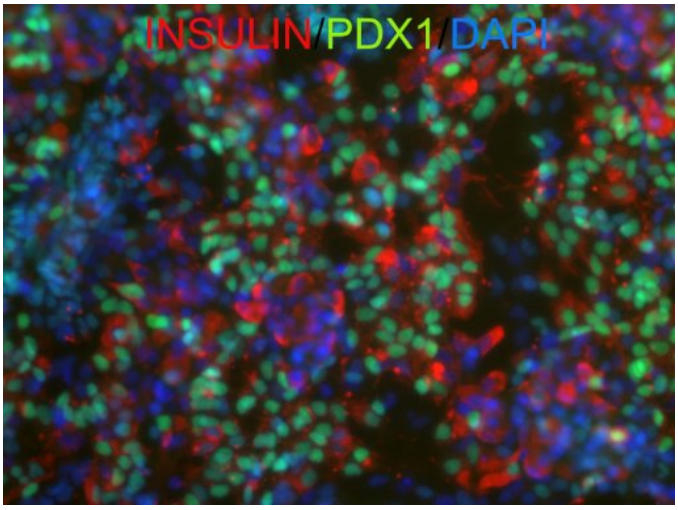
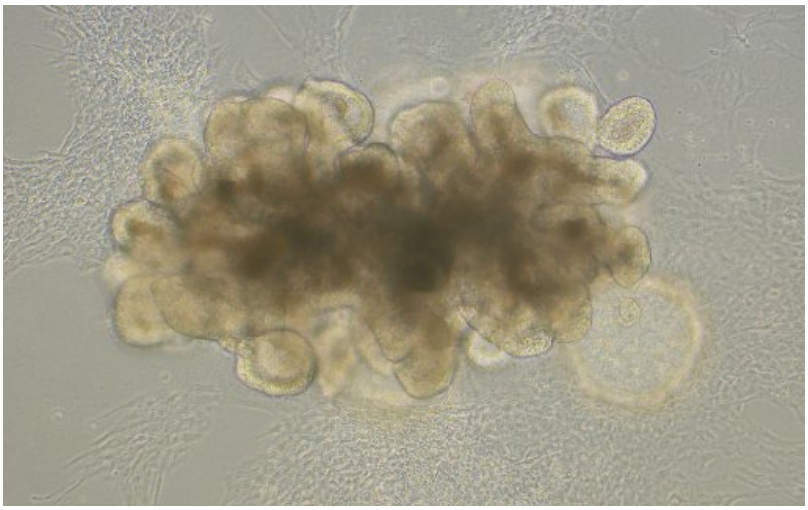
Human pluripotent stem cell-derived insulin-producing cells



Human Insulin-producing cells have been generated by directed differentiation of induced pluripotent stem cells (hiPSC). Immuno-fluorescence for Insulin (red) and transcription factor PDX1 (green). DAPI stains nuclei (Blue)

Human pluripotent stem cell-derived intestinal organoid



Human pluripotent stem cell-derived intestinal organoid generated by directed differentiation of induced pluripotent stem cells (Bright field).

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https://www.igbmc.fr/en/recherche/teams/differentiation-and-physiopathology-of-endocrine-cells-in-the-pancreas-and-intestine

Anne Bouloumie-Diehl

DINAMIX: Adipose tissues and vasculometabolic flexibility

Université de Toulouse 3
(Université Paul Sabatier)
Inserm UMR 1297
Dominique Langin
Toulouse

Our approaches on human and rodent adipose tissues that combine cell sorting, confocal analyses and primary culture of adipocytes, endothelial cells, immune cells and progenitor cells are unique allowing the study of native cells and their interactions.

Key facts

Team

- Researchers : 5
- Technicians : 2
- Postdoc fellows : 2
- PhD Students : 3

Translational approaches

- Patents : 0
- Clinical research grants : 1
- Industry partnerships : 2

International research links

- Sweden
- Spain
- Germany

Keywords

- Stem/progenitor cells
- Endothelial cells
- Metabolism
- Diabetes
- Obesity
- flow cytometry
- confocal microscopy
- cell culture
- immunoselection
- molecular biology

Biological Resources

- Native microvascular and lymphatic endothelial cells, progenitor cells (adipogenic and myofibrogenic subtypes) and adipocytes from human adipose tissues
- Matched subcutaneous (abdominal/gluteofemoral) and visceral (omental/perirenal) human adipose depots

Research Brief :

Our research aims to characterize the molecular and cellular mechanisms involved in metabolic adaptation in the context of natural and accelerated obesity-induced aging with a focus on the characterization of cellular and functional heterogeneity of white, beige and brown adipose depots in vasculo-metabolic flexibility.

• Methodologies Used :

Immunoselection/depletion cell sorting by the use of magnetic nano- and micro-beads
Flow cytometry and three dimensional confocal analyses of the adipose tissue
Primary cultures of human and murine mature adipocytes, adipose tissue endothelial cells, macrophages, lymphocytes, progenitor cells and preadipocytes.

Publications

Mejhert N, Wilfling F, Esteve D, Galitzky J, Pellegrinelli V, Kolditz CI, Viguerie N, Tordjman J, Näslund E, Trayhurn P, Lacasa D, Dahlman I, Stich V, Lång P, Langin D, Bouloumié A. (2013). Semaphorin 3C is a novel adipokine linked to extracellular matrix composition., Diabetologia. 56(8), 1792-801

Estève D, Boulet N, Volat F, Zakaroff-Girard A, Ledoux S, Coupaye M, Decaunes P, Belles C, Gaits-Iacovoni F, Iacovoni JS, Rémaury A, Castel B, Ferrara P, Heymes C, Lafontan M, Bouloumié A. (2015). Human white and brite adipogenesis is supported by MSCA1 and is impaired by immune cells., Stem Cells (Dayton, Ohio). 33(4), 1277-91

Ravaud C, Esteve D, Villageois P, Bouloumie A, Dani C, Ladoux A. (2015). IER3 Promotes Expansion of Adipose Progenitor Cells in Response to Changes in Distinct Microenvironmental Effectors., Stem Cells. 33(8), 2564-73

Gao H, Volat F, Sandhow L, Galitzky J, Nguyen T, Esteve D, Astrom G, Mejhert N, Ledoux S, Thalamas C, Arner P, Guillemot JC, Qian H, Ryden M, Bouloumié A (2017). CD36 Is a Marker of Human Adipocyte Progenitors with Pronounced Adipogenic and Triglyceride Accumulation Potential, Stem Cells. 35(7), 1799-1814

Briot A, Decaunes P, Volat F, Belles C, Coupaye M, Ledoux S, Bouloumié A (2018). Senescence Alters PPARgamma (Peroxisome Proliferator-Activated Receptor Gamma)-Dependent Fatty Acid Handling in Human Adipose Tissue Microvascular Endothelial Cells and Favors Inflammation, Arterioscler Thromb Vasc Biol. 38(5), 1134-1146

Estève, D.; Boulet, N.; Belles, C.; Zakaroff-Girard, A.; Decaunes, P.; Briot, A.; Veeranagouda, Y.; Didier, M.; Remaury, A.; Guillemot, J. C.; Ledoux, S.; Dani, C.; Bouloumié, A.; Galitzky, J. (2019). Lobular Architecture of Human Adipose Tissue Defines the Niche and Fate of Progenitor Cells, Nature communications. 10(1), 2549-

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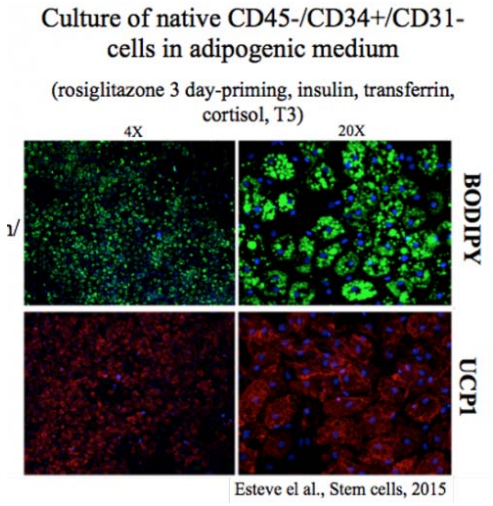
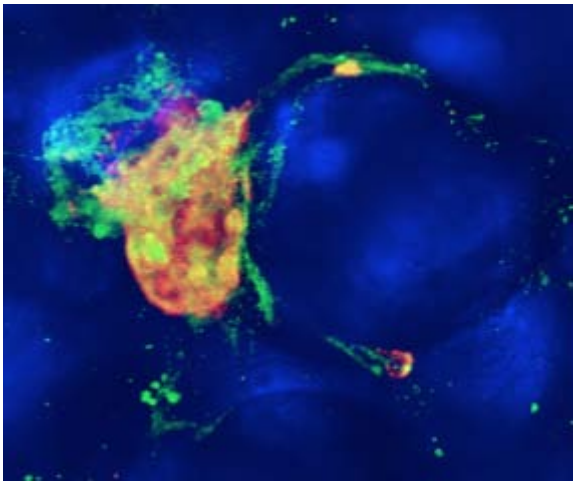
Identification of the human adipose tissue native white and brite progenitor cells



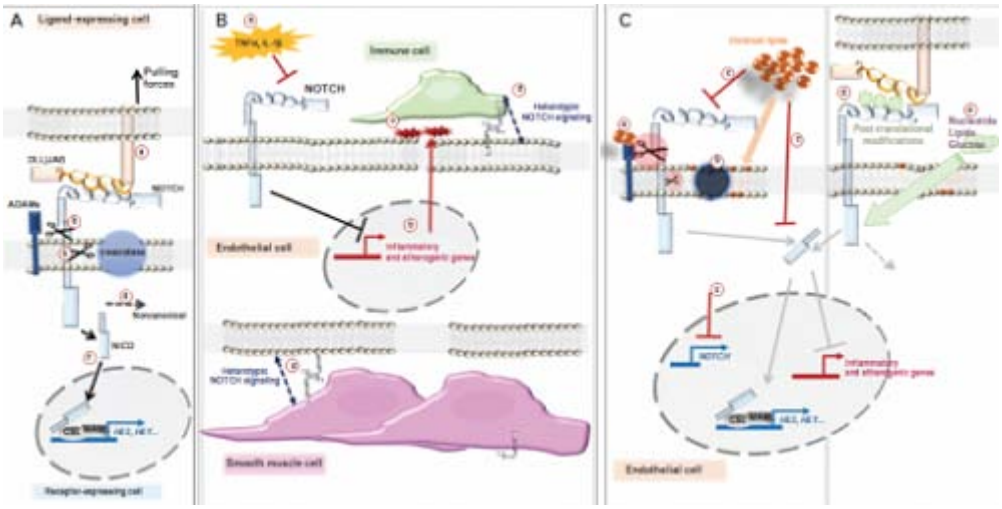
Flow cytometry of the human adipose tissue stroma-vascular cells after collagenase digestion allows the immunoselection of CD45-/ CD 34+/ CD 31- progenitor cells that can upon culture accumulate lipids in their multiple lipid droplets (BODIPY) or express the mitochondrial uncoupling protein 1 (UCP1), which are arker of mature white and brite fat cells.

Adipose tissue microenvironment and obesity



Lymphocyte T neighboring of mature adipocytes is increased with obesity . Here the immune cells are labelled in red (CD3) and green (CD45) while the adipocytes (in blue) are recognizable by their round-shaped profile.

Endothelial Notch signaling pathway and interactions with the microenvironment



(A) Dimerization of NOTCH receptor with DLL/JAG ligand, proteolytic cleavage by ADAM family proteases /g-secretase complex, NOTCH intracellular domain (NICD) translocation to nucleus, interaction with MAML/CSL and transcription of target genes.(B) Inflammation suppresses NOTCH in endothelial cells, expression of inflammatory and atherogenic mediators, immune cell recruitment, bi-directional heterotypic communication (C) Oxidized phospholipids repress NOTCH & promote endothelial activation.

Bouloumie-Diehl Anne - anne.bouloumie@inserm.fr - 0561325642 - https://www.i2mc.inserm.fr/a-bouloumie-2/

Key facts

Team

• Researchers : 13
• Technicians : 4
• Postdoc fellows : 3
• PhD Students : 4

Translational approaches

• Patents : 0
• Clinical research grants : 8
• Industry partnerships : 3

International research links

• United Kingdom
• Sweden
• Switzerland

Keywords

• Diabetes
• Inflammation
• Macrophage
• Pancreatic islets
• Bioenergetics
• Epigenetics
• Cell biology
• Molecular biology
• Epidemiology
• Genetics

Biological Resources

• Biobanking of human samples from clinical protocols (adipose tissue, muscle, plasma/sera, PBMCs, DNA, Urine)
• In-house production and amplification of adeno- and adeno-associated viruses
• Transgenic animals (tissue-specific KO models in myeloid, endothelial, adipose cells)
• Cre-restricted Cas9 expressing mice

Nicolas Venteclef

Immunity and Metabolism in Diabetes

Université Paris Cité
INSERM U1151 CNRS UMR8253
Fabiola Terzi
Paris

The IMMEDIAB team presents a holistic data-driven approach to research into the pathogenesis of type-2 diabetes and its complications. We interrogate mechanisms of metabolic inflammation, ranging from target discovery, to in vitro screening, in vivo validation and translational studies.

Research Brief :

Type-2 diabetes (T2D) is a disease of metabolic and inflammatory aetiology, where innate immune responses dictate disease course and susceptibility to complications. Deciphering mechanisms of physiological versus exuberant inflammation in circulation, adipose tissue, liver and the pancreas in T2D is the objective of the IMMEDIAB Team.

We operate in four working groups:

1. Genetic and epigenetic mechanisms of inflammation, severity of disease and risk of complications [nicolas.venteclef@inserm.fr]
2. Cellular bioenergetics controlling innate immunity in T2D pathogenesis [fawaz.alzaid@inserm.fr]
3. Immunoregulation of Metabolism: Physiological and pathological roles of innate immunity in pancreatic islet function and insulin signalling [elise.dalmas@upmc.fr]
4. Data science & functional genomics: Innovation in data science, bioinformatics and functional genomics of T2D risk and susceptibility to complications [claire.vandiedonck@inserm.fr; gilberto.velho@inserm.fr; frederic.fumeron@inserm.fr]

Our integrative project is highly translational, implicating two diabetes units, those of Bichat (ronan.roussel@aphp.fr, louis.potier@aphp.fr) and Lariboisière (jean-francois.gautier@aphp.fr, jeanpierre.riveline@aphp.fr) hospitals, Paris. We boast 3 constituted cohorts of cross-sectional and follow-up studies in diabetic patients and the general population; with 5 on-going cohorts (diabetes incidence, obesity, genetics, complications, intervention efficacy and at-risk populations).

• **Methodologies Used :**

- Molecular biology (CRISPR, viruses, RNAi, RNA and protein analysis, etc)
- High-throughput sequencing (ChIP-seq, RNA-seq, etc)
- Imaging (immunofluorescence, histology, metabolic imaging)
- Bioinformatics and Data science (big data, data integration)
- Cytometry and cell sorting (phenotypic analysis, cytokine staining, bioenergetic analysis)
- Primary (human and murine) and immortalised cell culture
- In vivo experimentation (dietary, surgical, transplantation and pharmacologic models)

Publications

Dalmas E, Toubal A, Alzaid F, Blazek K, Eames HL, Lebozec K, Pini M, Hainault I, Montastier E, Denis RG, Ancel P, Lacombe A, Ling Y, Allatif O, Cruciani-Guglielmacci C, André S, Viguerie N, Poitou C, Stich V, Torcivia A, Foufelle F, Luquet S, Aron-Wisnewsky J, Langin D, Clément K, Udalova IA, Venteclef N. (2015). Irf5 deficiency in macrophages promotes beneficial adipose tissue expansion and insulin sensitivity during obesity., Nature Medicine. 21(6), 610-8

Alzaid F, Lagadec F, Albuquerque M, Ballaire R, Orliaguet L, Hainault I, Blugeon C, Lemoine S, Lehuen A, Saliba DG, Udalova IA, Paradis V, Foufelle F, Venteclef N. (2016). IRF5 governs liver macrophage activation that promotes hepatic fibrosis in mice and humans., JCI Insight. 1(20), e88689

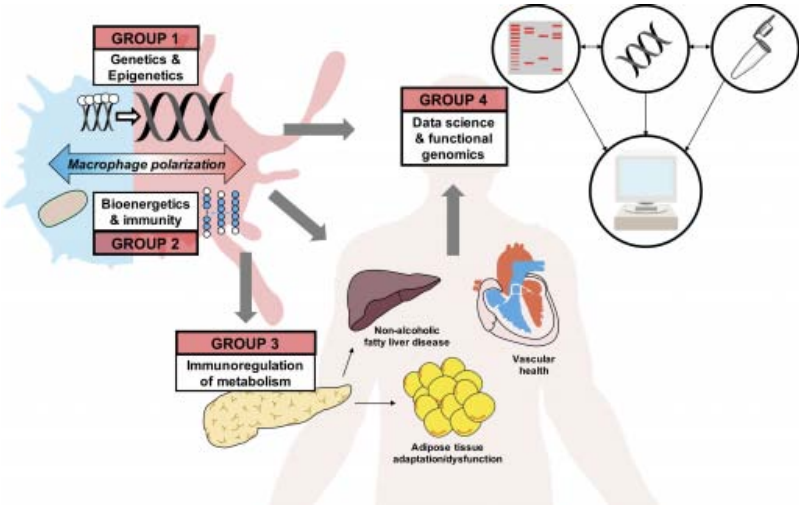
Fan R, Toubal A, Goñi S, Drareni K, Huang Z, Alzaid F, Ballaire R, Ancel P, Liang N, Damdimopoulos A, Hainault I, Soprani A, Aron-Wisnewsky J, Foufelle F, Lawrence T, Gautier JF, Venteclef N, Treuter E. (2016). Loss of the co-repressor GPS2 sensitizes macrophage activation upon metabolic stress induced by obesity and type 2 diabetes, Nature Medicine. 22(7), 780-91

Dalmas E, Lehmann FM, Dror E, Wueest S, Thienel C, Borsigova M, Stawiski M, Traunecker E, Lucchini FC, Dapito DH, Kallert SM, Guigas B, Pattou F, Kerr-Conte J, Maechler P, Girard JP, Konrad D, Wolfrum C, Böni-Schnetzler M, Finke D, Donath MY (2017). Interleukin-33-Activated Islet-Resident Innate Lymphoid Cells Promote Insulin Secretion through Myeloid Cell Retinoic Acid Production, Immunity. 47(5), 928-942

Drareni K, Ballaire R, Barilla S, Mathew MJ, Toubal A, Fan R, Liang N, Chollet C, Huang Z, Kondili M, Foufelle F, Soprani A, Roussel R, Gautier JF, Alzaid F, Treuter E, Venteclef N. (2018). GPS2 Deficiency Triggers Maladaptive White Adipose Tissue Expansion in Obesity via HIF1A Activation, Cell Reports. 24(11), 2957-2971

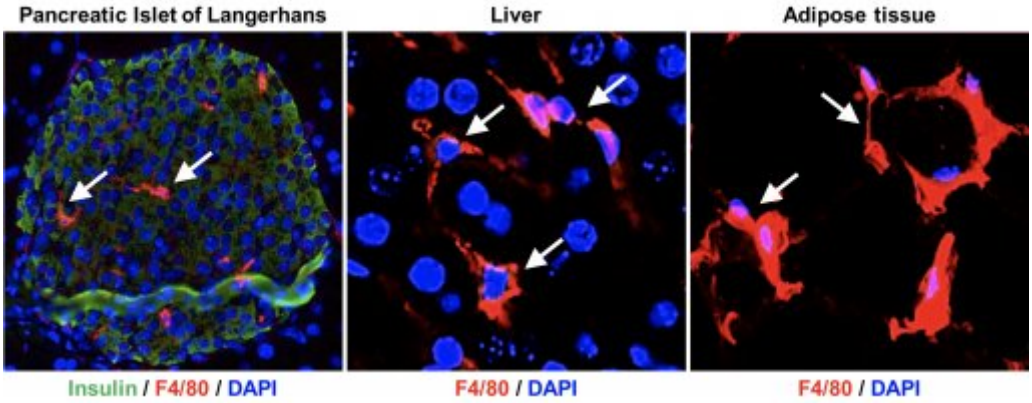
Nativel M, Schneider F, Saulnier PJ, Gand E, Ragot S, Meilhac O, Rondeau P, Burillo E, Cournot M, Potier L, Velho G, Marre M, Roussel R, Rigalleau V, Mohammedi K, Hadjadj S. (2018). Prognostic Values of Inflammatory and Redox Status Biomarkers on the Risk of Major Lower-Extremity Artery Disease in Individuals With Type 2 Diabetes, Diabetes Care. 41(10), 2162-2169

IMMEDIAB topic and strategy



The IMMEDIAB team has an integrated approach to research. The 4 working groups investigate the epigenetic and genetic mechanisms of inflammation, the bioenergetic control of immune responses and the immunoregulation of metabolism; the 4th working group 'Data science and functional genomics' spans the other groups through innovative integration of data. Furthermore, our work is highly translational with direct links to hospital services.

Visualisation of tissue macrophages in the liver, adipose tissue and pancreas



Immunofluorescent staining of tissue macrophages in our major target tissues. On the left, a pancreatic islet of Langerhans stained with insulin (green), F4/80 macrophage marker (red) and DAPI for nuclei (blue). Middle, Liver section stained with F4/80 macrophage marker (red) and DAPI for nuclei (blue). Right, section of adipose tissue visualising crown-like structures by staining with F4/80 macrophage marker (red) and DAPI for nuclei (blue).

Selected publications from the IMMEDIAB team

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UMR 1283
Functional (Epi)genomics and Mechanisms in Type 2 Diabetes and Related Diseases

Amélie Bonnefond

Metabolic functional (epi)genomics and their abnormalities in T2D and related disorders

University of Lille
Inserm UMR1283 CNRS UMR8199
Philippe Froguel
Lille

Key facts

Team

• Researchers : 15
• Technicians : 28
• Postdoc fellows : 7
• PhD Students : 11

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 1

International research links

• UK IRP Metabo-LIC

Keywords

• Diabetes
• Obesity
• Kidney disease
• Cardiometabolic disorders
• Monogenic/polygenic disorders
• Genome-wide association studies
• Whole-exome sequencing
• Next-generation sequencing
• Functional genetics/genomics
• Genome editing

Our team uses the integration of cutting-edge technologies (thanks to our own platform) to decipher the genomics of diabetes & related disorders (including both monogenic and polygenic forms), in order to find new mechanisms and drug targets, towards population stratification and precision medicine.

• **Methodologies Used :**

- next-generation sequencing (whole-exome sequencing, whole-genome sequencing, ChIP-seq, RNA-seq, single cell RNA-seq, methyl-seq, capture C)
- genome editing (CRISPR/cas9 developed in several cell models)
- genetic diagnosis of rare disorders
- DNA microarrays for genome-wide association studies
- methylation DNA arrays
- NanoString for RNA (mRNA, lncRNA, miRNA) count
- functional genomics
- integrative genomics (machine learning)

Publications

Bonnefond A, Keller R, Meyre D, Stutzmann F, Thuillier D, Stefanov DG, Froguel P, Horber FF, Kral JG (2016). Eating Behavior, Low-Frequency Functional Mutations in the Melanocortin-4 Receptor (MC4R) Gene, and Outcomes of Bariatric Operations: A Six-Year Prospective Study, Diabetes Care. 39(8), 1384-92

Abderrahmani A, Yengo L, Caiazzo R, Canouil M, Cauchi S, Raverdy V, Plaisance V, Pawlowski V, Lobbens S, Maillet J, Rolland L, Boutry R, Queniat G, Kwapich M, Tenenbaum M, Bricambert J, Saussenthaler S, Anthony E, Jha P, Derop J, Sand O, Rabearivelo I, Leloire A, Pigeyre M, Daujat-Chavanieu M, Gerbal-Chaloin S, Dayeh T, Lassailly G, Mathurin P, Staels B, Auwerx J, Schürmann A, Postic C, Schafmayer C, Hampe J, Bonnefond A, Pattou F, Froguel P (2018). Increased Hepatic PDGF-AA Signaling Mediates Liver Insulin Resistance in Obesity Associated Type 2 Diabetes, Diabetes. 67(7), 1310-1321

Saeed S, Bonnefond A, Tamanini F, Mirza MU, Manzoor J, Janjua QM, Din SM, Gaitan J, Milochau A, Durand E, Vaillant E, Haseeb A, De Graeve F, Rabearivelo I, Sand O, Queniat G, Boutry R, Schott DA, Ayesha H, Ali M, Khan WI, Butt TA, Rinne T, Stumpel C, Abderrahmani A, Lang J, Arslan M, Froguel P (2018). Loss-of-function mutations in ADCY3 cause monogenic severe obesity, Nature Genetics. 50(2), 175-179

Baron M, Maillet J, Huyvaert M, Dechaume A, Boutry R, Loiselle H, Durand E, Toussaint B, Vaillant E, Philippe J, Thomas J, Ghulam A, Franc S, Charpentier G, Borys JM, Lévy-Marchal C, Tauber M, Scharfmann R, Weill J, Aubert C, Kerr-Conte J, Pattou F, Roussel R, Balkau B, Marre M, Boissel M, Derhourhi M, Gaget S, Canouil M, Froguel P, Bonnefond A (2019). Loss-of-function mutations in MRAP2 are pathogenic in hyperphagic obesity with hyperglycemia and hypertension, Nature Medicine. 25(11), 1733-1738

Bonnefond A, Boissel M, Bolze A, Durand E, Toussaint B, Vaillant E, Gaget S, Graeve F, Dechaume A, Allegaert F, Guilcher DL, Yengo L, Dhennin V, Borys JM, Lu JT, Cirulli ET, Elhanan G, Roussel R, Balkau B, Marre M, Franc S, Charpentier G, Vaxillaire M, Canouil M, Washington NL, Grzymski JJ, Froguel P (2020). Pathogenic variants in actionable MODY genes are associated with type 2 diabetes, Nature Metabolism. 10(2), 1126-1134

Canouil M, Khamis A, Keikkala E, Hummel S, Lobbens S, Bonnefond A, Delahaye F, Tzala E, Mustaniemi S, Vääräsmäki M, Jarvelin MR, Sebert S, Kajantie E, Froguel P, Andrew T (2021). Epigenome-Wide Association Study Reveals Methylation Loci Associated With Offspring Gestational Diabetes Mellitus Exposure and Maternal Methylome, Diabetes Care. 44(9), 1992-1999

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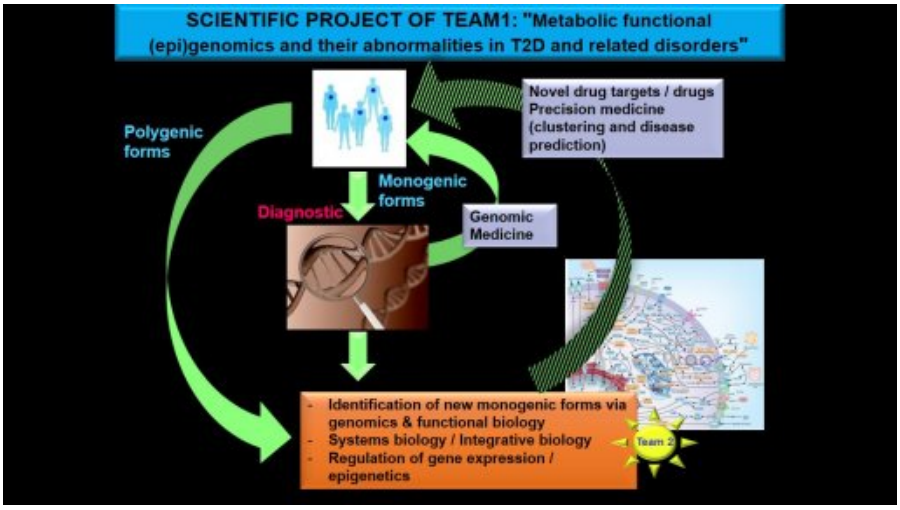
Team's project and link with the second team of the unit



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Jean-Sébastien Annicotte

Molecular and cellular pathophysiology of metabolic diseases

Université de Lille
Inserm, Institut Pasteur de Lille, Universiré de Lille, CHU de Lille UMR1167
Philippe Amouyel
Lille

Our team has identified key mechanisms by which cell cycle regulators and transcriptional cofactors control energy homeostasis through the use of original and unique mouse models and technologies.

Key facts

Team

- Researchers : 1
- Technicians : 1
- Postdoc fellows : 1
- PhD Students : 1

Translational approaches

- Patents : 1
- Clinical research grants : 0
- Industry partnerships : 2

Keywords

- Type 2 Diabetes
- Obesity
- Pancreatic beta cell
- Adipose tissue
- Epitranscriptome
- Mouse models
- Lineage tracing
- Single cell RNA-seq
- ChIP-seq
- 3D imaging

Biological Resources

- In vivo models including KO and KI mice, cell lines

Research Brief :

Type 2 diabetes is characterized by high blood glucose and develops due to a lack of pancreatic beta cell capacity to produce insulin in the face of insulin resistance of metabolic tissues such as liver, muscle or adipose tissue. The incidence and sensitivity of type 2 diabetes increases with aging, but the underlying mechanism (s) in metabolic tissues, such as the beta cells or adipose tissue, that contribute to this increased susceptibility have not been fully elucidated. In the team, our research projects aim at deciphering the contribution of molecular events that modify gene transcription to cellular plasticity associated to organ dysfunctions. In particular, we propose to study the molecular and cellular mechanisms involved in the loss of function of pancreatic beta cells and adipose tissue during obesity, type 2 diabetes and aging. We hope, through the project developed in the laboratory, to identify new targets responsible for the premature loss of function of insulin-producing cells and for the development of insulin resistance in order to develop original therapeutic strategies that will define potential future treatments.

- **Methodologies Used :**

- classical molecular biology and cellular tools (Crispr/Cas9), cell culture, immunofluorescence
- tissue clearing and 3D imaging
- mouse model for tissue and/or time specific genetic inactivation using the Cre/LoxP technology
- metabolic phenotyping experiments to study energy homeostasis in mice
- pancreatic islet isolation protocols and b-cell physiology experiments
- high-throughput approaches for a better understanding of b-cell physiology (ChIP-seq, RNA-seq, scRNA-seq)
- Seahorse XFe24 and Pamgene technologies
- lineage-tracing experiments using the Lox-STOP-Lox-TOMATO mouse model
- development of high-throughput screening strategies for discovering new drugs that stimulate insulin secretion.

Publications

Rabhi N, Denechaud PD, Gromada X, Hannou SA, Zhang H, Rashid T, Salas E, Durand E, Sand O, Bonnefond A, Yengo L, Chavey C, Bonner C, Kerr-Conte J, Abderrahmani A, Auwerx J, Fajas L, Froguel P, Annicotte JS. (2016). KAT2B Is Required for Pancreatic Beta Cell Adaptation to Metabolic Stress by Controlling the Unfolded Protein Response, Cell Reports. 15(5), 1051

Rabhi N, Hannou SA, Gromada X, Salas E, Yao X, Oger F, Carney C, Lopez-Mejia IC, Durand E, Rabearivelo I, Bonnefond A, Caron E, Fajas L, Dani C, Froguel P, Annicotte JS. (2018). Cdkn2a deficiency promotes adipose tissue browning, Molecular Metabolism. 8(1), 65

de Toledo M, Lopez-Mejia IC, Cavelier P, Pratlong M, Barrachina C, Gromada X, Annicotte JS, Tazi J, Chavey C. (2020). Lamin C Counteracts Glucose Intolerance in Aging, Obesity, and Diabetes Through beta-Cell Adaptation, Diabetes. 69(4), 647

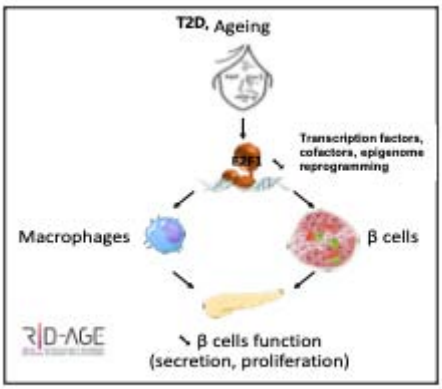
Duquenne M, Folgueira C, Bourouh C, Millet M, Silva A, Clasadonte J, Imbernon M, Fernandois D, Martinez-Corral I, Kusumakshi S, Caron E, Rasika S, Deliglia E, Jouy N, Oishi A, Mazzone M, Trinquet E, Tavernier J, Kim YB, Ory S, Jockers R, Schwaninger M, Boehm U, Nogueiras R, Annicotte JS, Gasman S, Dam J, Prevot V (2021). Leptin brain entry via a tanycytic LepR-EGFR shuttle controls lipid metabolism and pancreas function, Nature Metabolism. 3(8), 1071

Bornaque F, Delannoy CP, Courty E, Rabhi N, Carney C, Rolland L, Moreno M,Gromada X, Bourouh C, Petit P, Durand E, Pattou F, Kerr-Conte J, Froguel P, Bonnefond A, Oger F, Annicotte JS. (2022). Glucose Regulates m6A Methylation of RNA in Pancreatic Islets., Cells. 11(2), 291

Bourouh C, Courty E, Rolland L, Pasquetti G, Gromada X, Rabhi N, Carney C, Moreno M, Boutry R, Caron E, Benfodda Z, Meffre P, Kerr-Conte J, Pattou F, Froguel P, Bonnefond A, Oger F, Annicotte JS. (2022). The transcription factor E2F1 controls the GLP-1 receptor pathway in pancreatic ß cells, Cell Reports. 40(6), 111170

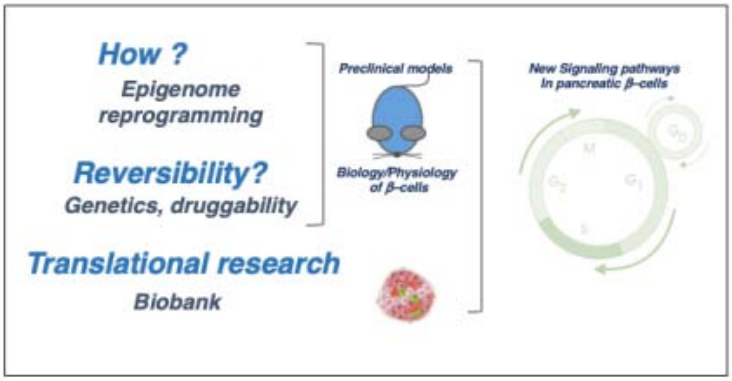
Annicotte Jean-Sébastien - jean-sebastien.annicotte@inser m.fr - +33 3 20 97 42 54 -
https://pasteur-lille.fr/en/center-of-research/research-units/risk-factors-and-molecular-determinants-of-aging-related-disease/

Deciphering the molecular and cellular mechanisms involved in age-related development of diseases



Based on our preliminary results, we postulate that the loss of transcriptional regulators activity and/or epigenomic reprogramming during aging will trigger macrophages and ß-cell inflammatory activity leading to ß-cell dysfunction and type 2 diabetes.

New pathways involved in age-related metabolic diseases and functional studies



In our team, we aim at discovering new pathways that may contribute to disease development, and develop original strategies to functionally dissect the molecular and cellular mechanisms involved in pathophysiology.

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https://pasteur-lille.fr/en/center-of-research/research-units/risk-factors-and-molecular-determinants-of-aging-related-disease/

NUDICE

Gilles Mithieux

Nutrition, Diabetes and the Brain

Université de Lyon 1
(Université Claude Bernard)
Inserm U1213
Gilles Mithieux
Lyon

We uncovered glucose production by the intestine and its paradoxical benefits on energy (food intake, energy expenditure) and glucose (insulin sensitivity, insulin secretion) homeostasis, which is a basis of our research project.

Key facts

Team

• Researchers : 3
• Technicians : 6
• Postdoc fellows : 1
• PhD Students : 3

Translational approaches

• Patents : 1
• Clinical research grants : 0
• Industry partnerships : 6

International research links

• Sweden, Portugal, USA
• The Netherlands, Italy

Keywords

• Endogenous glucose production
• insulin sensitivity
• diabetes, obesity
• liver, kidney
• intestine
• glucose-6 phosphatase
• hepatic tumorigenesis
• chronic kidney disease
• microsurgery
• determination of glucose fluxes
• transgenesis

Biological Resources

• cell lines
• transgenic mice

Research Brief :

The project deals with the respective roles of the glucose-producing organs (the liver, kidney and small intestine) in the control of glucose and energy homeostasis. We showed that endogenous glucose production (EGP) by the small intestine exerts a beneficial role in this homeostasis, through its detection by the nervous system of the portal vein. This signal positively influences parameters involved in glucose control and energy management regulated by the brain. This paradigm allowed us to explain the satiety effect of dietary proteins and the rapid amelioration of obesity and diabetes by fibers and gastric bypass surgery.
To further document the novel concept of a deleterious role of hepatic glucose production opposed to a beneficial role of intestinal glucose production (IGP) in energy homeostasis, we created original mouse models of time-dependent and organ-specific deletion or overexpression of glucose-6 phosphatase (the key enzyme of EGP). These models allow us to contrast diabetes with the mirror (rare) disease named glycogen storage disease type 1, which is due to glucose-6 phosphatase deficiency, for a better understanding of both diseases. Thus, we recently demonstrated the protection induced by IGP per se against obesity-linked hepatic steatosis and diabetes, and the leading role of hepatic metabolic reprogramming and of dietary lipids in the development of tumorigenesis, in the context of non-alcoholic fatty liver disease.

• **Methodologies Used :**

Microsurgery in rats and mice
Energy (food intake, energy metabolism) and glucose (glucose tolerance, insulin sensitivity) homeostasis in rodents
Time-dependent and tissue-specific deletion (or overexpression) of glucose production in mice
Use of glucose-labeled tracers to quantify whole body and organ-specific glucose fluxes
Behavioral studies in relation with food intake and anxiety-depression

Publications

CLAR J, GRI B, CALDERARO J, BIRLING MC, HERAULT Y, SMIT GPA, MITHIEUX G & RAJAS F (2014). Targeted deletion of glucose-6 phosphatase leads to nephropathy, Kidney International. 86(4), 747-756

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VILY-PETIT J, SOTY-ROCA M, SILVA M, RAFFIN M, GAUTIER-STEIN A, RAJAS F, MITHIEUX G (2020). Intestinal Gluconeogenesis Prevents Obesity-Linked Liver Steatosis and Non-Alcoolic Fatty Liver Disease, Gut. 69(12), 2193-2202

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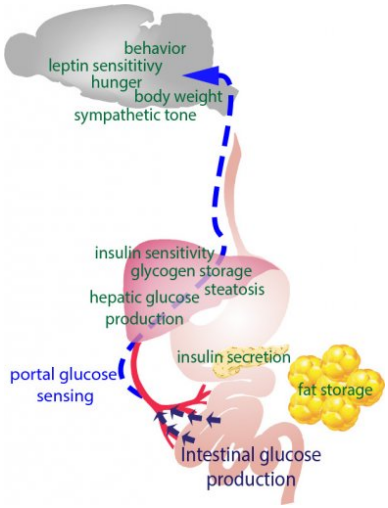
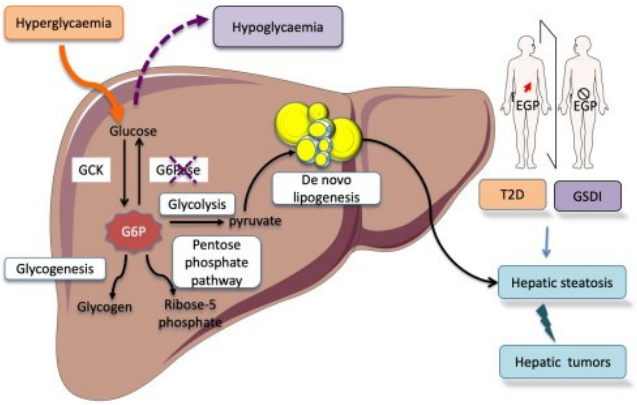
Functions controlled by intestinal glucose production via portal glucose sensing and brain signaling



The induction of intestinal glucose production (IGP) leads to glucose release in the portal vein, initiating a nervous signal to the brain. The functions controlled by IGP through this gut-brain axis are indicated in green.

Comparison and common pathways of hepatic glucose metabolism in glycogen storage disease type I GSDI



In GSDI (absence of EGP), the absence of G6Pase activity leads to hypoglycemia and glucose-6 phosphate (G6P) accumulation in the hepatocyte. In diabetes (increased EGP), hyperglycemia leads to increased flux downstream of G6P. In both cases, this leads to the activation of glycolysis, pentose phosphate pathway, and lipogenesis. This metabolic reprogramming promotes hepatic steatosis in both type 2 diabetes and GSDI, which is associated with increased risk of liver tumorigenesis in both diseases.

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Jennifer Rieusset

Organelle communication and diabetes

Université de Lyon 1
(Université Claude Bernard)
Inserm U1060
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Key facts

Team

• Researchers : 6
• Technicians : 3
• Postdoc fellows : 0
• PhD Students : 2

Translational approaches

• Patents : 2
• Clinical research grants : 6
• Industry partnerships : 2

Keywords

• Type 2 diabetes
• insulin resistance
• skeletal muscle
• endoplasmic reticulum
• mitochondria
• Organelle communication
• pancreas
• calcium signaling
• insulin signaling and secretion
• liver
• mice models of type 2 diabetes
• clinical intervention
• Primary cells in culture
• cellular signaling
• Membrane contact site
• Insulin sensitivity
• glucose-induced insulin secretion
• oxidatives capacities
• Mitochondria dynamics and function
• ER stress
• Subcellular fractionation
• In situ PLA
• Electronic microscopy

Biological Resources

• human myotubes in primary culture,
• human beta islets,
• tissues from high-fat and high-sucrose diet-fed mice and ob/ob mice
• Mitochondria-associated ER membranes (MAM) from midce models of T2D

Our major strengh is to have a double expertise in both skeletal muscle insulin sensitivity and beta cell function, in order to identify common mechanisms to their metabolic alterations and to propose new and more effective preventive and/or therapeutic targets against type 2 diabetes.

Research Brief :

Our team, managed by Charles Thivolet and myself, focuses on molecular mechanisms of altered insulin action and secretion in type 2 diabetes (T2DM). Among these mechanisms, we focus on the role of two key intracellular organelles: mitochondria and endoplasmic reticulum (ER). Both organelles interact at contact points, called MAM (mitochondria-associated endoplasmic reticulum membranes), in order to exchange both lipids and calcium, 2 metabolites that play a key role in metabolic homeostasis. We recently identified a new role of MAM in the control of insulin action and secretion, as well as organelle miscommunication in liver, skeletal muscle and beta cells of obese and diabetic mice.
The general goal of our research program is to better characterize the nature and the physiological significance of MAM in the control of glucose homeostasis and their roles in the pathogenesis of T2DM.
More specifically, our specific aims are:
1) To identify the molecular nature of MAM actors and their functional roles,
2) To characterize the physiological significance of MAM in the control of insulin action and secretion,
3) To identify the regulators of MAM and their functional impacts,
4) To validate if the MAM could be a new target for the treatment of T2DM.
Ultimately, our scientific project will clarify the mechanisms by which MAM are involved in the pathogenesis of T2DM and should determine if MAM could be a new target to improve both insulin action and secretion in T2DM.

• **Methodologies Used :**

- Primary cultures of human myotubes, hepatocytes and beta cells of pancreas
- Adenoviral overexpression or invalidation by RNAi of genes in vitro
- Analysis of the structure, density and the functions of mitochondria (electronic microscopy, respiration, ATP synthesis, fatty acids oxidation)
- Analysis of the homeostasis of endoplasmic reticulum (electronic microscopy, real-time PCR, Western blotting)
- Analysis of ER-mitochondria interactions (electronic microscopy, in situ PLA, subcellular fractionation)
- Analysis of insulin signalling (immuno-precipitation, western-blotting)
- Analysis of the mass and functions of beta cells

Publications

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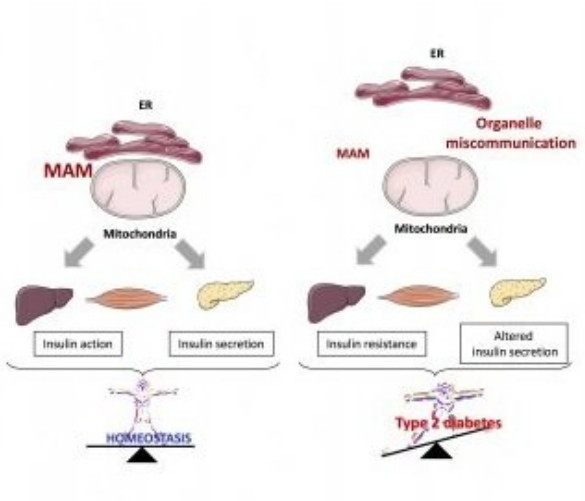
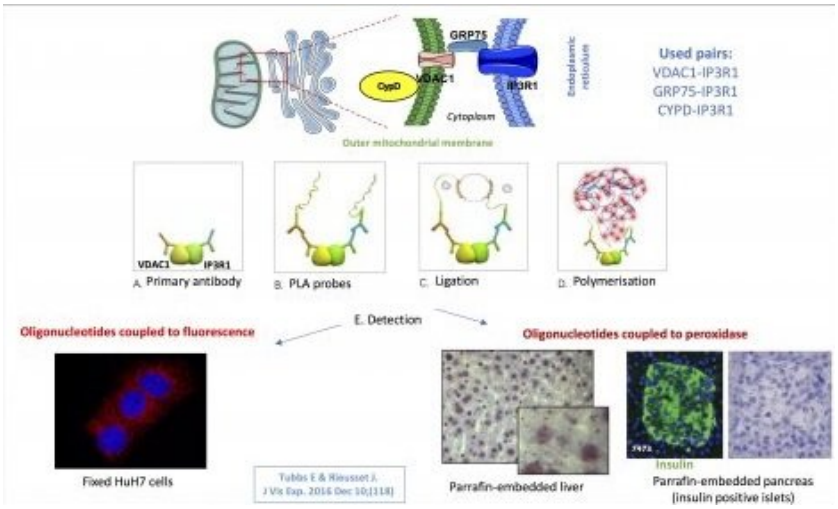
Scientific objectives of our team



The general goal of our research is to better understand the role of ER-mitochondria interactions (known as MAM for mitochondrial-associated membranes) in the control of glucose homeostasis (in insulin action and secretion) and in the pathogenesis of type 2 diabetes.

Visualization and quantification of ER-mitochondria interactions by in situ Proximity Ligation Assay



Schematic representation of the VDAC1/GRP75/IP3R1 complex at MAM interface and of in situ PLA steps for visualization of VDAC1/IP3R1, GRP75/IP3R1 or CypD/IP3R1 interactions.

A) incubation of cells or tissues with two different primary antibodies, one directed against the IP3R1 channel in the ER, and another one against a mitochondrial protein (VDAC or CypD) or the chaperone Grp75, B-C) circularization and ligation of connector oligonucleotides of secondary antibodies when proteins are less than 40 nm away, D) rolling circle amplification with polymerase and E) detection of the product with fluorescent or peroxidase-coupled probes.

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Key facts

Team

- Researchers : 4
- Technicians : 2
- Postdoc fellows : 0
- PhD Students : 2

Translational approaches

- Patents : 1
- Clinical research grants : 3
- Industry partnerships : 3

International research links

- Belgium
- USA

Keywords

- GLP-1
- Inflammation
- Pancreatic islet cells
- Signaling pathways
- G-protein coupled receptors
- Therapeutic strategies
- Diabetes
- Glucolipotoxicity
- Basic and translational researches

Biological Resources

- Cell lines (MIN6, INS1-E)
- Primary cultures of pancreatic islets (rat, mice)
- Human pancreatic islets
- Animal models of type 2 diabetes
- Transgenic mice (knock-out), beta-arrestin 1 and 2 knock-out mice

Stéphane Dalle Magalie Ravier

Physiopathology of pancreatic beta cells

Montpellier University
INSERM U1191 CNRS 5203
Jean-Philippe Pin
Montpellier

Our team performs basic and translational studies from molecular to cell and animal levels in order to have an integrative view of the dysfunction and death of pancreatic beta cells linked to diabetes.

Research Brief :

Pancreatic beta-cells are the unique cells of the organism with the capacity to biosynthesize, store and secrete insulin in response to physiological needs. Beta-cells play a central role in the etiology of Diabetes. Preservation or restoration of a functional beta-cell mass is essential. Our objectives, divided into basic and translational researches, are to examine the cellular and molecular mechanisms controlling function, survival and death of beta-cells, to investigate how these go awry in the pathogenesis of diabetes, and how stress and environnement influence beta-cell function and survival. The project is based on 4 interacting themes:
1) Molecular mechanisms of signaling cross-talks engaged by glucose, G-protein coupled receptors, and tyrosine kinase receptors regulating insulin secretion and beta-cell mass.
2) GLP-1 receptor dynamics and signaling: agonist-induced functional specificity, and GLP-1 receptor desensitization mechanisms (GLP-1 resistance) in beta-cells.
3) Identification of the mechanisms whereby prolonged exposure to elevated concentration of glucose (chronic hyperglycemia), fatty acids (lipotoxicity), inflammation, or high fat diet adversely affects beta-cell function and survival.
4) Validation of new therapeutic strategies aiming at preserving or restoring a functional beta-cell mass in diabetic subjects.

- **Methodologies Used :**

Cell lines (MIN6, INS1-E), primary cultures of pancreatic islets (rat and mice)
Animal models of type 2 diabetes and transgenic mice (knock-out)
Human pancreatic islets
Molecular biology and pharmacology, cellular signaling (Western blot, siRNA)
Pancreatic islet perifusion and isolated perfused pancreas
Live cell imaging (confocal microscopy and Total Internal Reflection Fluorescence)
FRET Technology: Insulin/Glucagon/GLP-1 secretion, kinases assays, cAMP production, Ca2+ measurements

Publications

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Figure: Islets of Langerhans, and GLP-1 receptor signaling measurements

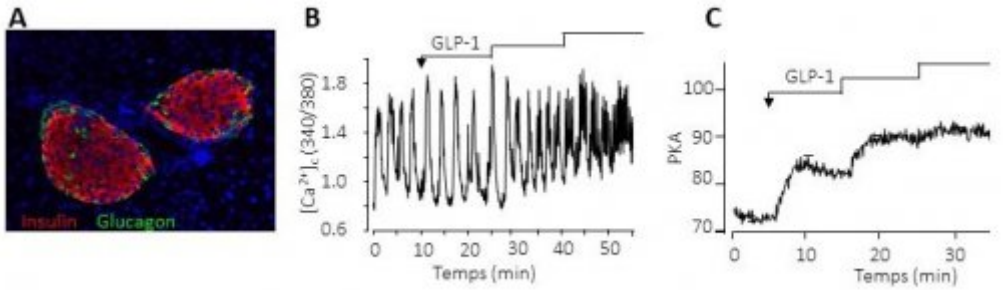

Figure: Islets of Langerhans, and GLP-1 receptor signaling measurements

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Metabolism
Nutrition

UR 1268 bia Biopolymères Interactions Assemblages

Marie Bodinier

Allergy team

INRAE
INRAE UR1268
Bernard Cathala
Nantes

The allergy team, by combining the study of food structure and its impact on the biological mechanisms of the host, is unique in the field of allergies and their prevention.

Key facts

Team

• Researchers : 5
• Technicians : 3
• Postdoc fellows : 3
• PhD Students : 3

Translational approaches

• Patents : 0
• Clinical research grants : 1
• Industry partnerships : 5

International research links

• - Australia, Perth, Telethon Kids Institute, Allergy prevention (Debbie Palmer)
• - Spain, Spanish National Research Council (CSIC), breastmilk microbiota (Maria Carmen Collado)
• - USA, Boston, The center «Food Allergy and Immunology» : cellular models of allergy prediction

Keywords

• Allergies
• Atopic march
• Allergens and epitopes, food additives, contaminants
• Mechanisms
• Prevention
• Immunology
• Biochemistry and Physicochemistry of proteins
• Functional exploration of organs
• Cell biology and in vitro models
• Translational research approaches: preclinical models and clinical studies

Biological Resources

• Animal models of food and respiratory allergies and atopic march
• In vitro model of immune cells (basophil degranulation RBL, dendritic cells, T cells ...)
• In vitro model of intestinal barrier (Caco-2, organoïds..)
• Mother/ child cohort PREGRALL
: GOS/inulin prebiotics supplementation in allergic women during pregnancy to prevent allergy in their chlid
• Biocollections: CIMMAP from the PREGRALL trial (blood, stool, breastmilk), Allergic patients sera: serotheque
• Polyclonal and monoclonal antibodies against food allergens (wheat, peas, rapeseed, egg, milk ...)

Research Brief :

The allergy team is attached to the INRAE BIA unit in Nantes. This unit hosting 110 incumbent agents aims in particular to improve and develop new healthy and sustainable formulated foods for targeted functionalities. Thanks its multidisciplinary (Food such as allergens, additives, contaminants, food/protein biochemistry and process and Immunology) the Allergy team aims to reduce the allergic risk through food by studying :
How does the food induce the allergy?
How can food prevent or treat allergies?
To answer these two questions, we are developing three lines of research :
Axis 1: Characterize and evaluate the allergenicity of foods by analyzing the molecular properties of allergens as well as the effects of the structure of food matrices, its constituents, and technological processes on allergenicity.
Axis 2: Understand the impact of allergens and model foods on the mechanisms that orchestrate the development of allergy and its evolution throughout life
Axis 3: Implement strategies for the treatment and prevention of allergies during the first 1000 days of life.

• **Methodologies Used :**

- Purification of allergens (sequential extraction, chromatography)
- Immunoglobulin detection and measurement by ELISA
- Characterization of allergens by proteomic (1D, 2D electrophoresis, immunoblotting and mass spectrometry)
- Identification of epitopes using synthetic peptides (pepscan)
- Digestive hydrolysis, in vitro study of allergen resistance
- Allergen detection (immunochemistry and mass spectrometry)
- Models for studying allergy mechanisms
o in vitro : epithelial cells (Caco 2, organoids ...), basophils (humanized RBLs)
o ex vivo : intestinal biopsy, primary cells (spleen, mesenteric lymph nodes ...)
o in vivo : preclinical allergy models
- Analysis of cell populations and receptors by flow cytometry

Publications

Cabridain C, Aubert H, Kaeffer B, BadonV , Boivin M, Dochez V, Winer N, Faurel-Paul E, Planche L, Riochet D, Barbarot S, Bodinier M (2019). Effectiveness of an antenatal maternal supplementation with prebiotics for preventing atopic dermatitis in high-risk children (the PREGRALL study): protocol for a randomised controlled trial, BMJ Open. 9(4),

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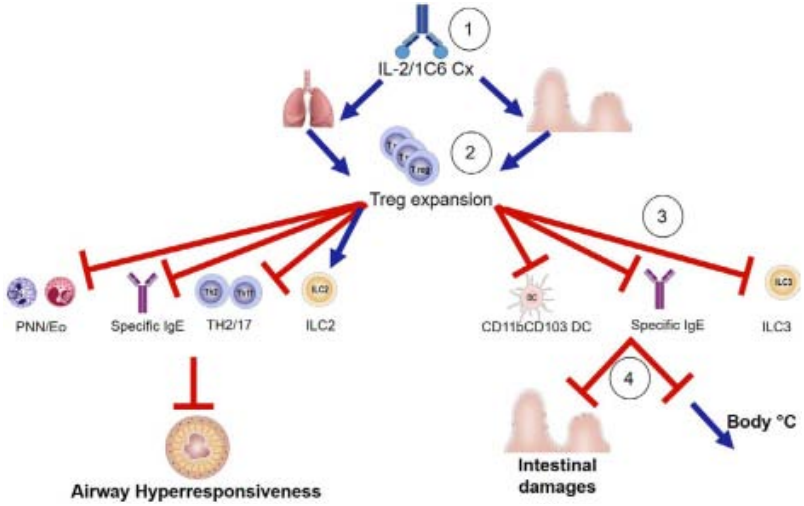
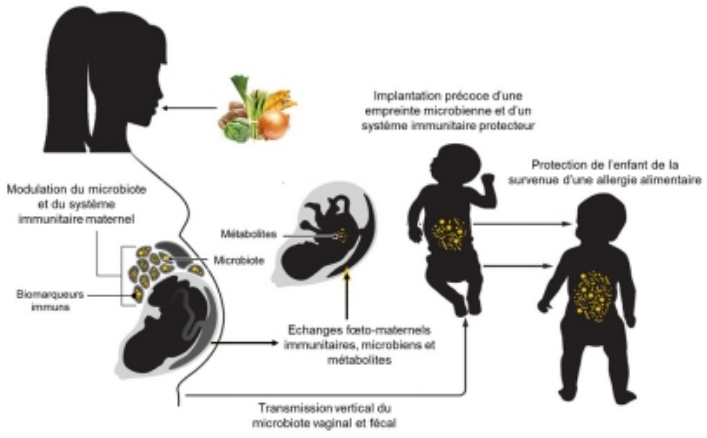
Research strategy of the Allergy team - BIA unit

IL-2/1C6 mechanism in asthma and food allergy



1-After intraperitoneal injection in asthmatic and food-allergic mice, IL-2/1C6 spreads throughout the entire organism and reaches both the lung and gut. 2-IL-2/1C6 binds to its high-affinity
receptor on Treg cells, leading to their expansion. 3-This expansion allows Tregs to modulate both innate and adaptive immunity. In asthmatic mice, newly expanded Treg cells reduce BAL eosinophils, neutrophils, lung Th2 and Th17 responses, HDM-specific IgE in blood and increase lung ILC2s. In food-allergic

A prebiotic supplementation during pregnancy to prevent allergy: PREGRALL trial



Our hypothesis is that a maternal supplementation with GOS/inulin prebiotics during pregnancy will be effective to prevent allergy in child. We think that this supplementation will modified the gut microbiota and the immune system of the mother and will allow the transfer of immune, microbial and metabolic factors in the f?tus and in the baby at delivery to implant a protective microbiota and a tolerogenic environment able to protect the child against allergy.

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Charles-Henri Malbert

Ani-SCANs

Adelaide University National Academy of Medicine
INRAE US1395
Charles-Henri Malbert
Saint-Gilles

Aniscan performs nuclear imaging of adults miniature and growing pigs either in anaesthetised conscious animals. Multimodal investigations include central and peripheral receptor occupancy, metabolism and inter-organs function with specific interest in gut-brain axis.

Key facts

Team

- Researchers : 1
- Technicians : 1
- Postdoc fellows : 0
- PhD Students : 0

Translational approaches

- Patents : 1
- Clinical research grants : 2
- Industry partnerships : 3

International research links

- Center of research excellence in translating nutritional science in good health; University of Adelaide, Australia

Keywords

- Obesity
- Type 2 Diabetes
- Vagal stimulation
- GLP-1
- Nuclear medicine
- Brain imaging
- Portal sensor
- Insulin sensitivity

Biological Resources

- Miniature Pig
- Pig brain atlas and associated PET/SPECT templates
- 68Ga labelled Peptides

Research Brief :

Aniscan aimed to quantify the metabolic alterations induced by diet induced obesity with specific reference to brain-gut axis using nuclear imaging in a large animal model. To do so, we have developed several minimally invasive research tools to investigate receptor occupancy, glucose metabolism and blood flow in the miniature pig. We have build a unique three dimensional brain atlas of the pig together with additional ressources mandatory to quantify the information issued from the imaging assets. The unit has internationally recognised expertise in evaluating gastric emptying in conscious pigs using scintigraphy considered as the gold standard either in humans or in animals. PET and SPECT imaging were made truly quantitative, a mandatory improvement for using the full capability of the methods within the scope of nutrition physiopathology, using innovative conceptual frameworks including continuous measurement of the input arterial function to key organs. In addition to classical radioligands, we have developed 68Ga labelled peptides with specific interest towards the GLP-1 receptor and other ligands relevant for glucose homeostasis. The unit aims to the understanding and further manipulations of the gut-brain axis in the obese insulin resistant patient. They included chronic vagal stimulation at the abdominal level and up regulation of the GLP-1r at the portal sensor level.

- **Methodologies Used :**

PET imaging using 18F or 68Ga derivatives. Dynamic PET imaging with measurement of the arterial input function.
Brain SPECT imaging using 99Tc and 123 Iodine derivatives
Dynamic planar abdominal imaging measurement of solids and liquids gastric emptying in conscious pigs
CT based body composition
Image guided surgery including in situ neuronal recordings
Minimally invasive ultrasound guided surgery
Indirect calorimetry in anaesthetised animals
Microstructure of the meal and meal preferences

Publications

Charles-Henri Malbert, Chloé Picq, Jean-Louis Divoux, Christine Henry and Michael Horowitz (2017). Obesity-associated alterations in glucose metabolism are reversed by chronic bilateral stimulation of the abdominal vagus nerve, Diabetes. 66(4), 848-857

Malbert CH, Bobillier E, Picq C, Divoux JL, Guiraud D, Henry C (2017). Effects of chronic abdominal vagal stimulation of small-diameter neurons on brain metabolism and food intake, Brain stimulation. 10(4), 735-743

Bahri S, Horowitz M, Malbert CH (2018). Inward Glucose Transfer Accounts for Insulin-Dependent Increase in Brain Glucose Metabolism Associated with Diet-Induced Obesity, Obesity. 26(8), 1322-1331

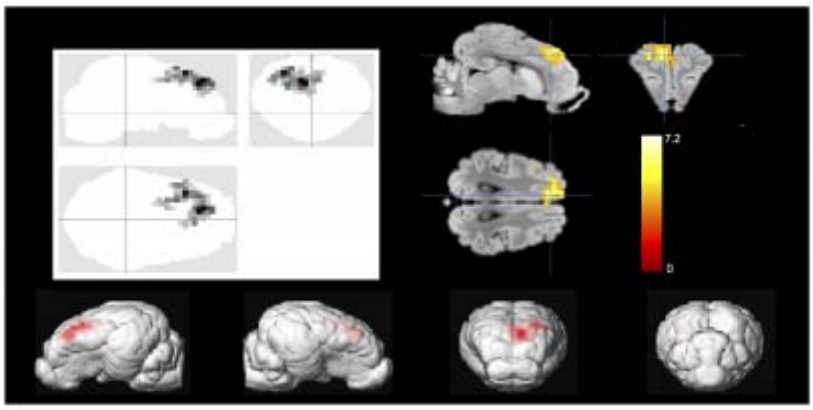
Malbert CH, Horowitz M, Young R L (2019). Low-calorie sweeteners augment tissue-specific insulin sensitivity in a large animal model of obesity, European journal of nuclear medicine and molecular imaging. 46(11), 2380-2391

Malbert, CH Chauvin, A Horowitz, M Jones, K L (2020). Pancreatic GLP-1r binding potential is reduced in insulin-resistant pigs, BMJ Open Diabetes Res Care. 8(2), 1540-1549

Malbert, CH Chauvin, A Horowitz, M Jones, K L (2021). Glucose-Sensing Mediated by Portal GLP-1 Receptor is Markedly Impaired in Insulin-Resistant Obese Animals, Diabetes. 70(1), 99-110

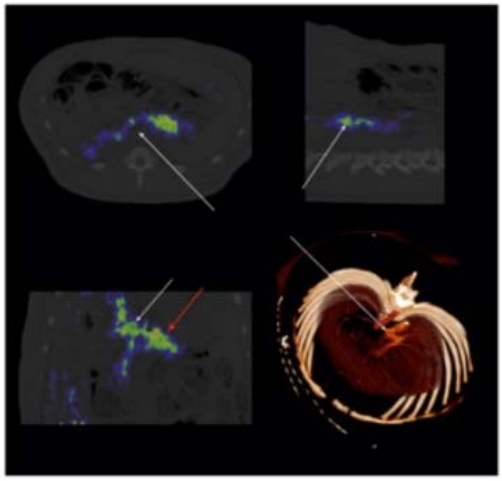
Malbert Charles-Henri - charles-henri.malbert@inrae.fr - 0608918989

Brain glucose metabolism during low-calorie sweeteners consumption



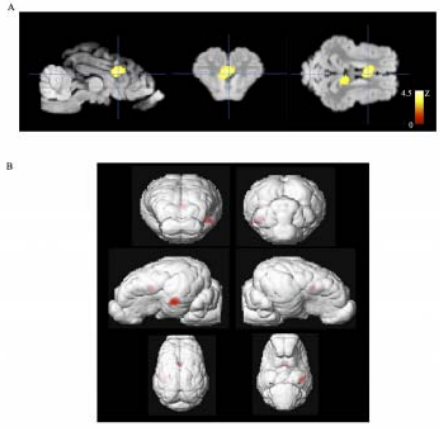
The combination of sucralose and acesulfame K, the most used low-calorie sweetener substitute, is biologically active. While not affecting whole-body insulin resistance, it increases insulin sensitivity and glucose uptake in specific tissues mimicking the effects of obesity in the adipose tissue and in the brain.

Glucose-sensing mediated by portal GLP-1 receptor is impaired in insulin-resistant obese



GLP-1-dependent portal glucose signaling was identified, in vivo, using a novel 68Ga labeled GLP-1r probe that supplied a quantitative in situ tridimensional representation of the portal sensor. We determined that, in insulin-resistant animals, portal vagal afferents failed to inhibit their spiking activity during glucose infusion, a GLP-1r-dependent function. This reflected a reduction in portal GLP-1r binding potential, particularly between the splenic vein and the entrance of the liver.

Obesity-associated alterations in metabolism are reversed by Stimulation of the abdominal vagus



Chronic abdominal vagal stimulation improves insulin sensitivity substantially in diet-induced obesity by both peripheral and central mechanisms. Mean whole body insulin sensitivity was restored and vagal stimulation was associated with increased glucose metabolism in the cingular and prefrontal brain areas.

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Yves Boirie

ASMS - Diet, Muscle Health and Sarcopenia

Université d'Auvergne
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INRAe UMR1019
Didier Rémond
Clermont-Ferrand

Our team has strong expertise in studying protein metabolism, molecular mechanism regulating skeletal muscle mass and function and promoting nutritional intervention in Human and animal models to maintain muscle activity during aging.

Key facts

Team

- Researchers : 18
- Technicians : 5
- Postdoc fellows : 2
- PhD Students : 6

Translational approaches

- Patents : 3
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- Italy, Sweden, Belgium, Switzerland, Canada, Spain

Keywords

- Food and Nutritional intervention
- Skeletal muscle mass and function
- Protein metabolism
- Chronic and metabolic diseases
- Sarcopenia - Aging
- muscle function (Catwalk, rotarod, openfield)
- Mitochondrial activity (oxygraph, oroboros)

Biological Resources

- Human studies on healthy volunteers
- Animal models (transgenic mice, aged rodent...)
- Cell lines
- Access to human cohorts and human biopsies

Research Brief :

Aging results in a decreased muscle mass/function, called sarcopenia. The gradual loss of mobility that results from this sarcopenia promotes the development of metabolic syndrome, sedentary lifestyle, and increased risk of falls. Furthermore, a low skeletal muscle mass/strength is a predictor of morbidity and mortality. Therefore, prevention of muscle loss in aging is critical to maintain physical abilities at an advanced age and to optimize the quality of life of the aged people.

The ASMS team has a long research tradition on skeletal muscle, protein / energy metabolisms and dietary lipids/ proteins, with specific emphasis on the crosstalk between skeletal muscle and adipose tissue. The research programs of the team mainly focus on the impact of the aging process and chronic diseases on muscle anabolic responses and impaired metabolisms.

The objective of the team focus on the preservation of mobility through new strategies involving nutrition and physical activity to improve muscle function and prevent sarcopenia-related comorbidities. We developed expertise in 1) molecular mechanisms of skeletal muscle loss, 2) interactions between skeletal muscle and body or ectopic adiposity, 3) specific and synergistic actions of food/nutrients and physical activity on muscle mass, metabolism and function, 4) clinical research and investigations on sarcopenia in ageing and chronic diseases.

- **Methodologies Used :**

Cellular and molecular biology
Cell line and primary cell culture
Gene knockdown (shRNA...)
Proteolysis and protein synthesis determination
Analysis of protein synthesis by stable isotope techniques
Gene expression measurement (RT-qPCR)
Immunohistochemistry
Mitochondrial activity and respiration
Skeletal muscle function evaluation
Nutritional interventions in Human and animal models
Access to human cohorts

Publications

Salles J, Chanet A, Berry A, Giraudet C, Patrac V, Domingues-Faria C, Rocher C, Guillet C, Denis P, Pouyet C, Bonhomme C, Le Ruyet P, Rolland Y, Boirie Y, Walrand S. (2017). Fast digestive, leucine-rich, soluble milk proteins improve muscle protein anabolism, and mitochondrial function in undernourished old rats., Mol Nutr Food Res.. 61(11),

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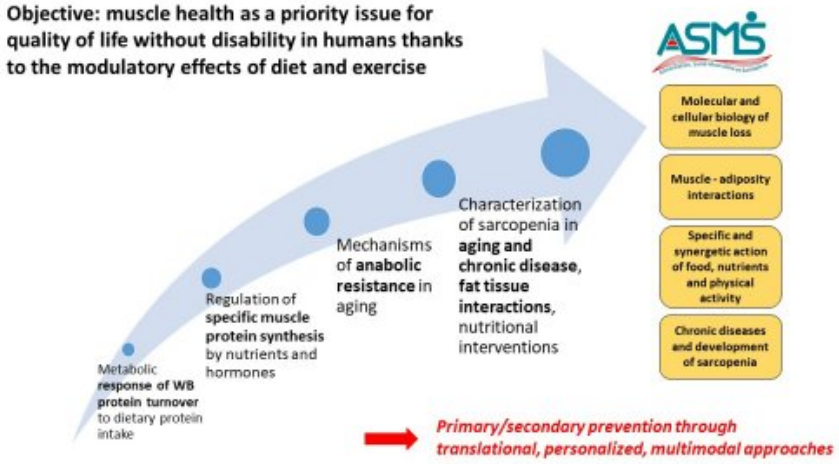
Pinel A, Rigaudière JP, Jouve C, Capel F. (2018). Modulation of Insulin Resistance and the Adipocyte-Skeletal Muscle Cell Cross-Talk by LCn-3PUFA., Int J Mol Sci.. 19(9), 2778

Le Bacquer O, Combe K, Patrac V, Ingram B, Combaret L, Dardevet D, Montaurier C, Salles J, Giraudet C, Guillet C, Sonenberg N, Boirie Y, Walrand S. (2019). 4E-BP1 and 4E-BP2 double knockout mice are protected from aging-associated sarcopenia., J Cachexia Sarcopenia Muscle. 10(3), 696-709

Le Bacquer O, Lanchais K, Combe K, Van Den Berghe L, Walrand S. (2020). Acute rimonabant treatment promotes protein synthesis in C2C12 myotubes through a CB1-independent mechanism., J Cell Physiol. 236(4), 2669-2683

Pinel A, Rigaudière JP, Jouve C, Montaurier C, Jousse C, LHomme M, Morio B, Capel F. (2021). Transgenerational supplementation with eicosapentaenoic acid reduced the metabolic consequences on the whole body and skeletal muscle in mice receiving an obesogenic diet., Eur J Nutr .. (),



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Key facts

Team

- Researchers : 9
- Technicians : 2
- Postdoc fellows : 2
- PhD Students : 3

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- mexico
- germany

Keywords

- mitochondria, energy metabolism, mitochondrial dynamics, Crabtree, Warburg
- Oxygraphy, Sepctrophotometry, Fluorimetry

Anne Devin

Cell energy metabolism

Université de Bordeaux
CNRS UMR 5095
Bertrand Daignan-Fornier
Bordeaux

Unique combination of competencies in our team that studies cell energy metabolism and dynamics in isolated mitochondria, permeabilized cell and whole cells in a wide range of models : yeast, cultured cells, mouse. Our lab is at the forefront of research on mitochondrial energetics and dynamics.

Research Brief :

Cell energy metabolism includes energy conversion that leads to NADH reoxydation and ATP production. Two cellular pathways are involved in these processes: glycolysis and oxidative phosphorylation (mitochondria). Our laboratory is primarily involved in studying the control and regulation of oxidative phosphorylation during cell proliferation. Indeed the cellular needs for both ATP synthesis and NADH reoxydation are susceptible to huge variations with rapid kinetics and this requires tight adjustments from the cell. We thus study the mechanisms that allow such adjustments. This is achieved at three levels of integration: the cellular level, the isolated mitochondria level and the oxidative phosphorylation complexes level.
Furthermore, the influence of alterations of mitochondrial dynamics on energy metabolism is studied. Mitochondrial dysfunction is a common cause of disease in both children and adults. Within the cell mitochondria form a dynamic network as a result of balanced fusion and fission. Mammalian mitofusin 1 and mitofusin 2 belong to the GTPase family of proteins and are required for mitochondrial outer membrane fusion. The recent discovery of the role of MFN2 in maintaining the activity of the mevalonate pathway could help to address the great diversity of phenotypes related to the loss of MFN2 through a common metabolic origin.

- **Methodologies Used :**

The Laboratory possesses last generation Oroboros oxygraphs, Hitachi F7000 fluorimeter highly sensitive bioluminometer, spectrophotometers, thermal cycler....
The methodologies used range from molecular biology, western blotting, energy metabolism assessment, cell biology.

Publications

Diaz-Ruiz R, Rigoulet M, Devin A. (2011). The Warburg and Crabtree effects: On the origin of cancer cell energy metabolism and of yeast glucose repression., BBA bioenergetics. 1807(6), 568-76

Sauvanet C, Duvezin-Caubet S, Salin B, David C, Massoni-Laporte A, di Rago JP, Rojo M (2012). Mitochondrial DNA mutations provoke dominant inhibition of mitochondrial inner membrane fusion., PLOS one. 7(11), e49639

Mazat JP, Ransac S, Heiske M, Devin A, Rigoulet M. (2013). Mitochondrial energetic metabolism-some general principles., IUBMB Life. 65(3), 171-9

Yoboue ED, Mougeolle A, Kaiser L, Averet N, Rigoulet M, Devin A. (2014). The role of mitochondrial biogenesis and ROS in the control of energy supply in proliferating cells., BBA bioenergetics. 1837(7), 1093--8

Mourier A, Motori E, Brandt T, Lagouge M, Atanassov I, Galinier A, Rappl G, Brodesser S, Hultenby K, Dieterich C, Larsson NG. (2015). Mitofusin 2 is required to maintain mitochondrial coenzyme Q levels., J Cell Biol.. 208(4), 429-42

Hammad N, Rosas-Lemus M, Uribe-Carvajal S, Rigoulet M, Devin A. (2016). The Crabtree and Warburg effects: Do metabolite-induced regulations participate in their induction?, BBA bioenergetics. 1857(8), 1139-46.

Devin Anne - Anne.Devin@ibgc.cnrs.fr - 0556999035 - http://ibgc.cnrs.fr/?page=equipe&eq=mec

Mario Pende

Cell growth control by nutrients

Paris Cité university
INSERM U1151
Fabiola Terzi
Paris

Key facts

Team

- Researchers : 3
- Technicians : 2
- Postdoc fellows : 5
- PhD Students : 5

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- Growth
- Signal transduction
- mTOR
- Biochemistry
- Cell biology
- Mouse models

Biological Resources

- Mouse models

Functional studies to dissect the growth and metabolic control by signal transduction pathways

Research Brief :

In metazoans, nutrient and growth factor availability control cell number, size and metabolic homeostasis. We investigate the specific programs underlying these responses, and their coordination by signal transduction mechanisms.

- **Methodologies Used :**

Mouse models of cancer and metabolic diseases
Metabolomics
Genome editing
Viral vectors
Signal transduction
Autophagy flux
Translation

Publications

Espeillac C., Mitchell C., Celton-Morizur S., Chauvin C., Koka V., Gillet C., Albrecht J.H., Desdouets C., Pende M. (2011). S6 kinase 1 activity is required for rapamycin-sensitive liver proliferation after mouse hepatectomy, Journal of Clinical Investigation. (),

Panasyuk G., Espeillac C., Chauvin C., Pradelli L.A., Horie Y., Suzuki A., Annicotte J.S., Fajas L., Foretz M., Verdeguer F., Pontoglio M., Ferré P., Scoazec J.Y., Birnbaum M.J., Ricci J.E., Pende M. (2012). PPAR? contributes to PKM2 and HK2 expression in fatty liver., Nature Communications. (),

Liang N., Zhang C., Dill P., Panasyuk G., Pion D., Koka V., Gallazzini M., Olson E.N., Lam H., Henske E.P., Dong Z., Apte U., Pallet N., Johnson R.L., Terzi F., Kwiatkowski D.J., Scoazec J-Y., Martignoni G., Pende M. (2014). Regulation of YAP by mTOR and autophagy reveals a therapeutic target of tuberous sclerosis complex., Journal of Experimental Medicine. (),

*Class III PI3K regulates organismal glucose homeostasis by providing negative feedback on Nemazanyy I., Montagnac G., Russell R.C., Morzyglod L., Burnol A.F., Guan K.L., Pende M. *, Panasyuk G. hepatic insulin signalling. (2015). Class III PI3K regulates organismal glucose homeostasis by providing negative feedback on hepatic insulin signalling., Nature Communications. (),*

Barilari M., Bonfils G., Treins C., Koka V., De Villeneuve D., Fagrega S., Pende M. (2017). ZRF1 is a novel S6 kinase substrate that drives the senescence program, EMBO Journal. (),

Patitucci C., Couchy G., Bagattin A., Cañeque T., de Reyniès A., Scoazec J-Y, Rodriguez R., Pontoglio M., Zucman-Rossi J., Pende M. and Panasyuk G. (2017). HNF1? suppresses steatosis associated liver cancer by inhibiting PPAR? transcription, Journal of Clinical Investigation. (),*

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Institut Valrose Biologie

Ez-Zoubir Amri

Cellular and molecular regulation of fat mass

Université Côte d'Azur
CNRS UMR 7277 Inserm U1091
Stéphane Noselli
Nice

Key facts

Team

• Researchers : 3
• Technicians : 1
• Postdoc fellows : 0
• PhD Students : 1

Translational approaches

• Patents : 2
• Clinical research grants : 1
• Industry partnerships : 0

Keywords

• brown/brite adipocytes
• oxytocin
• differentiation
• Obesity
• human adipose derived stem cells
• lipid metabolism
• microRNA
• gene expression
• Cell culture
• oxygen consumption

Biological Resources

• Human multipotent adipose tissue derived stem cells

Use of unique cellular model, human multipotent adipose-derived stem (hMADS) cells, which differentiate into white adipocytes and convert into functional brown adipocytes

Research Brief :

Obesity reached epidemic proportions with no satisfactory treatment so far. Furthermore weight gain and fat mass redistribution represent a worldwide problem with aging as a larger proportion of the adult population is at risk of developing obesity, osteoporosis and associated diseases. Development of new therapies to control fat mass and its associated diseases, will be of great interest in terms of public health.
The objectives of our research program deal with the regulation of fat mass by two complementary approaches that are i) to favor the recruitment of functional brown adipocytes to enhance energy expenditure and ii) to lower the recruitment of white adipocytes by studying the role of oxytocin.
In contrast to early contention, healthy adult humans possess active brown adipose tissue with a potential for metabolic significance. Identification of factors leading to increased mass/activity of human brown adipose tissue are of great interest for the treatment of overweight/obesity. For this purpose, we set up a unique cellular model, human multipotent adipose-derived stem (hMADS) cells, which differentiate into white adipocytes and are able to convert into functional brown adipocytes. Our first aim deals with the analysis of mechanisms of conversion of human white to brown adipocytes and to identify potential therapeutic targets. Our second aim focus on the oxytocin involvement in the control of fat mass and in its distribution between adipose depots in animal models.

• **Methodologies Used :**

-Molecular and cellular biology
- Cell signalling
- Primary cell culture
- Animal models

Publications

Beranger GE, Pisani DF, Castel J, Djedaini M, Battaglia S, Amiaud J, Boukhechba F, Ailhaud G, Michiels JF, Heymann D, Luquet S, Amri EZ (2014). Oxytocin reverses ovariectomy-induced osteopenia and body fat gain., Endocrinology. 155(4), 1340-52

Pisani DF, Beranger GE, Corinus A, Giroud M, Ghandour RA, Altirriba J, Chambard JC, Mazure NM, Bendahhou S, Duranton C, Michiels JF, Frontini A, Rohner-Jeanrenaud F, Cinti S, Christian M, Barhanin J and Amri EZ (2016). The K+ channel TASK1 modulates beta-adrenergic response in brown adipose tissue through the mineralocorticoid receptor pathway, FASEB J. 30(2), 909

Ghandour RA, Colson C, Giroud M, Maurer S, Rekima S, Ailhaud G, Klingenspor M, Amri EZ, Pisani DF (2018). Impact of dietary omega3 polyunsaturated fatty acid supplementation on brown and brite adipocyte function., J Lipid Res. 53(452), 461

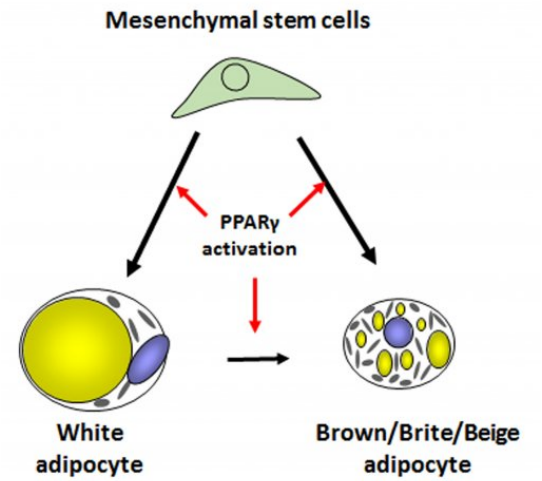
Didier F. Pisani, Valentin Barquissau, Jean-Claude Chambard, Diane Beuzelin, Rayane A. Ghandour, Maude Giroud, Aline Mairal, Sophie Pagnotta, Saverio Cinti, Dominique Langin, Ez-Zoubir Amri (2018). Mitochondrial fission is associated with UCP1 activity in human brite/beige adipocytes, Molecular Metabolism. 7(35), 44

Breuil V, Panaia-Ferrari P, Fontas E, Roux C, Kolta S, Eastell R, Ben Yahia H, Faure S, Gossiel F, Benhamou CL, Euller-Ziegler L, Amri EZ (2020). The Rosmarinus Bioactive Compound Carnosic Acid Is a Novel PPAR Antagonist That Inhibits the Browning of White Adipocytes, Cells. 9(11),

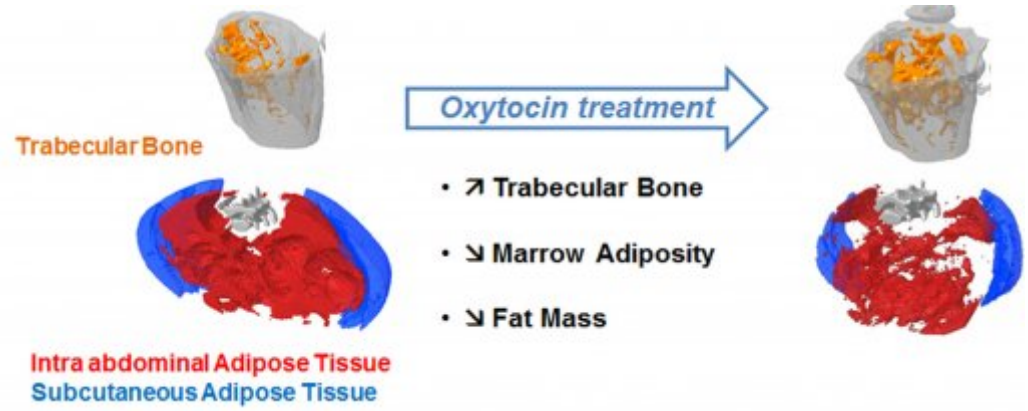
Roux CH, Pisani DF, Gillet P, Fontas E, Yahia HB, Djedaini M, Ambrosetti D, Michiels JF, Panaia-Ferrari P, Breuil V, Pinzano A et Amri EZ (2020). Oxytocin Controls Chondrogenesis and Correlates with Osteoarthritis, Int J Mol Sci. 21(11),

Amri Ez-Zoubir - amri@unice.fr - +33 493 37 70 82 - http://ibv.unice.fr/research-team/amri/

Conversion of white to brite adipocyte



Oxytocin controls fat and bone mass



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Serge Luquet

Central Control of Feeding Behaviour and Energy Expenditure C2OFFEE

Université de Paris Université de Paris
CNRS UMR 8251
Jean-Marie Université de Paris
paris

Key facts

Team

- Researchers : 3
- Technicians : 2
- Postdoc fellows : 1
- PhD Students : 1

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 8

International research links

- Netherland
- USA
- Germany

Keywords

- regulation of energy balance
- central nervous system
- feeding behavior
- Mice model for neuron-specific cell knock out
- euglycemic hyperisulinemic clamp study
- Fiber photometry (calcium imaging in vivo)
- Chemogenetic approaches

Biological Resources

- -Mice model for conditional inactivation of the N-acylphosphatidylethanolamine phospholipase-D (NAPE-PLD), a key enzyme in the processing of endocannabinoid and N-acyl ethanolamide such as oleoylethanolamide (OEA).
- -Mice model for conditional expression of Peroxisome Proliferator-Activated Receptors delta (PPARd) or a dominant negative form of this receptor

Fully integrated approaches are combined with genetic tools to study the mechanism that link the central nervous system with the regulation of energy balance and peripheral glucose metabolism.

Research Brief :

The core approach of my research group C2OFFEE (http://bfa.univ-paris-diderot.fr/equipe-5/) is to leverage the power of modern molecular genetic tools and mouse models in integrated approaches in order to dissect out the role of discrete neural circuit elements in the control of different aspect of energy balance including feeding behavior notably in its rewarding & motivational component together with energy expenditure and nutrient partitioning. A recent achievement was to identify a novel role for a hypothalamic circuitry in AgRP-neurons in the coordination of efferent organ activity and nutrient partitioning, providing a mechanistic link between obesity and obesity-related disorders. In addition we recently demonstrated that when AgRP-neurons ?activity is compromised through genetic, pharmacologic or dietary intervention (such as diet-induced obesity)-feeding behaviour is no longer dependent on metabolic demands but prominently rely on dopamine-encoded reward and leads to compulsive/comfort feeding. Finally we also highlighted a unique mechanism by which nutritional lipids can directly act on the brain to modulate food reward as a possible mechanism for addictive-like behaviour associated with high fat diet.

- **Methodologies Used :**

- Viral-mediated genetic modification of brain nuclei through stereotactic approaches, optogenetic and pharmacogenetic approaches
- Neurons-specific depletion (genetic engineering of Diphtheria receptor specific expression)
- In vivo indwelled chronic perfusion (carotid & jugular vein, intracerebroventricular)
- In vivo analysis of insulin sensitivity (euglycemic hyperinsulinemic clamp, insulin tolerance test)
- Microsurgery (catheter, cannula implant, vagal deafferentation, bariatric surgery in mice)
- In vivo assessment of motivated behaviour and positive reinforcement (conditioned place preference and operant behaviour)
- In vivo assessment of metabolic efficiency and energy balance using integrated indirect calorimetry

Publications

Sun, X., Luquet, S., Small, DM (2017). DRD2: Bridging the genome and ingestive behavior, Trends Cogn Sci. 21(273), 372-384

Berland, C., Montalban, E., Perrin, E., Di Miceli, M., Nakamura, Y., Martinat, M., Sullivan, M., Davis, X.S., Shenasa, M.A., Martin, C., Tolu, S., Marti, F., Caille, S., Castel, J., Perez, S., Salinas, C.G., Morel, C., Hecksher-Sorensen, J., Cador, M., Fioramonti, X., Tschop, M.H., Laye, S., Venance, L., Faure, P., Hnasko, T.S., Small, D.M., Gangarossa, G., and Luquet, S.H. (2020). Circulating Triglycerides Gate Dopamine-Associated Behaviors through DRD2-Expressing Neurons. Cell Metab, Cell Metabolism. 31(e711), 773-790

Bakker, W., Salinas, C.G., Imbernon, M., Chao, D.H.M., Hassouna, R., Morel, C., Martin, C., Gangarossa, G., Denis, R.G., Castel, J., Peter, A., Heni, M., Maetzler, W., Nielsen, H.S., Duquenne, M., Secher, A., Hecksher-Sørensen, J., Åskov Pedersen, T., Prevot, V., and Luquet, S (2020). Acute changes in systemic glycaemia gate access and action of GLP-1R agonist on brain structures controlling energy homeostasis, bioRxiv. 2007(2011), 198341

Dalenberg, J.R., Patel, B.P., Denis, R., Veldhuizen, M.G., Nakamura, Y., Vinke, P.C., Luquet, S., and Small, D.M (2021). Short-Term Consumption of Sucralose with, but Not without, Carbohydrate Impairs Neural and Metabolic Sensitivity to Sugar in Humans, Cell Metabolism. 31(e497), 493-502

Berland, C., Castel, J., Montalban, E., Foppen, E., Martin, C., Muccioli, G.G., Luquet, S., and Gangarossa, G (2021). Identification of an endocannabinoid gut-brain vagal mechanism controlling food reward and energy homeostasis, bioRxiv. 2011(2014), 382291

Denis, RG., Joly, A., Webber, E., Langlet, F., Schaeffer, M., Padilla, S., Cansell, C., Dehouck, B., Castel, J., Delbes, AS., Martinez, S.,Lacombe, A., Rouch, C., Kassis, N., Fehrentz,J-A., Martinez, J, Verdié, P., Hnasko, T, Palmiter, RD., Krashes, MJ., Güler, A., Magnan, C., Luquet, S (201515). Palatability can drive feeding independent of AgRP neurons, Cell Metabolism. 22(646),

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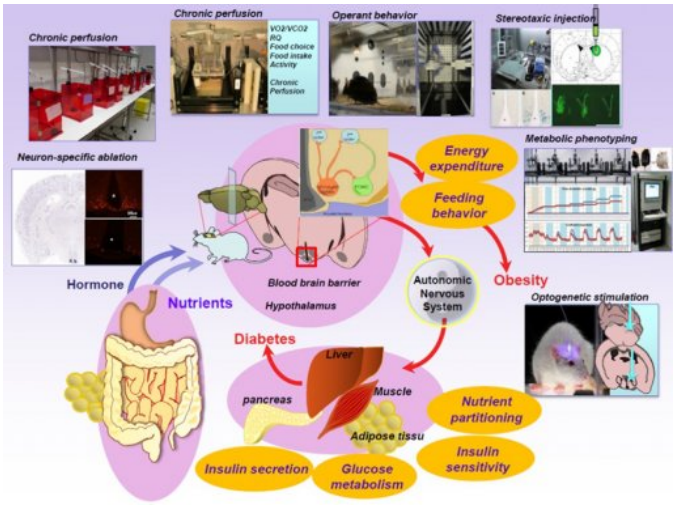
C2OFFE team main Technic & goals



The core approach of my research group C2OFFEE (http://bfa.univ-paris-diderot.fr/equipe-5/) is to leverage the power of modern molecular genetic tools and mouse models in integrated approaches in order to dissect out the role of discrete neural circuit elements in the control of different aspect of energy balance including feeding behavior notably in its rewarding & motivational component together with energy expenditure and nutrient partitioning.

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Key facts

Team

- Researchers : 5
- Technicians : 3
- Postdoc fellows : 0
- PhD Students : 2

Translational approaches

- Patents : 2
- Clinical research grants : 0
- Industry partnerships : 2

International research links

- Switzerland
- Italy
- UK

Keywords

- obesity
- animal models
- brain lipid sensing
- central nervous system
- olfaction
- hyperinsulinemic-euglycemic clamps
- isolated islets
- feeding behavior
- electrophysiology
- indirect calorimetry

Biological Resources

- In vivo models of obesity and type 2 diabetes
- Database (RNAseq, lipidomics) in tissues (liver, B cell, skeletal muscles) and plasma

Christophe Magnan

REGLYS (Regulation of glycemia by nervous system)

Université Paris Cité
CNRS UMR8251
Jean-Marie Dupret
Paris

Recognized expertise in study of brain lipid sensing and regulation of energy balance in rodents

Research Brief :

Our research is aimed at studying nervous control of energy balance in preclinical models of obesity and type 2 diabetes. Three main topics are studied: i/ effect of peripheral signals (hormones, nutrients) conveying to central nervous system on sensitive neurons located in specific brain areas (hypothalamus, brainstem, hippocampus). ii/ Identification of molecular mechanisms underlying effect of peripheral singal in those neurons ; iii/ signal emerging from SNC and regulating energy balance (including insulin secretion and action, feeding behavior, hepatic glucose production). Preclinical models are mice or rats either made obese and/or diabetic using genetic approaches or high fat/high feeding food. Measured parameters include : glucose turnover rate, insulin sensitivity, energy expenditure (indirect calorimetry), food intake, body weight composition, etc.

- **Methodologies Used :**

Hyperinsulinemic-euglycemic clamp in freely moving mice and rats
Chronic infusion
AAV, lentiviral injection
Indirect calorimetry

Publications

Wigger L, Cruciani-Guglielmacci C, Nicolas A, Denom J, Fernandez N, Fumeron F, Marques-Vidal P, Ktorza A, Kramer W, Schulte A, Le Stunff H, Liechti R, Xenarios I, Vollenweider P, Waeber G, Uphues I, Roussel R, Magnan C, Ibberson M, Thorens B (2017). Plasma Dihydroceramides Are Diabetes Susceptibility Biomarker Candidates in Mice and Humans, Cell Reports. (),

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Bravo-San Pedro JM, Sica V, Martins I, Pol J, Loos F, Maiuri MC, Durand S, Bossut N, Aprahamian F, Anagnostopoulos G, Niso-Santano M, Aranda F, Ramírez-Pardo I, Lallement J, Denom J, Boedec E, Gorwood P, Ramoz N, Clément K, Pelloux V, Rohia A, Pattou F, Raverdy V, Caiazzo R, Denis RGP, Boya P, Galluzzi L, Madeo F, Migrenne-Li S, Cruciani-Guglielmacci C, Tavernarakis N, López-Otín C, Magnan C, Kroemer G (2019). Acyl-CoA-Binding Protein Is a Lipogenic Factor that Triggers Food Intake and Obesity, Cell Metabolism. (),

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Meneyrol K, Estévez-Salguero Á, González-García I, Guitton J, Taouis M, Benomar Y, Magnan C, López M, Le Stunff H. (2022). Ovarian insufficiency impairs glucose-stimulated insulin secretion through activation of hypothalamic de novo ceramide synthesis, Metabolism. (),

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Gaëlle Boudry

Control of eating behaviors

Rennes University
INRAE U1341 Inserm U1241
Olivier Loreal
Rennes

Our uniqueness is to gather experts in behavior, neurosciences, psychology, gut physiology, microbiota and to use various models, including the porcine model and clinical trials, and tools, from organoid culture to brain imaging, to tackle altered eating behaviors leading to overweight and obesity

Key facts

Team

- Researchers : 14
- Technicians : 10
- Postdoc fellows : 0
- PhD Students : 9

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- New Zealand
- China
- Brazil

Keywords

- eating behavior
- microbiota-gut-brain axis
- cortico-striatal interactions
- development origin of health and disease (DoHAD)
- brain imaging
- porcine model
- organoids

Biological Resources

- animal models, including pig and mini-pig
- in vitro tools (intestinal organoids, multi-cellular epithelium models)
- cohorts with biological samples (feces, plasma, urine, breast milk)

Research Brief :

The objectives of the 'Control of eating behaviors' team composed of 14 scientists and 10 technicians from INRAE, University of Rennes, Rennes Hospital and EHESP with complementary expertise in nutrition, intestinal physiology, gut microbiota, neonatology, ethology, neurobiology, addictology, brain imaging and health psychology are 1- to unravel the links between western-type diet consumption and the development of eating behavior abnormalities or pathologies leading to overconsumption and ultimately to overweight and obesity and 2- to validate innovative interventions aimed at preventing or restoring altered eating behaviors.
Two thematic axis have been defined to reach these two specific objectives. The first axis is to investigate how diet, through its impact on microbiota composition and metabolic activity, alters the intestinal signals regulating food intake. Attention will be paid on how this microbiota-gut-brain axis develops in early life. The second axis focus on the dysregulation of the cortical bilateral interactions with the reward system leading to hyperphagia, cravings or even food and alcohol addiction. Brain imaging assisted-innovative interventions, from motivational brief therapeutic interventions, alimentary and pharmacological approaches to neurofeedback will be implemented to prevent and treat these eating behavior alterations.

- **Methodologies Used :**

brain imaging (fMRI both in Humans and in animal models)
behavior tests especially in the porcine model
metabolomic (mass spec, MNR) and metagenomic (16S, MinION) analyses of the gut microbiota
cell culture models
(immuno)-histology, molecular biology
questionnaire approaches

Publications

Coquery N., Menneson S., Meurice P., Janvier R., Etienne P., Noirot V., Val-Laillet D. (2019). fMRI-Based Brain Responses to Olfactory Stimulation with Two Putatively Orexigenic Functional Food Ingredients at Two Different Concentrations in the Pig Model, Journal of Food Science. 84(9), 2666-2673

Constant A., Boulic G., Lommez A., Chaillou R., Guy-Grand B., Raffin S. (2020). Locally implemented prevention programs may reverse weight trajectories in half of children with overweight/obesity amid low child-staff ratios: results from a quasi-experimental study in France, BMC Public Health. 20(), 941

Fouesnard M, Zoppi J, Petera M, Le Gleau L, Migné C, Devime F, Durand S, Benani A, Chaffron S, Douard V, Boudry G. (2021). Dietary switch to Western diet induces hypothalamic adaptation associated with gut microbiota dysbiosis in rats, Int J Obes (Lond). 45(6), 1271-1283

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Charton E, Bourgeois A, Bellanger A, Le-Gouar Y, Dahirel P, Romé V, Randuineau G, Cahu A, Moughan PJ, Montoya CA, Blat S, Dupont D, Deglaire A, Le Huërou-Luron I (2022). Infant nutrition affects the microbiota-gut-brain axis: Comparison of human milk vs. infant formula feeding in the piglet model., Front Nutr. 9(1), 976042

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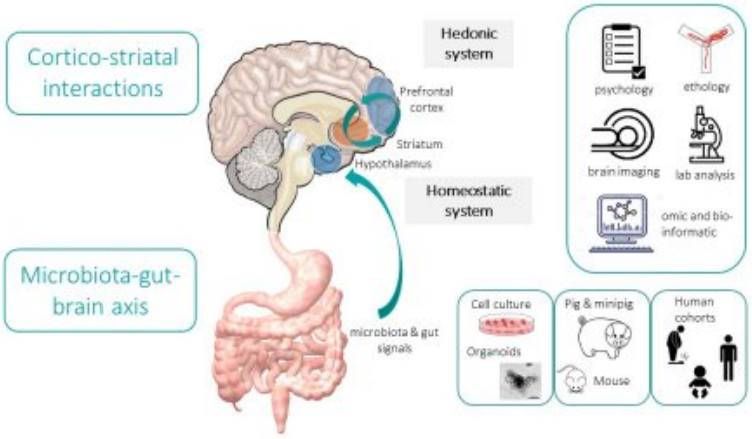
Graphical abstract of the team



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David Jacobi

Diurnal mitochondrial rhythms and metabolic diseases

Université de Nantes
CNRS UMR6291 Inserm UMR1087
Richard Redon
Nantes

A unique approach combining circadian and mitochondrial biology

Key facts

Team

- Researchers : 2
- Technicians : 0
- Postdoc fellows : 1
- PhD Students : 1

Translational approaches

- Patents : 0
- Clinical research grants : 1
- Industry partnerships : 0

Keywords

- Metabolic diseases
- Mitochondrial dynamics
- Circadian rhythms
- Mouse metabolic phenotyping
- Mouse models of overnutrition

Research Brief :

Over 50% of adults in European Union (EU) countries are overweight and therefore at risk of developing metabolic diseases such as type 2 diabetes or non-alcoholic steatohepatitis. The characteristics of modern lifestyle, such as excessive consumption of food and sedentary behaviour, contribute to this situation. But we also see changes in feeding and sleep / wake rhythms that contribute to overweight and metabolic complications. However, the mechanisms linking irregular lifestyles to overweight and metabolic complications are poorly understood.

The rationale for our research program is based on the following observations:
1. The liver plays a central role in adapting to physiological alternation between fasting / fed state.
2. Liver metabolism is regulated by an internal clock.
3. The control of mitochondria by the hepatic clock is essential to the normal functioning of the liver (Jacobi et al., Cell Metabolism 2015).

We therefore use in vitro and in vivo approaches to study hepatocyte metabolism. Genetic, pharmacological, and metabolic approaches are used to delineate the molecular mechanisms by which overnutrition and loss of circadian synchrony disturbs mitochondrial rhythms. Then, we establish how these alterations trigger metabolic diseases.
We take advantage of the unique environment of the Institut du Thorax and its research unit to demonstrate the relevance of our results in clinical populations of obese patients.

Methodologies Used :

Clock deficient and time-restricted fed mice
Synchronized hepatocytes
Super resolution microscopy
Mitochondrial lipidomics
Resonance paramagnetic spectrometry

Publications

Jacobi D, Liu S, Burkewitz K, Kory N, Knudsen NH, Alexander RK, Unluturk U, Li X, Kong X, Hyde AL, Gangl MR, Mair WB, Lee CH (2015). Hepatic Bmal1 Regulates Rhythmic Mitochondrial Dynamics and Promotes Metabolic Fitness, Cell Metab. 22(4), 709-20

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http://www.umr1087.univ-nantes.fr/team-v-diurnal-mitochondrial-rhythms-and-metabolic-diseases--2109816.kjsp?RH=1357742119874

Bertrand Cariou

Dyslipidemias and lipotoxicity

Université de Nantes
Inserm UMR1087 CNRS UMR6291
Richard Redon
Nantes

Key facts

Team

- Researchers : 6
- Technicians : 8
- Postdoc fellows : 3
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- Canada
- The Netherlands
- Sweden

Keywords

- lipoprotein metabolism
- PCSK9 & TICE
- Lipodystrophy and adipocyte function
- iPSC
- dyslipidemia
- Cell culture, cell biology
- Target discovery
- Gene/function analysis

Research Brief :

The team uses translational research to study molecular and clinical aspects of dyslipidemias, particularly the metabolism of LDL-cholesterol, which is a major independent cardiovascular risk factor. We are trying to identify new pathways for cholesterol excretion.
Our projet relies on 3 main research programs:
1.Extrahepatic function of PCSK9: (i) focused on the role of PCSK9 in the intestine (C. Le May); (ii) focused on iPSCs differentiated into hepatocytes, as a research model for PCSK9 mutations (K. Si Tayeb)

2.Identification of novel therapeutic targets in the metabolism of LDL cholesterol (B. Cariou) : Familial hypobetalipoproteinemia is a pathology characterized by spontaneous very low levels of LDL-C. In more than 50% of cases, the genetic cause remains unknown. In close collaboration with clinicians, we are constituting cohorts of patients with FHBL. Genetic studies by exome sequencing are carried out in families with no mutations in the known genes in order to identify new genes and potential novel therapeutic targets.

3. Seipin and lipotoxicity (X. Prieur) : The model of lipodystrophic mice invalidated for seipin allows us to study the consequences of lipotoxicity in different organs. We are also developing a project focused on the study of the role of seipin in mature adipocytes.

Our team lead the RHU CHOPIN project (CHolesterol Personalized INnovation) which aims to establish personalized hypercholesterolemia care. www.rhuchopin.fr

Publications

Le May C, Berger JM, Lespine A, Pillot B, Prieur X, Letessier E, Hussain MM, Collet X, Cariou B, Costet P. (2013). Transintestinal cholesterol excretion is an active metabolic process modulated by PCSK9 and statin involving ABCB1., Arterioscler Thromb Vasc Biol. 33(7), 1484-1493

Bonnefond A, Yengo L, Le May C, Fumeron F, Marre M, Balkau B, Charpentier G, Franc S, Froguel P, Cariou B, DESIR study group. (2015). The loss-of-function PCSK9 p.R46L genetic variant does not alter glucose homeostasis., Diabetologia. 58(9), 2051-2055

Si-Tayeb K, Idriss S, Champon B, Caillaud A, Pichelin M, Arnaud L, Lemarchand P, Le May C, Zibara K, Cariou B. (2016). Urine-sample-derived human induced pluripotent stem cells as a model to study PCSK9-mediated autosomal dominant hypercholesterolemia., Dis Model Mech. 9(1), 81-90

Dollet L, Levrel C, Coskun T, Le Lay S, Le May C, Ayer A, Venara Q, Adams AC, Gimeno RE, Magré J, Cariou B, Prieur X. (2016). FGF21 Improves the Adipocyte Dysfunction Related to Seipin Deficiency., Diabetes. 65(11), 3410-3417

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Blanchard C, Moreau F, Ayer A, Toque L, Garçon D, Arnaud L, Borel F, Aguesse A, Croyal M, Krempf M, Prieur X, Neunlist M, Cariou B, Le May C. (2018). Roux-en-Y gastric bypass reduces plasma cholesterol in diet-induced obese mice by affecting trans-intestinal cholesterol excretion and intestinal cholesterol absorption., Int J Obes. 42(3), 552-560

Key facts

Team

- Researchers : 6
- Technicians : 4
- Postdoc fellows : 3
- PhD Students : 3

Translational approaches

- Patents : 2
- Clinical research grants : 1
- Industry partnerships : 3

International research links

- Switzerland; Germany
- Spain; Denmark
- USA; Canada

Keywords

- brain-periphery cross-talk
- hypothalamus
- obesity
- energy balance
- glucose metabolism
- genetically-modified mice
- neuroanatomy
- molecular biology
- pharmacology
- Clinical studies in patients with obesity

Biological Resources

- genetically-modified mice
- Cohorts of patients suffering from obesity/diabetes

Daniela Cota

Energy Balance and Obesity

University of Bordeaux
Inserm U1215
Stephane Oliet
Bordeaux

Recognized expertise in the use of integrated approaches to study brain-periphery cross-talk in animal models of obesity, and clinical investigations in patients suffering from obesity and type 2 diabetes.

Research Brief :

Obesity represents a global epidemic lacking efficient therapeutic options. This highlights the insufficient knowledge of the biological mechanisms regulating energy balance and the lack of therapeutically relevant targets. The brain and in particular the hypothalamus plays a key role in the regulation of energy balance. Hence, the main scope of our research is to understand how exactly hypothalamic cells and related circuits adapt and respond to energy availability in order to control food intake, body weight and peripheral metabolism. To address our research questions we use an integrated approach spanning from the generation and in depth metabolic characterization of genetic animals models to the use of state-of-the-art neuroscience techniques for the investigation of neuronal circuits of interest. Our work has so far critically contributed to understanding the roles of lipid-based, energy-related signaling systems, such as the endocannabinoid-CB1 and, more recently, the bile acids-TGR5 systems, and the energy sensor mTOR, in the brain-periphery crosstalk regulating energy balance. In addition, we perform clinical research studies aimed at characterizing obese phenotypes in humans, which are expected to lead to better, personalized therapies.

Methodologies Used :

Genetic mouse models; in vivo mouse phenotyping in terms of energy intake and use (feeding behavior, indirect calorimetry, locomotor activity); in vivo glucose metabolism (GTT, ITT, PTT); in vivo body composition analysis; stereotaxic approaches for viral-mediated genetic modification in brain structures / cell types of interest; in vivo chemogenetics and neuronal calcium imaging coupled with feeding behavior analysis; neuroanatomical approaches (CUBIC clearing, RNAscope, FISH, Immunofluorescence); western blots; pharmacology (ip, gavage, sc, intracerebroventricular). The team has also access to several platforms within the INSERM U1215 Magendie Institute (qPCR, MACS, NGS, LC-MSMS, mice breeding, genotyping, laser capture microdissection).

Publications

André C, Guzman-Quevedo O, Rey C, Remus-Borel J, Ladeveze E, Leste-Lasserre T, Abrous DN, Nadjar A, Layé S, Cota D (2017). Inhibiting Microglia Expansion Prevents Diet-induced Hypothalamic and Peripheral Inflammation., Diabetes. 66(4), 908-919

Zizzari P, He R, Falk S, Bellocchio L, Allard C, Clark S, Lesté-Lasserre T, Marsicano G, Clemmensen C, Perez-Tilve D, Finan B, Cota D, Quarta C* (2021). CB1 and GLP-1 Receptors Cross Talk Provides New Therapies for Obesity., Diabetes. 7(2), 415-422*

Quarta C, Claret M, Zeltser LM, Williams KW, Yeo GSH, Tschöp MH, Diano S, Brüning JC, Cota D. (2021). POMC neuronal heterogeneity in energy balance and beyond: an integrated view., Nature Metabolism. 3(3), 299-308

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Saucisse N, Mazier W, Simon V, Binder E, Catania C, Bellocchio L, Romanov RA, Léon S, Matias I, Zizzari P, Quarta C, Cannich A, Meece K, Gonzales D, Clark S, Becker JM, Yeo GSH, Fioramonti X, Merkle FT, Wardlaw SL, Harkany T, Massa F, Marsicano G, Cota D (2021). Functional heterogeneity of POMC neurons relies on mTORC1 signaling., Cell Reports. 37(2), 109800

Castellanos-Jankiewicz A, Guzmán-Quevedo O, Fénelon VS, Zizzari P, Quarta C, Bellocchio L, Tailleux A, Charton J, Fernandois D, Henricsson M, Piveteau C, Simon V, Allard C, Quemener S, Guinot V, Hennuyer N, Perino A, Duveau A, Maitre M, Leste-Lasserre T, Clark S, Dupuy N, Cannich A, Gonzales D, Deprez B, Mithieux G, Dombrowicz D, Bäckhed F, Prevot V, Marsicano G, Staels B, Schoonjans K, Cota D (2021). Hypothalamic bile acid-TGR5 signaling protects from obesity., Cell Metabolism. 33(7), 1483-1492.e10.

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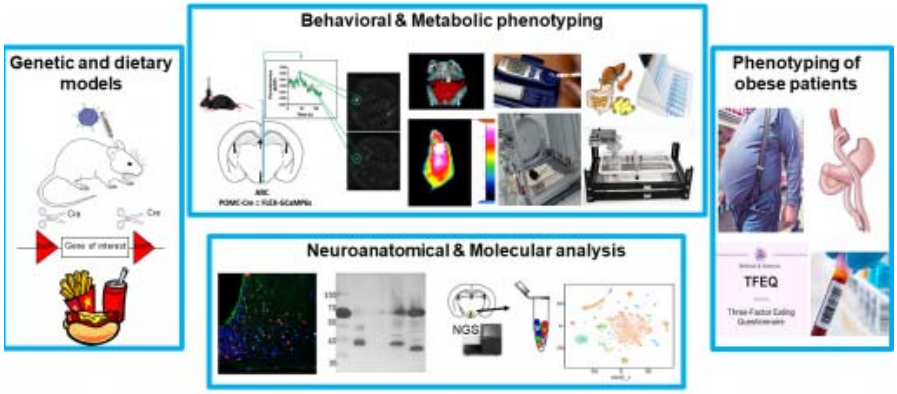
General Research Strategy Team Energy Balance and Obesity



Schema illustrating the general research strategy developed by the Team Cota at the Neurocentre Magendie, INSERM U1215, in Bordeaux (for more details please visit: http://www.neurocentre-magendie.fr/cota)

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Institut NeuroMyoGène

Vincent Jacquemond

Excitability and calcium signaling in normal and diseased skeletal muscle

Univ Claude Bernard Lyon 1
INSERM U1315 CNRS UMR5261
Laurent Schaeffer
Lyon

The team is the only one in Europe and one of the 2-3 worldwide to master a combination of electrophysiology and fluorescence detection on differentiated muscle fibers isolated from normal or in vivo-transfected mouse muscles.

Key facts

Team

- Researchers : 3
- Technicians : 1
- Postdoc fellows : 1
- PhD Students : 1

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- Japan
- Chile
- Hungary

Keywords

- excitation-contraction coupling
- calcium homeostasis
- ion channels
- skeletal muscle
- muscle diseases
- fluorescence
- confocal microscopy
- cellular and molecular biology
- electrophysiology

Biological Resources

- A collection of plasmids encoding biosensing fluorescent probes and a variety of wild-type and mutated forms of muscle proteins involved in membrane excitability and Ca2+ signalling

Research Brief :

Our research is focused on the physiology and pathophysiology of skeletal muscle function. It aims at understanding how specific mechanisms involved in the control of skeletal muscle Ca2+ homeostasis and excitation-contraction (EC) coupling operate under normal and disease conditions. Muscle contraction is initiated when action potentials fired at the end-plate of the muscle cells propagate throughout the plasma membrane and trigger a conformational change of the CaV1.1 protein which gates open a Ca2+ release channel (type 1 ryanodine receptor, RyR1) in the sarcoplasmic reticulum (SR) membrane. Ca2+ then gets released from the SR into the cytosol and triggers contraction. Besides Ca2+ release from the SR there is also Ca2+ entry from the extracellular medium. Our main current projects aim at: 1- Understanding basic mechanisms involved in the regulation of CaV1.1 and of RyR1 function. 2- Demonstrating how excitability and/or EC coupling are altered by specific disease mutations affecting the genes encoding CaV1.1, RyR1 and also other proteins involved in the function and/or maintenance of the EC coupling machinery. The overall project stands on a set of methods and expertise that includes molecular biology and biochemistry, in vivo gene transfer and a state of the art combination of electrophysiology and fluorescence detection on single isolated differentiated muscle cells from mouse.

- **Methodologies Used :**

Single-cell electrophysiology in all configurations (whole-cell voltage-clamp - current-clamp - single channel recording) - Intracellular Ca2+ detection under conventional and confocal microscopy - In vivo gene transfer through electroporation - Molecular and cellular biology.

Publications

Berthier C, Kutchukian C, Bouvard C, Okamura Y, Jacquemond V (2015). Depression of voltage-activated Ca2+ release in skeletal muscle by activation of a voltage-sensing phosphatase, J Gen Physiol. 145(315), 330

Robin G, Allard B (2015). Voltage-gated Ca2+ influx through L-type channels contributes to sarcoplasmic reticulum Ca2+ loading in skeletal muscle, J Physiol. 593(4781), 4797

Kutchukian C, Lo Scrudato M, Tourneur Y, Poulard K, Vignaud A, Berthier C, Allard B, Lawlor MW, Buj-Bello A, Jacquemond V (2016). Phosphatidylinositol 3-kinase inhibition restores Ca2+ release defects and prolongs survival in myotubularin-deficient mice., PNAS. 113(14432), 14437

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Fuster C, Perrot J, Berthier C, Jacquemond V, Allard B (2017). Elevated resting H+ current in the R1239H type 1 hypokalaemic periodic paralysis mutated Ca2+ channel., J Physiol. 595(6417), 6428

Fuster C, Perrot J, Berthier C, Jacquemond V, Charnet P, Allard B (2017). Na leak with gating pore properties in hypokalemic periodic paralysis V876E mutant muscle Ca channel., J Gen Physiol.. 149(1139), 1148

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Catherine Creuzot-Garcher
Niyazi Acar

Eye, Nutrition & Cell Signalling

AgroSup Dijon Université Bourgogne Franche-Comté
INRA UMR1324 CNRS UMR6265
Loïc Briand
Dijon

Through a translational research approach, our team aims to transform scientific discoveries arising from laboratory on the role of both endogenous and dietary lipids in the retina into clinical applications in the prevention of aging of the retina.

Key facts

Team

- Researchers : 7
- Technicians : 5
- Postdoc fellows : 0
- PhD Students : 3

Translational approaches

- Patents : 0
- Clinical research grants : 2
- Industry partnerships : 7

Keywords

- Prevention
- Lipid nutrition
- Pathophysiology
- Aging
- Retina
- Biomarker
- Flow cytometry
- Electroretinography
- Funduscopy
- Angiography
- Tonometry
- qPCR
- Western-blotting
- Chromatography / Mass Spectrometry

Biological Resources

- Human subjects and patients
- Rodents (rats, conventional and transgenic mice)
- Retinal cell lines and primary cell cultures of retinal cells

Research Brief :

The demographic forecasts expect the elderly population to increase sharply in the next decades. Since eye diseases are the second most prevalent pathologies after the age of 65 years in Western countries, patients suffering from ocular pathologies are expected to represent a sensitive and growing socio-economic burden. Among those pathologies, age-related macular degeneration (AMD) and glaucoma are the leading cause of visual loss. Aging of the retina is characterized by specific clinical, functional and morphological features. Although lipids are key components of the retina, their roles are not fully defined. Lipids may both promote and prevent aging of the retina. Epidemiological studies have reported that dietary omega 3 fatty acids prevent from the development of AMD.
Through a translational research approach, our team aims to transform scientific discoveries arising from laboratory on the role of both endogenous and dietary lipids in the retina into clinical applications in the prevention of aging of the retina. Our projects aim to delineate whether lipids ? namely plasmalogens, cholesterol, and gangliodides ? and lipid metabolism participate in the functioning and dysregulations of the retina. The projects focus on 1) the mechanisms of lipid uptake to the retina, 2) the metabolic pathways that involve lipids as cell mediators in the retina, and 3) the links between pathologies and dysregulations of the lipid metabolism in the retina.

- **Methodologies Used :**

Patient evaluation
Animal and cell culture experiments
Electroretinography, funduscopy, angiography, tonometry
Biological evaluation (qPCR, Western-blotting, flow cytometry)
Chromatography (thin-layer, gas, high performance liquid), in tandem with mass spectrometry

Publications

Simon E, Bardet B, Grégoire S, Acar N, Bron AM, Creuzot-Garcher CP, Bretillon L (2011). Decreasing dietary linoleic acid promotes long chain omega-3 fatty acid incorporation into rat retina and modifies gene expression., Experimental Eye Research. 93(5), 628-35

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Alassane S, Binquet C, Cottet V, Fleck O, Acar N, Daniel S, Delcourt C, Bretillon L, Bron AM, Creuzot-Garcher C (2016). Relationships of Macular Pigment Optical Density With Plasma Lutein, Zeaxanthin, and Diet in an Elderly Population: The Montrachet Study., Investigative Ophthalmology & Visual Science. 57(3), 1160-7

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Key facts

Team

• Researchers : 5
• Technicians : 3
• Postdoc fellows : 3
• PhD Students : 5

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 0

International research links

• USA
• Israel
• Italy

Keywords

• Cognitive/executive function
• Fronto-striatal system
• Hippocampal system
• brain lipids
• obesogenic diet
• rodent behaviors
• manipulation of neuronal circuits
• in vivo calcium imaging
• ex vivo electrophysiology

Guillaume Ferreira Pierre Trifilieff

FoodCircus

Université de Bordeaux
INRAE UMR1286
Lucile Capuron
Bordeaux

The general objective of FoodCircus is to establish causal mechanistic links between nutrients biostatus and behavioral dimensions with symptomatic relevance for neurological and psychiatric disorders, through the identification of discrete neuronal circuits.

Research Brief :

The general objective of FoodCircus is to establish causal mechanistic links between nutrients biostatus and behavioral phenotypes/dimensions with symptomatic relevance for neurological and psychiatric disorders, through the identification of the underlying cellular/molecular mechanisms within discrete neuronal circuits.
Investigators of FoodCircus focus on neuronal circuits within two main vulnerable brain systems: the hippocampal and fronto-striatal circuits which control cognitive processes such as mnemonic and executive functions. Nutrient status mainly concern saturated /unsaturated fats and the fat-soluble vitamin A, which have been consistently linked with the etiology of several brain disorders. This multidisciplinary research program is based on the following specific aims:
i) To elucidate the neuronal mechanisms by which obesogenic diet impairs hippocampal-dependent memory.
ii) To identify the mechanisms by which polyunsaturated fatty acids and vitamin A biostatus impact neuronal circuits modulated by dopamine transmission and related to executive functions.
Beyond the prerequisite for a better understanding of the processes by which nutrients biostatus can alter specific brain functions, the perspectives of such a project are to identify targetable factors for the alleviation or prevention of specific symptomatic dimensions of brain disorders.

• **Methodologies Used :**

- Rodents behaviors (operant conditioning, memory tasks, motor tasks)
- Manipulation of neuronal circuits (transgenic mice, viral-gene transfer, chemogenetics)
- in vivo fiber photometry/sensors (calcium, neurotransmitters)
- ex vivo electrophysiology
- Histology/immunohistochemistry
- Biochemistry/molecular biology

Publications

Busquets-Garcia A, Oliveira da Cruz JF, Terral G, Pagano Zottola AC, Soria-Gómez E, Contini A, Martin H, Redon B, Varilh M, Ioannidou C, Drago F, Massa F, Fioramonti X, Trifilieff P, Ferreira G, Marsicano G* (2018). Hippocampal CB1 Receptors Control Incidental Associations, Neuron. 99(6), 1247-1259*

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Andrianarivelo A, Saint-Jour E, Pousinha P, Fernandez SP, Petitbon A, De Smedt-Peyrusse V, Heck N, Ortiz V, Allichon MC, Kappès V, Betuing S, Walle R, Zhu Y, Joséphine C, Bemelmans AP, Turecki G, Mechawar N, Javitch JA, Caboche J, Trifilieff P, Barik J, Vanhoutte P (2021). Disrupting D1-NMDA or D2-NMDA receptor heteromerization prevents cocaine's rewarding effects but preserves natural reward processing, Science Advances. 7(43), eabg5970

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Key facts

Team

- Researchers : 10
- Technicians : 5
- Postdoc fellows : 1
- PhD Students : 3

Translational approaches

- Patents : 1
- Clinical research grants : 1
- Industry partnerships : 0

Keywords

- regeneration
- redox metabolism
- stroma
- adipose tissue
- cell therapy
- mesenchymal stem cell
- 3D whole tissue imaging (spectral analysis)
- cytometry
- cell expansion
- animal model for cell transplantation
- primary culture

Biological Resources

- transgenic mice
- biobanks of ASC

Louis Casteilla

Guided Organization Of Tissue For Innovative Therapeutics - Got-I

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Philippe Valet
Toulouse

We are one of the rare team in the world with a double expertise in adipose tissue biology and regenerative medicine.

Research Brief :

Adipose tissue (AT) displays great plasticity and interests a large scientific community working not only on obesity epidemic but also on plastic and reconstructive surgery and regenerative medicine. The discovery that AT hosts a large pool of adipose derived stroma/stem cells (ASC) suitable for cell transplantation largely boosted this field, in which we are one of the world leaders (we published the 1st clinical trial on ASC transplantation in critical limb ischemia). ASC effects are mediated through their multipotent differentiation and mimicry potentials as well as their strong paracrine and immune-modulatory activity. We also showed that ASC egress from AT under immune/inflammatory stimuli suggesting their role in other tissues. Beside ASC, the importance of immune cells in AT physiology makes them a preponderant determinant of AT homeostasis. Recently, we showed that AT hosts a specific endogenous hematopoietic process, that generate immune cells contributing to tissue remodelling after lesion. Our hypothesis is that AT is a reservoir of regenerative and recruitable mesenchymal and immune cells and more particularly that ASC, through their pleiotropic effects, behave as orchestra conductor of stroma controlling proper tissue homeostasis.

- **Methodologies Used :**

Primary culture,
Cell transplantation,
Cell and 3D whole tissue imaging (spectral analysis),
Cytometry (multistaining analysis, cell sorting),
cell biology,
biochemistry (redox metabolism),
Animal models
molecular biology (microarray, Q RT-PCR...)

Publications

Carrière A, Jeanson Y, Berger-Müller S, André M, Chenouard V, Arnaud E, Barreau C, Walther R, Galinier A, Wdziekonski B, Villageois P, Louche K, Collas P, Moro C, Dani C, Villarroya F, Casteilla L. (2014). Browning of white adipose cells by intermediate metabolites: an adaptive mechanism to alleviate redox pressure., Diabetes. 63(10), 3253-65

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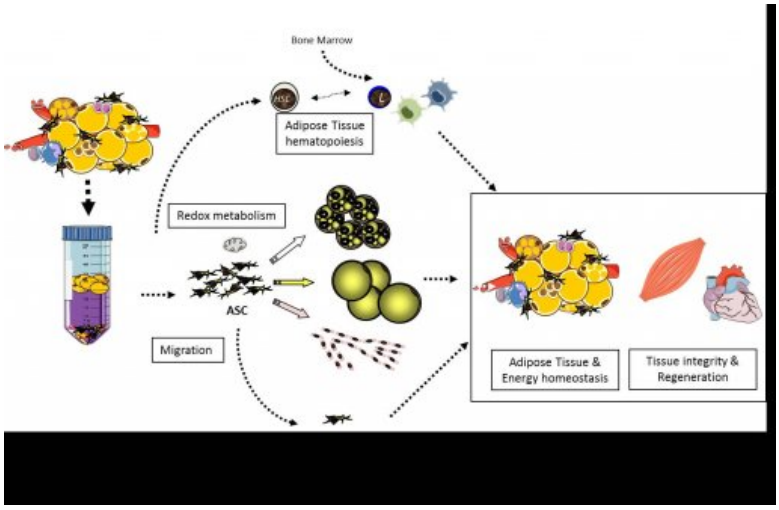
Role of ASC and adipose tissue derived immune cells in repair processes



Adipose Tissue (AT) is a reservoir of both Adipose Stromal Cells (ASC) and hematopoietic stem cells (HSC). ASCs differentiation potentials are controlled at least in part by redox metabolism, and are able to migrate to other organs under specific signals. AT-HSC generate immune cells involved in the control of AT-homeostasis and tissue remodelling after lesion. AT may thus be considered as a reservoir of regenerative and recruitable stromal and immune cells that control tissue homeostasis.

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Key facts

Team

- Researchers : 10
- Technicians : 2
- Postdoc fellows : 1
- PhD Students : 4

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 1

Keywords

- Adipose Stem Cells
- Regeneration
- Stroma
- Cell migration
- Skelatal muscle
- Flow Cytometry
- Imunohistochemistry
- Microsurgery
- Single Cell RNA Seq
- Metabolic profiling

Biological Resources

- Muscle injury mouse model
- Bank of Dorsophila models
- Primary cell culture of adipose stem cells (murine human)
- Primary culture of fibroadipogenic progenitors
- Fluorescently labeled adipose stromal cell grafted mouse model

Coralie Sengenès

STROMAGICS

Université Paul Sabatier
Toulouse III
INSERM U 1301 CNRS UMR 5070
Philippe Valet
Toulouse

Studying the inter-organ dynamics of native ASCs is unique and needs disruptive in vivo approaches.

Research Brief :

Every organ is a combination of a functional compartment, the parenchyma, and a stromal compartment, the stroma, supporting the parenchymal cells of the organ. Within the stroma, a subset of cells with multipotent differentiation capabilities, referred to as Mesenchymal Stromal Cells (MSCs) exists. MSCs exhibit strong regenerative potential and are thought to be implicated as key players in regenerating injured tissues. Adipose tissue is the richest reservoir of MSCs in adults where they are named Adipose Stromal Cells or ASCs.
The project of the STROMAGICS team is to decipher the relation between stroma dynamics and aging, and is driven by the following working hypothesizes:
Stroma homeostasis is needed to ensure organ homeostasis
Stroma homeostasis is allowed via a fine-tuned dynamic of MSCs within and between organs
Aging-associated progressive decline in homeostasis and regeneration is related to perturbations of MSCs dynamic
Our objectives are:
(i) To identify the molecular and the cellular features of mobililzable ASCs and the mechanisms controlling ASC dynamic
(ii) To capitalize the results coming from this project to characterize the dynamic of ASCs in the context of aging

- **Methodologies Used :**

In vivo assays
Metabolic profiling
Muscle regeneration analysis
Flow Cytometry
Single Cell RNA Seq
Immunohistology
Spectral imaging
Machine learning/Deep learning

Publications

Labit E, Rabiller L, Rampon C, Guissard C, Andre M, Barreau C, Cousin B, Carriere A, Eddine MA, Pipy B, Penicaud L, Lorsignol A, Vriz S, Dromard C, Casteilla L (2018). Opioids prevent regeneration in adult mammals through inhibition of ROS production, Scientific Reports. (),

Contreras X, Salifou K, Sanchez G, Helsmoortel M, Beyne E, Bluy L, Pelletier S, Rousset E, Rouquier S, Kiernan R (2018). Nuclear RNA surveillance complexes silence HIV-1 transcription, Plos Pathogens. (),

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Girousse A, Gil-Ortega M, Bourlier V, Bergeaud C, Sastourné-Arrey Q, Moro C, Barreau C, Guissard C, Vion J, Arnaud E, Pradère JP, Juin N, Casteilla L, SENGENES C (2019). The Release of Adipose Stromal Cells from Subcutaneous Adipose Tissue Regulates Ectopic Intramuscular Adipocyte Deposition., Cell Rep. (),

Alexandre Carayon, Laetitia Bataillé, Gaëlle Lebreton, Laurence Dubois, Aurore Pelletier, Yannick Carrier, Antoine Wystrach, Alain Vincent, Jean-Louis Frendo (2020). Intrinsic control of muscle attachment sites matching, ELife. (),

Sastourné-Arrey Q, Mathieu M, Contreras X, Monferran S, Bourlier V, Gil-Ortega M, Murphy E, Laurens C, Varin A, Guissard C, Barreau C, André M, Juin N, Marquès M, Chaput B, Moro C, O'Gorman D, Casteilla L, Girousse A, Sengenès C. (2023). Adipose tissue is a source of regenerative cells that augment the repair of skeletal muscle after injury., Nat Commun. (),

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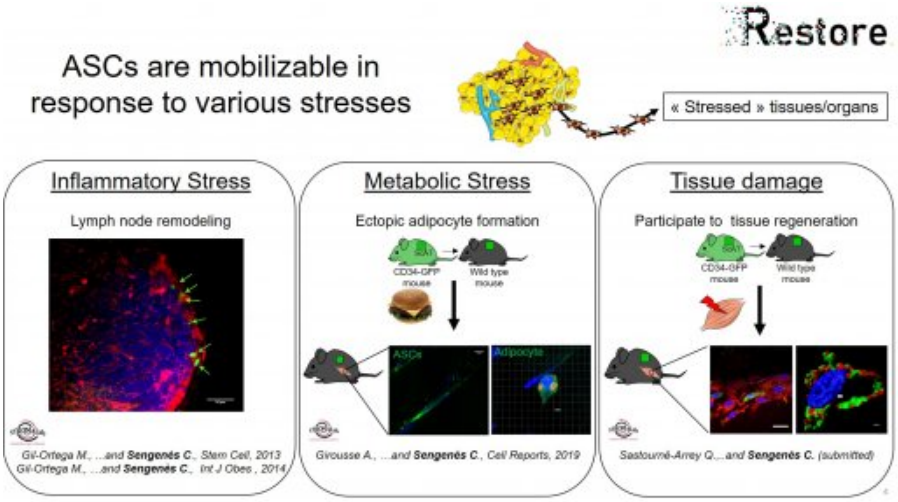
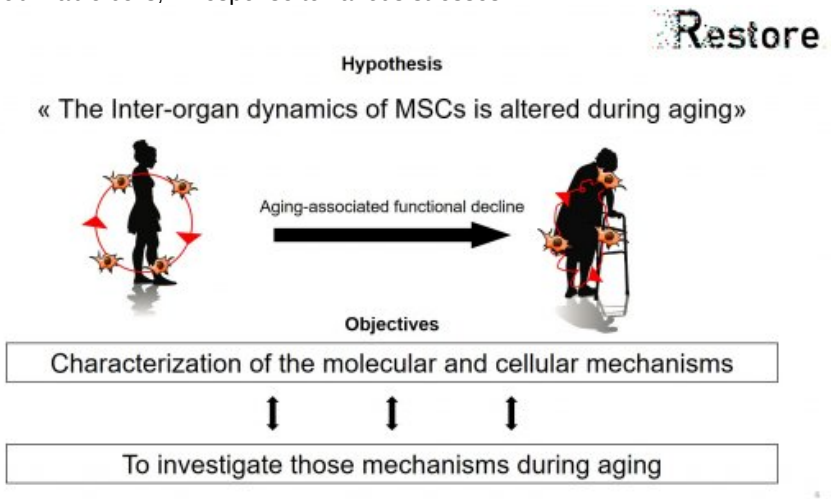


Adipose tissue is a source of mobilizable cells, in response to various stresses



STROMAGICS hypothesis

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C2VN Centre de Recherche en CardioVasculaire et Nutrition

Patrick Borel

Human Micronutrition

Aix-Marseille University
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Marie-Christine Alessi
Marseille

Key facts

Team

- Researchers : 18
- Technicians : 14
- Postdoc fellows : 0
- PhD Students : 16

Translational approaches

- Patents : 0
- Clinical research grants : 10
- Industry partnerships : 14

International research links

- Spain
- Hungary
- USA

Keywords

- Carotenoids
- Obesity
- Epigenetic
- Nutrigenomic
- Adipose tissue
- Fat-soluble vitamins
- Nutrigenetic
- Bioavailability
- Metabolomics
- Digestion
- Insect for feed and food

Biological Resources

- in vitro digestion model
- Intestinal and adipose tissue cell lines
- Animal experiments in rodents (including transgenic mice)
- Clinical studies in nutrition

Our main objective is to study the impact of lipid micronutrients (mainly vitamins and carotenoids) on etiology of vascular and cardiometabolic diseases. We are the only team able to study both the fate of these compounds from the meal to their site of action as well as their health effects.

Research Brief :

Numerous lines of evidence suggest that lipid micronutrients (LM: mainly fat soluble vitamins, carotenoids and phytosterols and PUFA) have beneficial effects on several diseases including cardiovascular diseases. This can be explained by the fact that vitamin E and carotenoids exhibit antioxidant properties, phytosterols diminish cholesterol absorption, vitamins D, E, PUFA and carotenoids inhibit inflammation. However the bioavailability of these compounds is very low, it is affected by numerous factors (from the effect of the food matrix to the effect of genetic variations in genes involved in their absorption) and it is very variable among individuals. The objective of the team will be to assess the effects of LM and lipids on metabolic deteriorations that participate in the etiology of vascular and cardiovascular diseases, e.g. obesity, inflammation and insulin sensitivity, taking into account the factors that govern and affect their bioavailability and their metabolism. This will be done thanks to an integrative biology approach that uses complementary models, from in vitro digestion models to clinical studies through cell cultures, wt or transgenic animals and metabolomics. These objectives not only meet the INRA strategic research policies, stating that in-depth knowledge is required on the relationships between food, nutrition, prevention and health, but also those of the Food and Nutrition thematic area of the ALLEnvi Alliance and those of the PMN ITMO.

- **Methodologies Used :**

Animal experiments
Cell culture
GC-MS
HPLC
Intervention studies on healthy subjects and on insulin resistant subjects (obese, type 2 diabetic and subjects with metabolic syndrome)
Molecular biology
Multivariate analysis
Stable isotope kinetic studies

Publications

Padilla N, Maraninchi M, Béliard S, Berthet B, Nogueira JP, Wolff E, Nicolay A, Bégu A, Dubois N, Grangeot R, Mattei C, Vialettes B, Xiao C, Lewis GF, Valéro R. (2014). Effects of bariatric surgery on hepatic and intestinal lipoprotein particle metabolism in obese, nondiabetic humans, Arterioscler Thromb Vasc Biol. 34(10), 2330-7

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Eva M Seipelt, Franck Tourniaire, Charlène Couturier, Julien Astier, Béatrice Loriod, Hortense Vachon, Michel Pucéat, Lourdes Mounien, Jean-François Landrier (2020). Prenatal maternal vitamin D deficiency sex-dependently programs adipose tissue metabolism and energy homeostasis in offspring, Faseb J. 34(11), 14905-14919

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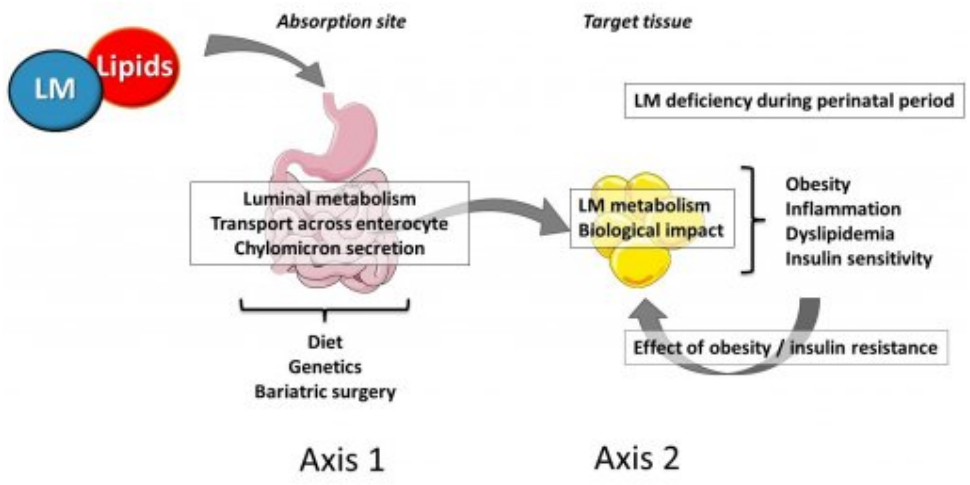
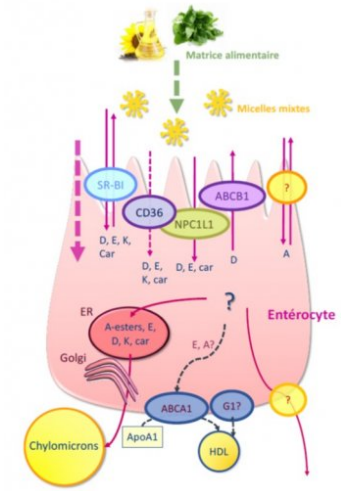
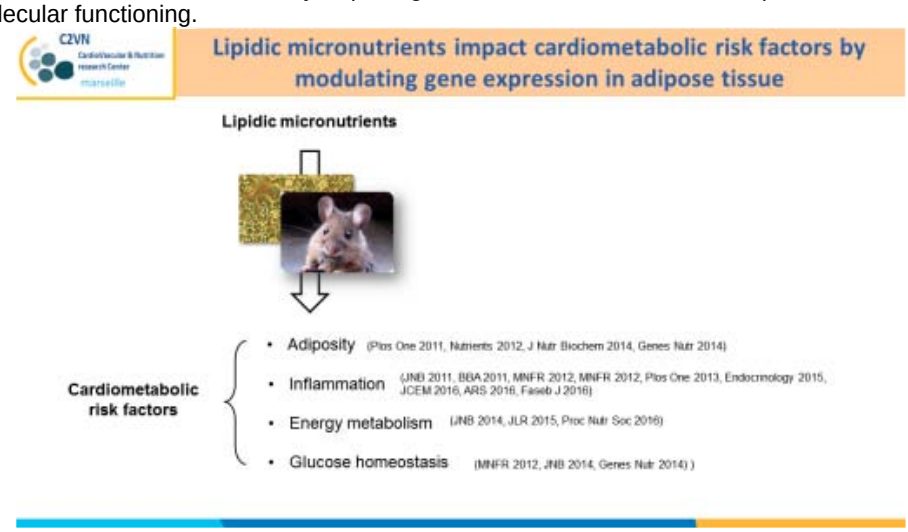


Western diet is associated to a decrease of energy expenditure, an increase of energy consumption, and a decrease of micronutrient consumption. The aim of the team is to study the impact of lipid micronutrients and lipids on etiology of vascular and cardiovascular diseases. Because these micronutrients are poorly absorbed we will take into account both their bioavailability and their metabolism. We are able to study the fate of vitamins and micronutrients from the meal to the cell nucleus.



We were the first to show that SR-B1, CD36 and/or NPC1L1 are involved in apical uptake of carotenoids, vitamin E, D and K. We also showed that ABCA1 is involved in vitamin E basolateral efflux. Recently we have shown that ABCB1 (P-glycoprotein) can mediate vitamin D intestinal and transintestinal efflux. We are currently exploring the involvement of other transporters in these processes. Besides, we investigate transporter molecular functioning.



We are one of the leading team in the world, working on the impact of lipidic micronutrients on adipose tissue biology and systemic consequences. We demonstrated that active derivates of vitamin D, carotenoids or vitamin A modulate gene expression in adipose tissue, leading to improvement of several risk factors such as adiposity, inflammation, energy metabolism or glucose homeostasis. These data pave the way for nutritional preventive approaches in the context of cardiometabolic diseases.

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CRNH Rhône-Alpes

Human Nutrition Research Center

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Julie-Anne NAZARE
Lyon, Grenoble, Saint-Etienne

Key facts

Team

- Researchers : 14
- Technicians : 6
- Postdoc fellows : 0
- PhD Students : 3

Translational approaches

- Patents : 1
- Clinical research grants : 5
- Industry partnerships : 5

Keywords

- insulin-resistance
- obesity and diabetes
- metabolics fluxes
- food quality modulation
- energy metabolism
- food bioavailability
- physical activity assessment
- metabolic phenotyping

Biological Resources

- Blood, plasma, breath, urines and stool samples, muscle and adipose tissue biopsies

A center of excellence in human nutrition and health from preclinical to clinical research

Research Brief :

The CRNH Rhône-Alpes is part of GIP (Public Interest Group) whose partners are: Research institutes (Inserm and INRAE), Universities (Lyon 1, University Grenoble Alpes, J. Monnet in Saint Etienne), Hospitals (Hospices Civils de Lyon, CHU Grenoble and CHU St Etienne).
The Human Nutrition Research Center Rhône-Alpes strives to improve human nutrition and health. It develops research programs in nutrition within the framework of national, european and international research programs, working closely with industrial partners and researchers worldwide.
It has three physical entities in Lyon: the clinical exploration center (938 m2) comprising 5 rooms with metabolic carts for day-long metabolic explorations, 6 examination rooms, an experimental restaurant, a fitness room and the administrative center housed in the CENS-ELI 2D building of the Lyon-Sud hospital (CHLS) and the mass spectrometry analysis center within the CHLS biology center. In Grenoble, the IBISA platform (HypE) studies the mechanisms of intermittent exposure to hypoxia in human, animal and cellular models.
The association of about 150 researchers and clinicians, from 22 hospital services, 3 universities and research units (CarMeN Inserm U1060-INRA USC1362-INSA, Inserm U1042 and Inserm UMR-S 884, EA 7423) makes it possible to set up studies on priority Public Health matters such as obesity, diabetes, cardiovascular diseases and malnutrition associated with chronic diseases and aging.

- **Methodologies Used :**

Bioavailability and metabolic fate of nutrients (including stable isotopes tracers).
Insulin sensitivity (hepatic and peripheral) by insulin clamp or OGTT.
Energy expenditure and metabolism (calorimetry, doubly labeled water), metabolic flexibility.
Test meals (lipids, CHOs, with or without stable isotopes tracers).
Body composition (impedancemetry, bodpod, DEXA, MRI).
Tissue biopsies (muscle, fat) and stool sampling for metagenomics.
Satiety (hormonal, behavioural, subjective) and eating behavior.
Hormonal profiling, cardiometabolic profiling.
Microbiota and métabolites.
Comprehensive dietary patterns and overall diet quality.
Ecological approach and real life settings: in situ, experimental restaurant, biologgers, sensors?).

Publications

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Key facts

Team

• Researchers : 8
• Technicians : 3
• Postdoc fellows : 5
• PhD Students : 1

Translational approaches

• Patents : 2
• Clinical research grants : 2
• Industry partnerships : 3

Keywords

• Atherosclerosis
• Vascular cells
• Immune cells
• Lipoproteins
• Lipids
• Lipid sensors/receptors
• Inflammation
• Immunity
• Macrophages
• Dendritic cells
• Apoptosis
• Postprandial
• Development of mouse models for cardiometabolic diseases
• Axenic mice, faecal transfert.
• Lipidomic, Metabolomic
• Metabolic phenotyping of mouse models
• Reverse cholesterol transport in vivo and in vitro.

Biological Resources

• Cohorts of dyslipidemic patients,
• Bank of mRNA from human Monocytes,
• Experimental models of atherosclerosis,
• Genetically-modified mice (tg CD68-hBcl2, tg CD11c-hBcl2, SR-BI flox/flox, ABCG1 flox/flox)

Philippe Lesnik

Integrative biology of cardiovascular and metabolic diseases

Université de Paris 06
(Université Pierre et Marie Curie)
Inserm
Stéphane Hatem
Paris

Expertise in lipoprotein metabolism, atherosclerosis, vascular diseases and mononuclear phagocytes.

Research Brief :

Our research goals are based on the premise that lipid-related inflammation and the associated immune responses are dominant components in atherogenesis. The underlying pathogenesis involves an imbalance of lipid and lipoprotein metabolism and a maladaptive immune response entailing a chronic inflammation of the arterial wall. The validity of this premise is becoming increasingly stronger as basic and clinical data demonstrate disturbed equilibrium of lipid metabolism and immune responses and resolution, shaped by lipoprotein retention, leukocyte trafficking and homeostasis. Our research focus on the clarification of cellular and molecular mechanisms of such lipido-inflammatory and immune responses, with a goal that new diagnostic and therapeutic approaches will emerge from this work. Indeed new reliable biomarkers allowing monitoring of the critical stages of vascular remodeling and thereof of potential complications are urgently required.

Novel molecular mechanisms, translational development and clinical strategies for studying lipid-related inflammation in atherosclerosis and vascular disease represent three major axes of our research program

Axe 1: To determine how lipids lipoproteins and immune cells crosstalk to influence atherogenesis
Axe 2: To assess the clinical relevance of novel mechanisms, genes, and biomarkers by studies of human diseases
Axe 3: To develop novel therapeutic strategies for inflammatory and metabolic disorders and atherosclerosis.

• **Methodologies Used :**

Development of mouse models for cardiometabolic diseases.
Metabolic phenotyping of mouse models.
Transcriptomic, Lipidomic, Metabolomic, Metagenomic, Epigenomic, Multivariate analysis.
Phenotyping and quantification of circulating and tissue leucocytes: flow cytometry/cell sorting.
Reverse cholesterol transport in vivo and in vitro.
Axenic mice, Faecal transfert.

Publications

Gautier EL, Ivanov S, Williams JW, Huang SC, Marcelin G, Fairfax K, Wang PL, Francis JS, Leone P, Wilson DB, Artyomov MN, Pearce EJ and Randolph GJ. (2014). Gata6 regulates aspartoacylase expression in resident peritoneal macrophages and controls their survival., J Exp Med. 211(1525), 1531

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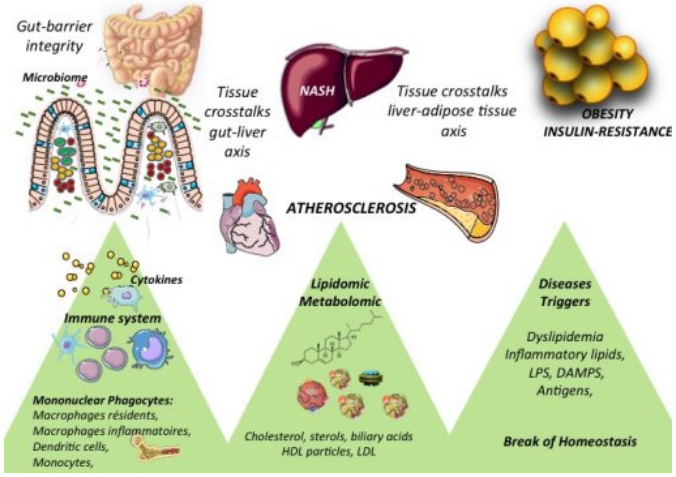
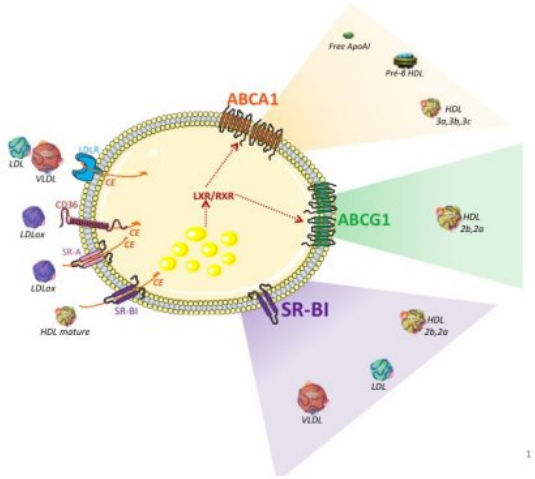
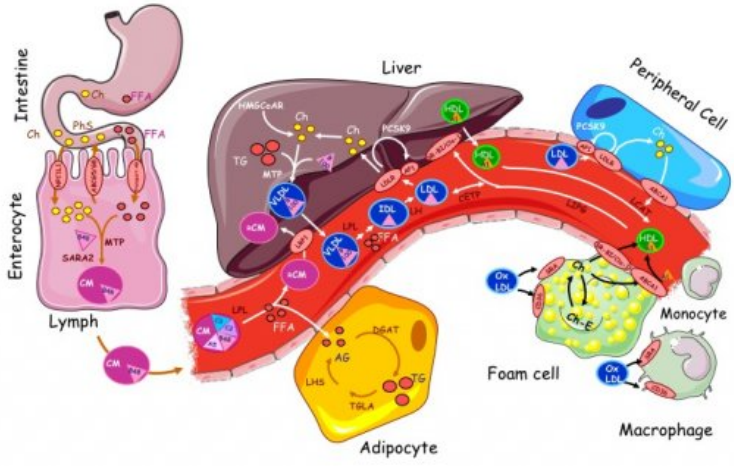
BENEFICIAL OR DETRIMENTAL IMPACT OF LIPID & MONONUCLEAR PHAGOCYTES ON METABOLIC DISORDERS



CHOLESTEROL HOMEOSTASIS IN MONONUCLEAR MACROPHAGES



OVERVIEW OF THE LIPOPROTEIN METABOLISM



Lesnik Philippe - philippe.lesnik@sorbonne-unive rsite.fr - www.insermu1166.fr

Wilfried Le Goff

SLIM - Systemic and Cellular Lipid Metabolism in Cardiometabolic Diseases

Sorbonne Université
Inserm UMR_S1166
Stéphane Hatem
Paris

Key facts

Team

• Researchers : 9
• Technicians : 3
• Postdoc fellows : 1
• PhD Students : 4

Translational approaches

• Patents : 4
• Clinical research grants : 0
• Industry partnerships : 5

International research links

• Argentina, Australia, Belgium, Brazil, Croatia, Denmark, Lebanon, Mexico, Netherlands, Russia, Thailand, Ukraine, USA

Keywords

• Cardiometabolic diseases
• Lipids
• Lipoproteins
• Biomarkers
• Macrophage
• Lipidomic
• Metabolomic
• Genomic
• Epigenetic
• Lipoproteinomic

Biological Resources

• Annotated DNA bank of Familial Hypercholesterolemia patients
• Plasma and DNA banks of patients with Metabolic Syndrome (MetS)

Our research team has an internationally recognized expertise in the integrative study of lipid and lipoprotein metabolism in human physiology and physiopathology.

Research Brief :

Cardiovascular diseases still remain the major cause of morbidity and mortality worldwide due to the growing prevalence of obesity and associated metabolic disorders, including insulin resistance and Type 2 diabetes. Dyslipidemia, characterized by altered circulating concentrations of lipoproteins and lipids is a major component in the development of cardiometabolic diseases (CMD). As a consequence, lipid-lowering therapies are the privileged therapeutic strategy in CMD. Mechanisms through which lipids contribute to the development of metabolic disorders are multiple and involve complex signaling and regulation pathways at the both cellular and systemic levels. Importantly, it is now clear that a large spectrum of lipid species not only restricted to cholesterol and triglycerides participates actively in alterations of lipid and lipoprotein metabolism in CMD. Then, deciphering of dysfunctional lipid metabolic pathways might help to propose new therapeutic targets to prevent or hamper the occurrence and development of CMD.
Our recent pioneering studies leading to the identification by omics approaches of lipid networks and metabolic pathways controlling biological activities of plasma lipoproteins and cell activation in CMD open up new insights in understanding how alterations in lipid metabolism contribute to CMD onset. Building on tight interactions with clinical and valorization departments, our team aims to propose new candidate pathways, genes and biomarkers in CMD.

• **Methodologies Used :**

- Lipoproteinomic : Isolation, omic characterization and structure-function analysis of lipoproteins.
- Integrative exploration of reverse cholesterol transport (RCT) : From cellular cholesterol efflux to liver elimination
- Reverse remnant cholesterol transport (RRT) analysis : Acquirement by high-density lipoproteins (HDL) of surface remnant from triglyceride-rich lipoproteins (TGRL) upon lipolysis (Figure 1)
- Generation of reconstituted HDL for preclinical studies
- Isolation of human pre?-HDL for clinical studies
- NGS, methylation analysis, long-read sequencing

Publications

Frisdal E., Le Lay S., Hooton H., Poupel L., Olivier M., Alili R., Plengpanich W., Villard E., Gilibert S., Lhomme M., Superville A., Miftah-Alkhair L., Chapman M.J., Dallinga-Thie G., Venteclef N., Poitou C., Tordjman J., Lesnik P., Kontush A., Huby T., Dugail I., Clement K., Guerin M., Le Goff W. (2015). Adipocyte ATP-Binding Cassette G1 promotes triglyceride storage, fat mass growth and human obesity, Diabetes. 64(3), 1133

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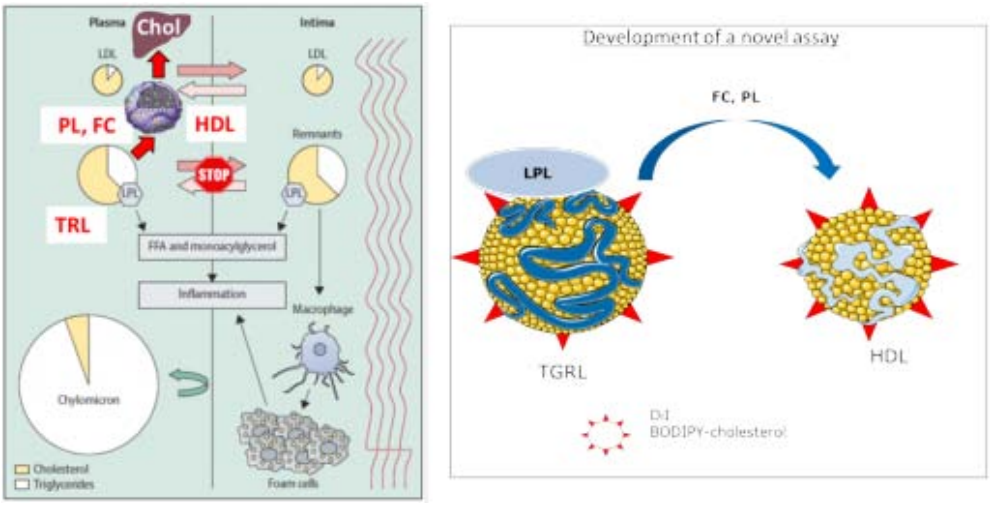
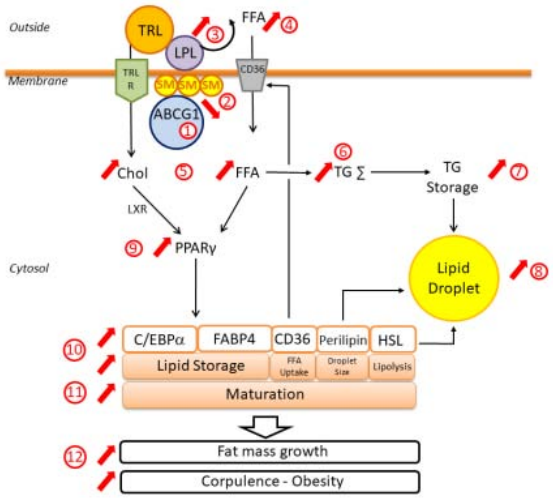
Witztum JL, Gaudet D, Freedman SD, Alexander VJ, Digenio A, Williams KR, Yang Q, Hughes SG, Geary RS, Arca M, Stroes ESG, Bergeron J, Soran H, Civeira F, Hemphill L, Tsimikas S, Blom DJ, O'Dea L, Bruckert E. (2019). Volanesorsen and Triglyceride Levels in Familial Chylomicronemia Syndrome, New England Journal of Medicine. 381(6), 531

Reverse Remnant cholesterol Transport (RRT)



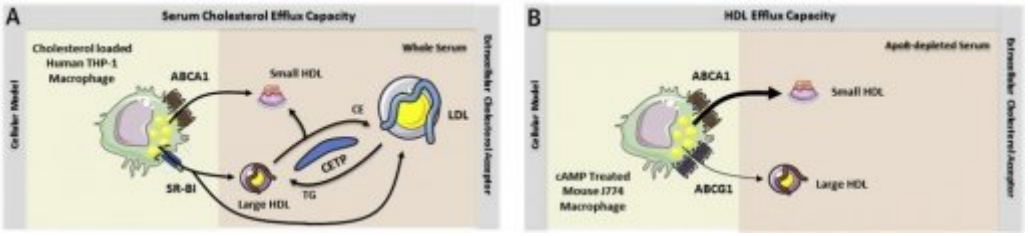
HDL prevents surface TRL remnants from accumulation in the arterial wall via acquiring phospholipid (PL) and free cholesterol (FC) during TG lipolysis (left panel). An in vitro fluorescence-based assay to evaluate the capacity of HDL to acquire PL and FC from TRL upon LPL-mediated lipolysis (right panel) (Ma F. et al. European Journal of Preventive Cardiology. 2019, PMID: 31840535).

Role of Adipocytes ABCG1 in regulating adipocyte differentiation and maturation



ABCG1 expression in adipocytes (1) promotes cellular sphingomyelin (SM) efflux and decreases SM-rich lipid raft formation (2). Low amounts of membrane SM ensures optimal LPL activity and hydrolysis of triacylglycerol-rich lipoproteins (TRL) (3), contributing to the release of free fatty acids (FA) (4). Released FFAs are then taken up by the cell (5) and used for triglycerides synthesis (6), leading to TG storage (7) and to increased lipid droplet size in adipocytes (8) (Adipocyte. 2015;4(4):315)

Simplified Schematic Representation of Serum Cholesterol Efflux Capacity



Serum cholesterol efflux capacity was measured in the presence of whole serum using cholesterol-loaded human macrophage (A), and of standard system measuring HDL efflux capacity performed in the presence of apoB-depleted serum using cholesterol-loaded mouse macrophage in which ABCA1 is up-regulated by cAMP (B). The size of the arrow indicates relative contribution of major cholesterol efflux pathways in both cellular models (Guerin M. et al. J Am Coll Cardiol. 2018;72(25):3259).

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https://recherche-cardiovasculaire-metabolique.fr/teams/teams/cellular-and-systemic-lipid-metabolism-in-cardiometabolic-diseases/

Key facts

Team

- Researchers : 3
- Technicians : 2
- Postdoc fellows : 3
- PhD Students : 2

Translational approaches

- Patents : 3
- Clinical research grants : 0
- Industry partnerships : 3

Keywords

- Microbiota
- Microbiome
- Probiotics
- Lactobacilli
- Drosophila
- Growth
- Nutrition
- Functional genomics
- genetics
- gnotobiology
- nutritional manipulation
- metabolism

Biological Resources

- Library of Lactobacilli isolates for functional screening
- in vivo animal models for functional screening of candidate probiotics

François Leulier

Integrative Physiology of host-bacteria interactions

Université de Lyon 1
(Université Claude Bernard) Ecole Normale Supérieure de Lyon
CNRS UMR5242
François Leulier
Lyon

We have developped an original model to study host/microbiota interaction which has a great potential for functional and mechanistic studies thanks to its simplicity and genetic tractability

Research Brief :

In the animal kingdom, juvenile growth takes place during the post-natal stages preceding sexual maturation. These changes are governed by the complex interplay between the animal's genotype and its nutritional environment. In humans, 155 million kids today are plagued by childhood malnutrition worldwide and chronic undernutrition at the juvenile stage, a condition defined as a prolonged reduced intake of key nutrient (such as proteins), leads to severe stunting (i.e. flattened linear growth) and long-term negative neurological, immunological, metabolic and reproductive consequences.
Recent studies, including our own, establish that the microbial communities colonizing the body surfaces (i.e microbiota), especially the activities and constituents of the gut microbiota, can alter animal growth trajectory. In fact, children suffering malnutrition carry an "immature" gut microbiota that fails to be remedied by classical re-nutrition strategies. In addition, in various animal models, we and others, have shown that selected strains of microbiota members can buffer the deleterious impact of undernutrition on juvenile growth dynamics.
Our research aim at deciphering how commensal bacteria shape the juvenile animals' response to their nutritional environment and how juveniles in such nutritional environment influence the ecology and physiology of their bacterial partners. Hence, we study microbial ecology and physiology as well as animal development and physiology.

Methodologies Used :

Drosophila and Mouse gnotobiology
Functional genomics
Drosophila and Lactobacilli forward and reverse genetics
Experimental Evolution.
Nutritional manipulation

Publications

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M. Schwarzer, K. Makki, G. Storelli, I. Machuca-Gayet, D. Srutkova, P. Hermanova, M. E Martino, S. Balmand, T. Hudcovic, A. Heddi, J. Rieusset, H. Kozakova, H. Vidal, and F. Leulier (2016). Lactobacillus plantarum strain maintains growth of infant mice during chronic undernutrition, Science. 351(6275), 854

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Uwe Schlattner

LBFA - Laboratoire de Bioénergétique Fondamentale et Appliquée

Université Grenoble Alpes
Inserm U1055
Uwe Schlattner
Grenoble

Key facts

Team

- Researchers : 12
- Technicians : 9
- Postdoc fellows : 3
- PhD Students : 6

Translational approaches

- Patents : 3
- Clinical research grants : 2
- Industry partnerships : 3

International research links

- USA
- UK
- Spain

Keywords

- energy homeostasis
- mitochondria
- AMP-activated protein kinase
- nutrition
- regenerative medicine
- microscopy
- animal models
- metabolic analysis
- proteomics
- fluorescent sensors

Biological Resources

- recombinant proteins
- cell lines
- primary cells (hepatocytes, cardiomyocytes)
- animal models (rats, transgenic mice)

Research at LBFA is integrating molecular, cellular, whole organism and clinical research in bioenergetics.

Research Brief :

The main focus of LBFA research is on energy homeostasis and mitochondrial physiology, as well as their dysfunction in human disease and ageing. This includes projects on cell signaling, cell compartmentation, nutrition, exercise, epigenetics and maintenance of beta-cell fonction.
LBFA research is organized in three axes:
(1) "Energy signalling & systems bioenergetics" (U Schlattner) is working on molecular mechanisms in the regulation of cellular energy state and energy homeostasis, in particular structure, function and signaling of AMP-activated protein kinase and NME proteins, and topology, dynamics and function of mitochondrial microcompartments.
(2) "Mitochondria, cell death and survival" is working on mitochondrial physiology, beta-cell survival for regenerative medicine, and mechanisms of cell death (mitochondrial permeability transition).
(3) "Nutrition, muscle, & healthy living and aging" is working on nutritional end exercise effects on metabolic regulation, nutritional status, nutrition and nutritional supplements.
LBFA also develops and applies interdisciplinary and integrative approaches, including innovative technologies (e.g. in vivo imaging with intracellular sensors, animals models).

• Methodologies Used :

Recombinant protein expression, purification and biochemical/biophysical characterization.
Experimental models of nutritional regimes, metabolic or energy disorders in vitro and in vivo (cell culture, mice, rats)
Proteomics (2D-PAGE etc., mass spectrometry) and transcriptomics (RT-PCR, microarrays)
Interactomics (innovative yeast-two-hybrid systems, surface plasmon resonance)
Microscopy (fluorescence, confocal)
Metabolic and metabolite analysis (metabolic cage with gas exchange and movement analysis, cell perifusion, oxygraphy, HPLC)

Publications

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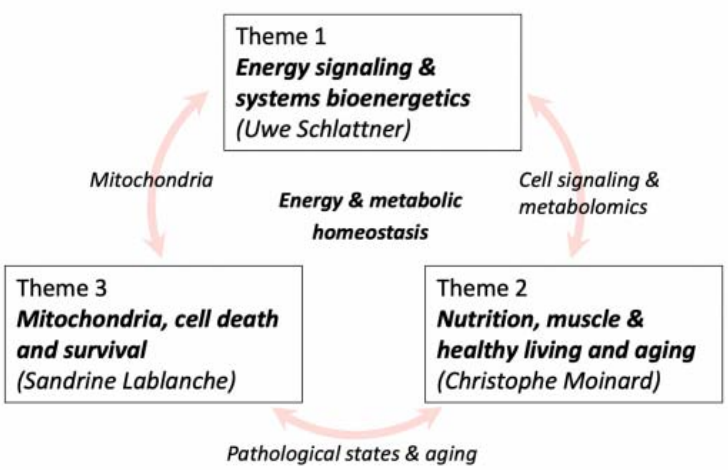
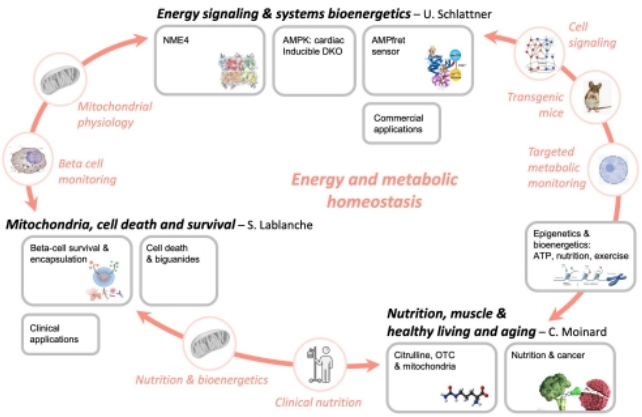
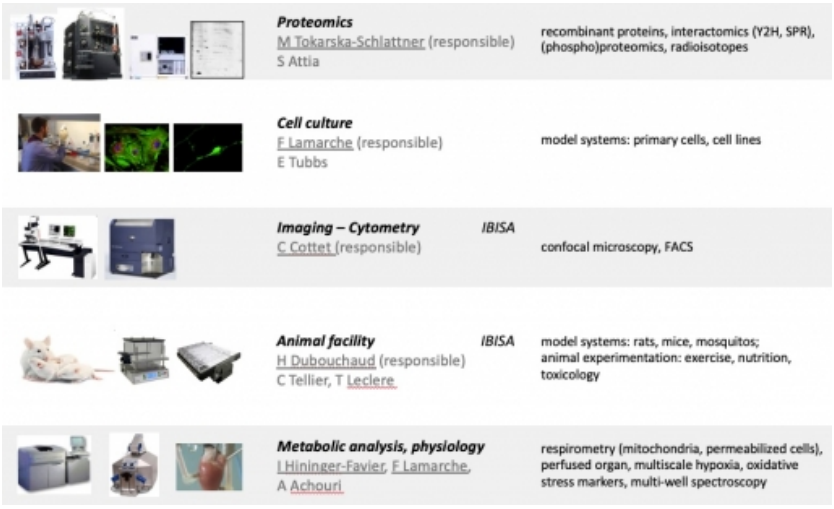
LBFA organization



LBFA research projets



LBFA technical facilities & competences



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Key facts

Team

- Researchers : 4
- Technicians : 1
- Postdoc fellows : 2
- PhD Students : 1

Translational approaches

- Patents : 2
- Clinical research grants : 2
- Industry partnerships : 3

International research links

- The Netherlands
- Australia
- Chile

Keywords

- Aging
- Nonalcoholic steatohepatitis
- Metabolic syndrome
- High Density Lipoprotein
- Energy Metabolism
- ATP synthase
- Autophagy
- Mitophagy
- Endothelial dysfunction
- Cholesterol and bile acids

Biological Resources

- Primary mouse hepatocytes
- Models of NASH and metabolic syndrome
- Models of endothelial dysfunction
- Cohorts of Coronary Heart Disease patients

Laurent Martinez

Lipoproteins and Mitochondrial adaptations in Age-related vascular & metabolic diseases (LiMitAging)

Université de Toulouse 3
(Université Paul Sabatier)
INSERM UMR1297
Dominique Langin
Toulouse

Our projects use unique genetic and pharmacological approaches to explore mitochondrial-mediated mechanisms of aging, with the ultimate goal to restore or enhance mitochondrial functions, limit aging process and benefit cardiometabolic health.

Research Brief :

The aging process affects numerous organs, including the liver and the cardiovascular system, leading to cardiometabolic diseases. Gerontological studies have revealed different molecular pathways involved in the aging process and pointed out mitochondrial as one of the key regulator of longevity. Particularly, mitochondrial dysfunction drives cellular senescence and a deterioration of respiratory chain activity is associated with age in mammals.
The project of the LiMitAging team is to study the relation between some actors of mitochondrial functions and aging, and is driven by the hypothesis that enhancing mitochondrial health and mitochondrial quality-control mechanisms will promote healthy aging.
Our expertise in the field of lipoprotein and mitochondria led us to identify original actors associated to lipid and mitochondrial energy metabolism.
Our objectives are to explore the physiological and pathophysiological roles of those molecular actors that regulate:
1) The respiratory chain complex V, also called ATP synthase
2) Autophagy, particularly mitophagy.
3) Ectopic ATP synthase and G protein-coupled P2Y receptors signaling pathways
Our research has led to the development of original drug candidates and biomarkers that are currently being validated on preclinical models and cohorts, to be used for early detection and resolution of mitochondrial dysfunctions in pre-frail individuals or in population at high risk of cardiometabolic diseases.

• **Methodologies Used :**

1. Preclinical models of NAFLD and NASH (ex-vivo and in-vivo).
2. Analyses of endothelial function: murine model of vascular endothelial injury and reendothelialization, in-vivo femoral artery blood flow, in-vitro and ex-vivo nitric oxide production.
3. Lipoprotein metabolism: Isolation of VLDL, LDL, HDL (human and mouse), purification of human apoA-I, hepatic VLDL production, lipoproteins endocytosis, plasma lipoprotein profiling (HPLC, Lipoprint, RMN), gallbladder cannulation for biliary lipid flux analyzes.
3. Glucose metabolism: OGTT, ITT.
4. Ex-vivo organ model: Precision-Cut tissue Slices.

Publications

Genoux A, Lichtenstein L, Ferrières J, Duparc T, Bongard V, Vervueren PL, Combes G, Taraszkiewicz D, Elbaz M, Galinier M, Nassar B, Ruidavets JB, Perret B, Martinez LO (2016). Serum levels of mitochondrial inhibitory factor 1 are independently associated with long-term prognosis in coronary artery disease: the GENES Study, BMC Med. 14(1), 125

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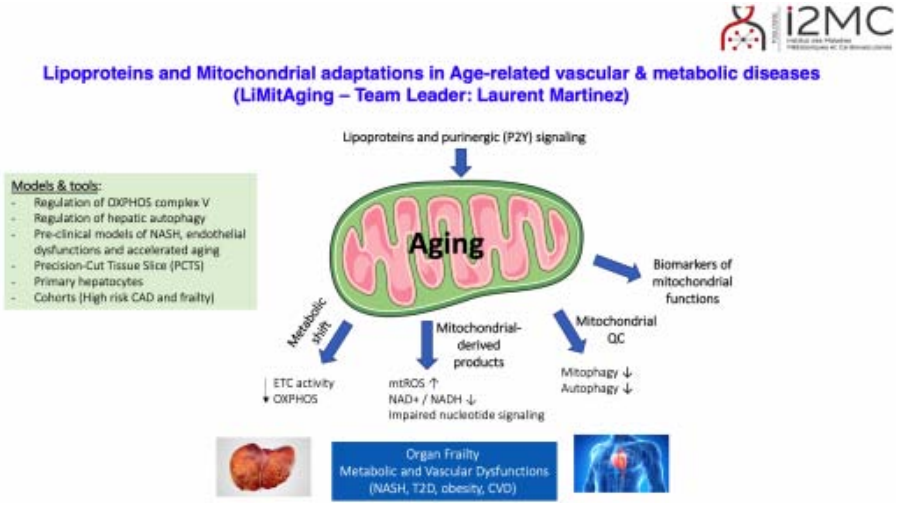
Martinez Laurent - laurent.martinez@inserm.fr - 0531224147 - http://www.i2mc.inserm.fr

Research areas, models and tools of the LiMitAging team



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Key facts

Team

• Researchers : 14
• Technicians : 6
• Postdoc fellows : 2
• PhD Students : 4

Translational approaches

• Patents : 3
• Clinical research grants : 1
• Industry partnerships : 2

International research links

• Karolinska Institute (Sweden, Prof. M. Ryden)
• NUTRIM Centre Maastricht (Netherlands, Prof. P. Schrauwen)
• Pennington Biomedical Research Centre (Baton Rouge, USA, Prof. E. Ravussin)

Keywords

• Metabolism
• Obesity
• Type 2 Diabetes
• Nutrition
• Exercise
• Human primary skeletal muscle cells
• Human adipocytes
• Transgenic mice
• -omics
• Metabolic fluxes

Biological Resources

• Human adipose tissue and skeletal muscle biobank
• Human primary skeletal muscle cells biobank
• Primary cultures of adipocytes, myocytes and hepatocytes

Cédric Moro Dominique Langin

MetaDiab - Pathophysiology of Metabolic Disorders and Diabesity

Université Paul Sabatier
Toulouse III
Inserm UMR1297
Dominique Langin
Toulouse

METADIAB uses a highly translational medicine approach of the study of metabolism combining innovative cell and mouse models to decipher molecular mechanisms of metabolic disorders, and clinical studies in nutrition and exercise with deep phenotypic investigation.

Research Brief :

The team aims at understanding the biological determinants and molecular mechanisms of metabolic disorders in various pathophysiological contexts (obesity, aging, type 2 diabetes, physical inactivity). Using a highly integrative bedside-to-bench approach, we investigate novel targets and mechanisms in cell and mouse models as well as in humans. Our projects are focused on the underlying mechanisms of insulin resistance, lipid droplet and metabolic dysfunction in skeletal muscle and adipose tissue, as well as their crosstalk in metabolic regulation and diseases.

• **Methodologies Used :**

Our projects are focused on the underlying mechanisms of insulin resistance, lipid droplet and metabolic dysfunction in skeletal muscle and adipose tissue, as well as their crosstalk in metabolic regulation and diseases. These topics are tackled by approaches combining clinical studies in humans (obesity, dietary interventions and physical activity), phenotyping of transgenic mouse models and studies on various cell models (primary cultures of adipocytes, myocytes and hepatocytes).

Publications

Barquissau V, Leger B, Beuzelin D, Martins F, Amri EZ, Pisani DF, Saris WHM, Astrup A, Maoret JJ, Iacovoni J, Dejean S, Moro C, Viguerie N, Langin D. (2018). Caloric Restriction and Diet-Induced Weight Loss Do Not Induce Browning of Human Subcutaneous White Adipose Tissue in Women and Men with Obesity, Cell Rep. 22(), 1079-1089

Morigny P, Houssier M, ..., Moro C, Viguerie N, Harms M, Hallen S, Vidal-Puig A, Postic C, Vidal H, Langin D (2019). Interaction between Hormone-Sensitive Lipase and ChREBP in Fat Cells Controls Insulin Sensitivity, Nat Metab. 1(133), 146

Carper D, Coue M, Nascimento E, Barquissau V, ..., Bourlier V, Lezoualc'h F, Carrière A, Saris WHM, Astrup A,Casteilla L, Mithieux G, Van Marken Lichtenbelt W, Langin D, Schrauwen P, and Moro C (2020). Atrial natriuretic peptide orchestrates a coordinated physiological response to fuel non shivering thermogenesis, Cell Rep. 32(8), 108075

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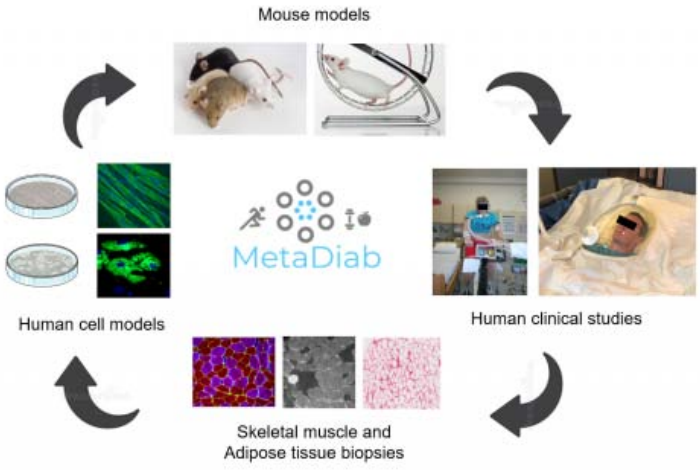
Translational Medicine Approach of MetaDiab



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Key facts

Team

- Researchers : 5
- Technicians : 3
- Postdoc fellows : 1
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 1

International research links

- USA
- Italy
- Germany

Keywords

- Mitochondria
- Bioenergetics
- Metabolism
- Oxidative stress
- Cancer
- Respirometry
- Metabolic fluxes
- Fluorescence
- Biochemistry

Frédéric Bouillaud

Mitochondria, bioenergetics, metabolism and signaling

Université de Paris 05
(Université Rene Descartes)
Inserm U1016 CNRS UMR8104
Pierre-Olivier Couraud
Paris

Our general objective is to study the crosstalk between mitochondrial function, metabolism and diseases by deciphering the molecular mechanisms involved in mitochondrial adaptation to intrinsic and/or environmental insults.

Research Brief :

The aim of the team is to study how mitochondrial bioenergetics constitutes a determining factor for complex phenotypes. We address two different situations:
1) Bioenergetics is known to be the primary target of genetic defects, environmental or endogenous modifying factors; we then analyze how bioenergetic machinery (essentially mitochondria) is affected and subsequently both deleterious impact and potential compensatory responses at the cellular level.
2) Bioenergetics appears modified in pathological states (over-nutrition, obesity, diabetes, cancer?). Firstly, one should substantiate and characterise the qualitative and quantitative bioenergetic changes associated to the pathological state. Then the question of bioenergetic?s role is to be considered : does it constitute an adaptive response, an aggravating factor or could it be directly causative of the pathological state.
Our models are derived from human mitochondrial diseases or are based on modulation of specific genes (Ucp2, Cpt1, Sqr).

We consider that the transport of substrates across the mitochondrial is a critical control point and consider two systems the mitochondrial carrier UCP2 and the carnitine palmitoyl transferase 1 (CPT1. Our studies on sulfide bioenergetics illustrates the intrication between toxic, signaling and adaptive components.
Regular collaboration with teams needing to approach mitochondrial bioenergetics often provides additional models.

- **Methodologies Used :**

Respirometry (Oroboros and Seahorse)
Metabolic fluxes
ROS and membrane potential fluorescent probes
Molecular biology : recombinant DNA & immunodetection
Transgenic models

Publications

Esteves P, Pecqueur C, Ransy C, Esnous C, Lenoir V, Bouillaud F, Bulteau AL, Lombès A, Prip-Buus C, Ricquier D, Alves-Guerra MC (2014). Mitochondrial retrograde signaling mediated by UCP2 inhibits cancer cell proliferation and tumorigenesis., Cancer Res.. 74(4), 3971-82

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Bouillaud Frédéric - frederic.bouillaud@inserm.fr

Key facts

Team

• Researchers : 21
• Technicians : 10
• Postdoc fellows : 3
• PhD Students : 15

Translational approaches

• Patents : 3
• Clinical research grants : 0
• Industry partnerships : 0

International research links

• E-Rare program TreatOPON for
OPA1 gene therapy
• PHC Toubkal with Institut Pasteur Casablanca Morocco

Keywords

• mitochondria
• mitochondrial genome
• metabolism
• metabolomic
• optic nerve
• mitochondrial structure assessment
• cell respiration
• mtDNA analysis
• metabolomics pipelines

Biological Resources

• 4000 DNA samples of patients with inherited optic neuropathy
• 50 fibroblast cell lines from patients with inherited mitochondrial diseases (optic nerve, central and peripheral neuropathies)
• cohorts associated to the 7 Natl ref centers for rare diseases
• mouse models of mitochondrial diseases (Opa1, Drp1, ND6, Twnk, Tt19, Parl)

Guy Lenaers

MitoLab

Université d'Angers
INSERM U1083 CNRS UMR6015
Daniel Henrion
Angers

MitoLab has a unique expertise in the assessment of mitochondrial physiology in fundamental and clinical samples and promote a bed-to-bed strategy of investigations of mitochondrial inherited and common diseases.

Research Brief :

Created 20 years ago with the clinic and molecular diagnostic of hereditary mitochondrial pathologies, our expertise and technologic skills have improved with the aim to build a continuum of researches "bed to bed?, and the perspective to infer new rational and efficient treatments for patients.
Three fundamental strategic and thematic orientations have been developed, focusing on:
1) mitochondrial dynamics,
2) maintaining the integrity of the mitochondrial genome,
3) the metabolism of the mitochondria
With hereditary and common associated diseases:
1) Dominant optic atrophy, Charcot Marie Tooth disease, encephalopathies, and myopathies, myocardial infarction, arterial hypertension,
2) Mitochondrial DNA depletion syndromes, progressive external ophthalmoplegia and ovarian failure, intrauterine growth retardation,
3) Leber Optic Neuropathy, MELAS, Leigh Syndrome and Glaucoma, DMLA, Myopia, Thyroid and Kidney Cancer, Sickle Cell Disease, Endometriosis, Forensic medicine.

MitoLab is a team located at the interface between the University and the University Hospital Center of Angers, bringing together about fifty researchers, lecturer-researchers, doctors, engineers and technicians, post-doctoral and PhD students, Master students and internal in medicine.
The team involves the services of Biochemistry and Molecular Biology, Genetics, Ophthalmology Neurology, Urology and Reproductive Biology, and 7 National Reference Centers for rare diseases.

• **Methodologies Used :**

MitoLab has developped unique NGS + computer pipelines for the molecular diagnosis of mitochondrial inherited diseases, and the full assessment of the integrity of the mitochondrial genome.
We also developped the concept of Metabolomic Medicine to infer the metabolomic signature of a specific disease, using various patients sampling, as plasma, aqueous humor, CSF, cells and targeted and untargeted mass spectrometry.
The team has also a unique expertise in the assessment of mitochondrial respiration (oxygraphy, enzymatic activities and assembly of the respiratory chain complexes), metabolism (Krebs cycle and glycolysis) and structure (inner and outer membrane dynamics).

Lenaers Guy - guy.lenaers@inserm.fr - 0244688487 - http://mitovasc.univ-angers.fr/en/presentation/research-themes.html

Publications

Chao de la Barca JM, Simard G, Amati-Bonneau P, Safiedeen Z, Prunier-Mirebeau D, Chupin S, Gadras C, Tessier L, Gueguen N, Chevrollier A, Desquiret-Dumas V, Ferré M, Bris C, Kouassi Nzoughet J, Bocca C, Leruez S, Verny C, Miléa D, Bonneau D, Lenaers G, Martinez MC, Procaccio V, Reynier P. (2016). The metabolomic signature of Leber's hereditary optic neuropathy reveals endoplasmic reticulum stress., Brain. 139(11), 2864

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Key facts

Team

• Researchers : 3
• Technicians : 6
• Postdoc fellows : 4
• PhD Students : 1

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 0

International research links

• Belgium - United Kingdom - Switzerland - The Netherlands

Keywords

• Adipose tissue
• Lymphocytes
• Psoriasis
• Fc receptors
• Type 2 diabetes
• Nuclear receptors
• Atherosclerosis
• Inflammation
• Obesity
• Immune cells
• NASH
• Eosinophils
• Histology and Immunohistochemistry
• Flow and mass cytometry
• Pharmacology
• Genetically-modified mice
• Invasive and non invasive plethysmography
• Real-time PCR

Biological Resources

• Genetically-modified mice (hFcepsilonRIalpha Tg, FcepsilonRIalpha-/-, FcRbeta-/-, PPARbeta/gamma-/-, FXR-/-, RORalpha-/-)

David Dombrowicz

Nuclear receptors, immuno-inflammation and cardiometabolic diseases

Université de Lille
Inserm UMR1011 Institut Pasteur de Lille
Bart Staels
Lille

Research is centered on the regulation, by nuclear receptors, of immune cell contribution to cardiovascular diseases, atherosclerosis and type 2 diabetes.

Research Brief :

Building on our experience in allergic diseases and the immuno-regulatory role of nuclear receptors in asthma and atopic dermatitis, we develop a research on immuno-inflammation in cardio-metabolic diseases, atherosclerosis and type 2 diabetes.

1. We study the regulation by FXR and RORalpha of immune cell functions as well as of the development of atherosclerosis using whole body or cell-specific deletion of these genes in mice and feeding with high fat western diet. Expression of these genes in distinct lymphoid subsets downregulate metabolic inflammation.

2. Using both experimental models and a translational approach, we investigate the link between psoriasis, an inflammatory skin disease, and cardiovascular disease. We demonstrate that high fat diet increases psoriasis severity by altering innate and adaptive immune response through metabolic reprogramming.

3. We characterize the impact of type 2 diabetes on blood and adipose tissue immune cell subpopulations in obese patients with Non Alcoholic SteatoHepatitis and correlate blood phenotype with clinico-biological parameters as well as adipose tissue and liver transcriptome.

• **Methodologies Used :**

Genetically-modified mice
Pharmacology
Histology and Immunohistochemistry
Flow cytometry
Real-time PCR
Invasive and non invasive plethysmography
Laser capture microdissection

Publications

Kanda A, Driss V, Hornez N, Abdallah M, Roumier T, Abboud G, Legrand F, Staumont-Sallé D, Quéant S, Bertout J, Fleury S, Rémy P, Papin JP, Julia V, Capron M, Dombrowicz D (2009). Eosinophil-derived IFN-gamma induces airway hyperresponsiveness and lung inflammation in the absence of lymphocytes., The Journal of Allergy and Clinical Immunology. 124(3), 573-82, 582.e1-9

Mionnet C, Buatois V, Kanda A, Milcent V, Fleury S, Lair D, Langelot M, Lacoeuille Y, Hessel E, Coffman R, Magnan A, Dombrowicz D, Glaichenhaus N, Julia V (2010). CX3CR1 is required for airway inflammation by promoting T helper cell survival and maintenance in inflamed lung., Nature Medicine. 16(11), 1305-12

Staumont-Salle D, Fleury S, Lazzari A, Molendi-Coste O, Hornez N, Lavogiez C, Kanda A, Wartelle J, Fries A, Pennino D, Mionnet C, Prawitt J, Bouchaert E, Delaporte E, Glaichenhaus N, Staels B, Julia V, Dombrowicz D (2014). CX3CL1 (fractalkine) and its receptor CX3CR1 regulate atopic dermatitis by controlling effector T cell retention in inflamed skin., The Journal of Experimental Medicine. 211(6), 1185-96

Julia V, Macia L, Dombrowicz D (2015). The impact of diet on asthma and allergic diseases., Nature Reviews Immunology. 15(5), 308-22

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Everaere L, Ait-Yahia S, Molendi-Coste O, Vorng H, Quemener S, Le Vu P, Fleury S, Bouchaert E, Fan Y, Duez C, De Nadai P, Staels B, Dombrowicz D, Tsicopoulos A* with an Editors'Editorial p. 1299 (*senior communicating authors) (2016). Innate lymphoid cells contribute to allergic airway disease exacerbation by obesity., The Journal of Allergy and Clinical Immunology. 138(5), 1309-18*

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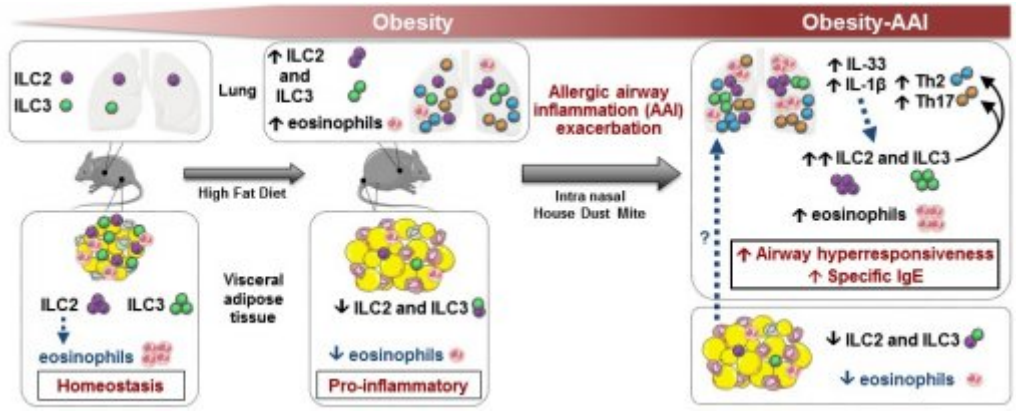
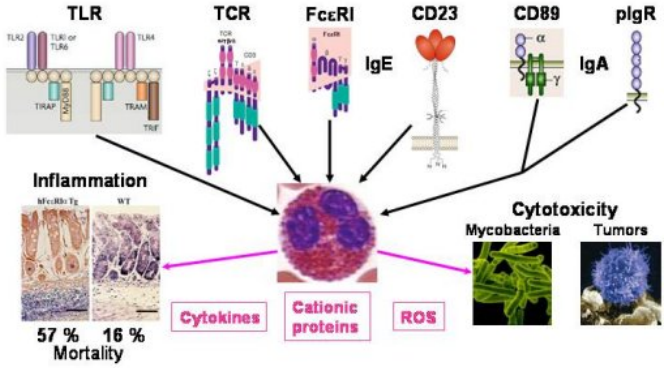
ILC in asthma exacerbation by obesity



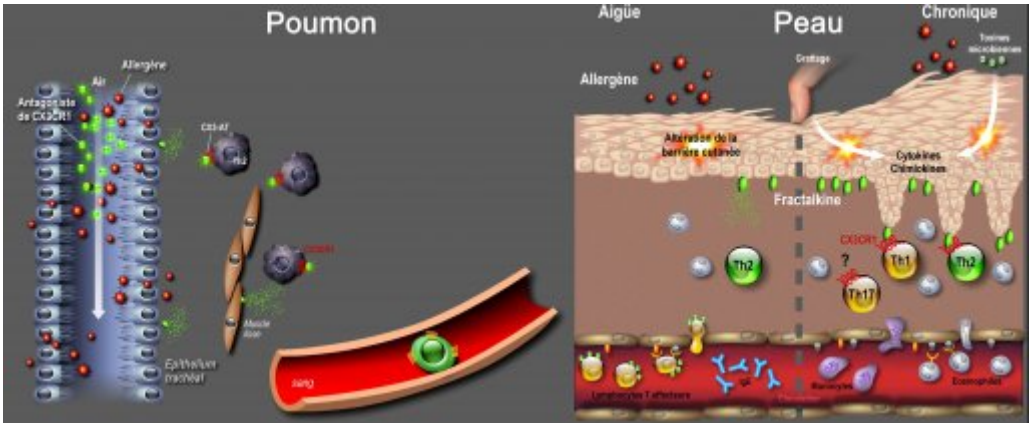
HFD feeding exacerbated allergic asthma. Obese mice show increased lung ILC and eosinophilia compared to lean mice. Lung ILC2 and ILC3 further increased in HDM-challenged obese mice compared to lean mice, with high IL-33 and IL-1? levels and decreased ILC markers in visceral adipose tissue. ILC depletions followed by T-cell reconstitution, led to a decrease in allergic asthma in obese mice, including TH2 and TH17 infiltration. (Julia et al. Nat. Rev. Immunol. 2015 & Everaere et al. JACI. 2016)

Receptor-induced eosinophil activation in inflammatory, infectious and oncologic diseases



Through release of cytotoxic mediators and cytokines, eosinophils exert a detrimental role in inflammatory diseases but are beneficial in immunity against helminths, mycobacteria and tumors. Cytotoxic and regulatory activities are triggered through the expression of several receptors associated to innate (TLR, TCRgammadelta) or acquired (FcR) immunity. (Decot et al. and Karagiannis et al. J. Immunol. 2005 and 2007; Legrand et al. PlosOne 2009; Driss et al. Blood 2009; Kanda et al. JACI. 2009)

Fractalkine and its receptor in allergic diseases



In lung and skin, antigen-specific Tcell migration is CX3CR1-independent.and CX3CR1 is only expressed once T cell reach the tissue. Interaction with CX3CL1, its unique ligand, expressed by epithelial or smooth muscle cells allows T cell survival within the inflamed lung while it regulates retention of Th1 and Th2 cells in skin. A CX3CR1 antagonist blocks survival signal and prevents airway hypereactivity and inflammation (Mionnet et al. Nat. Med. 2010 & Staumont-Salle et al. J. Exp. Med, 2014)

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Key facts

Team

• Researchers : 16
• Technicians : 10
• Postdoc fellows : 5
• PhD Students : 6

Translational approaches

• Patents : 1
• Clinical research grants : 6
• Industry partnerships : 5

International research links

• JPI-Microfiet
• IRP INSERM (Madison University
USA)
• leducq fondation

Keywords

• Fibrosis
• Nutrition
• Obesity
• Microbiota
• Inflammation
• IHC
• Cell culture
• Data mining and integration
• Trancriptomics, (meta)genomics
• animal models

Biological Resources

• Peripheral and portal blood
• DNA, RNA banks (human and bacteria)
• urine and feces
• Tissues (adipose tissue depots, liver, intestine)
• PBMC, adipose cells, Immune cells

Karine Clement

Nutriomique research unit

Sorbonne University
Inserm UMRS 1269
Karine CLEMENT
Paris

Targeting obesity: From bench to bedside.

Research Brief :

Our research theme in the field of obesity and metabolic diseases focuses on the characterization of tissue/cell disturbances and inter-organ dialogues, generated by weight variation and changes in metabolic status. From samples obtained in subjects with metabolic diseases at different stages of progression, large scale approaches and new bioinformatic methods for data analysis and integration are developed. Previous achievements have allowed:
-to increase our knowledge of the alterations of immunity and inflammatory status associated with obesity in adipose tissue depots, circulation and intestine,
-to demonstrate the pathophysiological importance of fibrosis in obese adipose tissue and to identify the cellular contributors,
-to identify major dysbiosis in human obesity and mediators that can link the imbalance of intestinal bacterial species and organ alterations.
New development exploring the interplay between environmental factors, intestine biology and host biology are undertaken to understand the progression of obesity and its complications (Axis 1&2). The consequences of adipose tissue remodelling, is also being explored (Axis 3). Bioinformatic aspects including systems biology and data integration approaches are pursued (Axis4). Axis 5 led by physicians in conjunction with clinical services associated with the team will aim to test in patients the relevance of biomarkers/predictors identified for new stratification approaches and innovative therapeutic strategies.

• **Methodologies Used :**

2D and 3D Cell cultures, migration, proliferation, differentiation
Cell biology (western blots, RT-PCR, immunofluorescence, confocal microscopy)
Immunochemistry, cell sorting FACS
siRNAs transfection, ChIPs, microarray, nanopore technology
Bioinformatics : predictive analysis, network analysis, data integration, data mining
Physiology in animal models, genetically modified animals, organ on chip
Metagenomics, genomics, Genotyping, metabolomics, lipidomics
clinical investigation

Publications

Clément K, Biebermann H, Farooqi IS, Van der Ploeg L, Wolters B, Poitou C, et al. (2018). MC4R agonism promotes durable weight loss in patients with leptin receptor deficiency., Nat Med. 24(5), 551?5

Vieira-Silva S, Falony G, Belda E, Nielsen T, Aron-Wisnewsky J, Chakaroun R, et al. (2020). Statin therapy is associated with lower prevalence of gut microbiota dysbiosis., Nature. 581(7808), 310-5

Clément K, van den Akker E, Argente J, Bahm A, Chung WK, Connors H, et al. (2020). Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials., Lancet Diabetes Endocrinol. 8(12), 960-70

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Rouault C, Marcelin G, Adriouch S, Rose C, Genser L, Ambrosini M, et al (2021). Senescence-associated ?-galactosidase in subcutaneous adipose tissue associates with altered glycaemic status and truncal fat in severe obesity., Diabetologia. 64(1), 240-54

Belda E, Voland L, Tremaroli V, Falony G, Adriouch S, Assmann K, Prifti E, Aron-Wisnewsky J, Debédat J, Le Roy T, Nielsen T, Amouyal C, André S, Andreelli F, Blüher M, Chakaroun R, Chilloux J, Coelho LP, Dao MC, Das P, Fellahi S, Forslund S, Galleron N, Hansen TH, Holmes B, Ji B, Pedersen HK, Le P, Le Chatelier E, Lewinter C, Mannerås-Holm L, Marquet F, Myridakis A, Pelloux V, Pons N, Quinquis B, Rouault C, Roume H, Salem JE, Sokolovska N, Sønderskov NB, Touch S, Vieira-Silva S, The MetaCardis consortium?, Galan P, Holst JJ, Gøtze JP, Køber L, Vestergaard H, Hansen T, Hercberg S, Oppert JM, Nielsen J, Letunic I, Dumas ME, Stumvoll M, Pedersen O, Bork P, Ehrlich SD, Zucker JD, Bäckhed F, Raes J, Clément K (2022). Impairment of gut microbial biotin metabolism and host biotin status in severe obesity: effect of biotin and prebiotic supplementation on improved metabolism, Gut. (),

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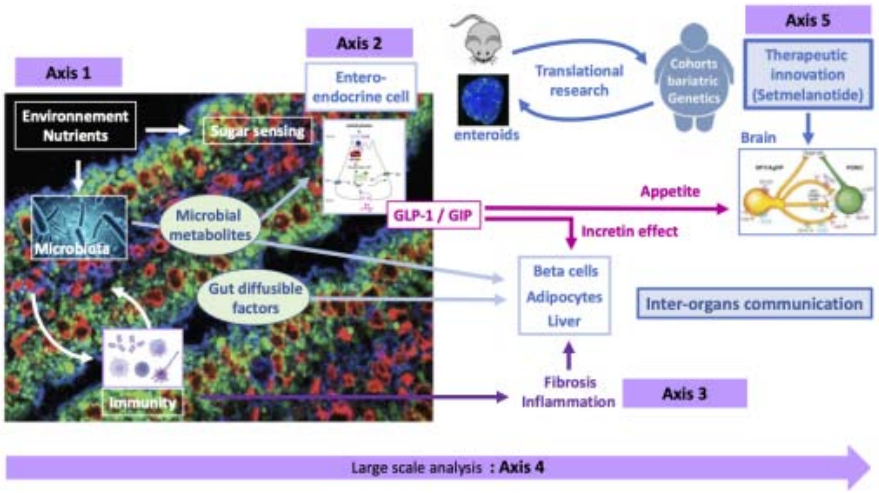
Organisation of Nutriomic research Activity



5 Axis are developed :
Axis 1 : Progression of obesity and related complications : role of gut microbiota?
Axis 2 : Intestine as a key player in metabolic disorders
Axis 3 : Adipose tissue remodeling
Axis 4 : Systems'biology and data integration
Axis 5 : Translating our fundamental research for the benefit of patients

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DMeM
Dynamique du Muscle et Métabolisme

Christine Feillet-Coudray Thomas Brioche

Nutrition and Metabolic Homeostasis

University of Montpellier
INRAE UMR 0866
Vincent Ollendorff
Montpellier

Key facts

Team

• Researchers : 5
• Technicians : 2
• Postdoc fellows : 1
• PhD Students : 1

Translational approaches

• Patents : 1
• Clinical research grants : 0
• Industry partnerships : 0

International research links

• Thailand
• Czech Republic
• Spain

Keywords

• Plant bioactive compounds
• Lipids
• Obesity
• Physical activity
• Skeletal muscle deconditioning
• Animal models
• Mitochondria

Wide range of expertise on physiological effects of bioactive food compounds on skeletal muscle metabolism through in vitro and in vivo approaches

Research Brief :

Our work aims to understand the role and impact of plant bioactive compounds from food (FAHFAs, FuFAs, Ergothioneine, Carnosol, HMB, ...) in the maintenance of skeletal muscle mass and strength and more broadly of metabolic homeostasis, looking in particular for new and more sustainable sources. Our studies are conducted on academic animal models (DIO mice or rats, db/db mice, Zucker rats, zebrafish, Hindlimb Unloading, Aged Mice), in humans (obese subjects, diabetic patients, ...) and also in animals of agronomic interest such as trout. Our objectives are to identify nutritional levers to promote muscle health and metabolic homeostasis in response to different physiological and environmental conditions (aerobic exercise, diets, inactivity...).

• **Methodologies Used :**

Primary rodent muscular cells, muscle cell lines
Animal experiments in rodents
Characterization of mice metabolism: body composition (EchoMRI 700) and indirect calorimetry (Clams®-Oxymax).
Influence of nutrition on muscle function
Evaluation of spontaneous activity : ActiWheel v5.1 software (IntelliBio); Rotarod NG UgoBasile, Grip-test
Strength or endurance training: Exer3/6 Treadmill , Columbus, Grip Strength, Rotarod, Climbing Ladder
Muscular deconditioning with immobilization system by suspension of the rear train

Publications

Djohan YF, Badia E, Bonafos B, Fouret G, Lauret C, Dupuy AM, Pinot E, Sutra T, Gaillet S, Lambert K, Gayrard N, Jover B, Vidé J, Aké Monde A, Cristol JP, Coudray C, Feillet-Coudray C (2018). Comparative effects of palm oils versus Mediterranean virgin olive oil on biological hepatic parameters and steatosis in rats, Eur J Nutr. 58(),

Wang Y, Fouret G, Bonafos B, Blachnio-Zabielska A, Leroy T, Crouzier D, Barea B, Gaillet S, Moro C, Lecomte J, Coudray C, Feillet-Coudray C (2019). Long-term follow-up of muscle lipid accumulation, mitochondrial activity and oxidative stress and their relationship with impaired glucose homeostasis in high fat high fructose diet-fed rats, J Nutr Biochem. 64(),

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Arc-Chagnaud C, Py G, Fovet T, Roumanille R, Demangel R, Pagano AF, Delobel P, Blanc S, Jasmin BJ, Blottner D, Salanova M, Gomez-Cabrera MC, Viña J, Brioche T, Chopard A (2020). Evaluation of an Antioxidant and Anti-inflammatory Cocktail Against Human Hypoactivity-Induced Skeletal Muscle Deconditioning, Front Physiol. 11(),

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Bonafos B, Cortés-Espinar AJ, Balas L, Pessemesse L, Lambert K, Benlebna M, Gaillet S, Pelletier F, Delobel P, Ávila-Román J, Abellán MM, Bertrand-Gaday C, Durand T, Coudray C, Casas F, Feillet-Coudray C (2023).). 9-PAHPA long term intake in DIO and db/db mice ameliorates insulin sensitivity but has few effects on obesity and associated metabolic disorders, J Nutr Biochem. 112(),

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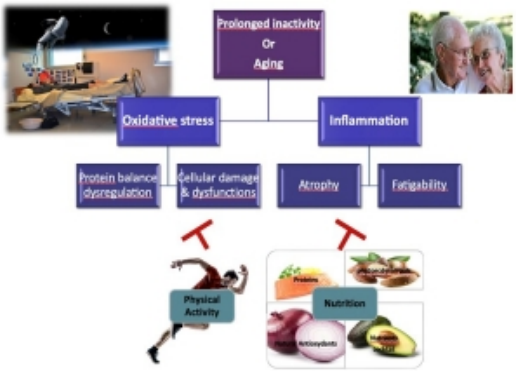
Impact of a bioactive fatty acid supplementation in DIO mice (Bonafos et al 2023 J Nutr Biochem)

Nutrition and Physical Activity against Muscle deconditionning



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Nutrition Croissance Cancer

Christophe Vandier

Nutrition, Growth and Cancer

Université de Tours
(Université Francois Rabelais)
Inserm UMR 1069 CHU UMR 1069
Christophe Vandier
Tours

Our objectives are to establish a rationale for implementing clinical trials using specific lipid to increase anticancer treatment efficacy, to prevent metastasis, to limit therapeutic relapse in chronic forms of prostate/breast cancers, to fight cancer cachexia and allow better tolerance to drugs.

Key facts

Team

• Researchers : 23
• Technicians : 9
• Postdoc fellows : 2
• PhD Students : 6

Translational approaches

• Patents : 4
• Clinical research grants : 4
• Industry partnerships : 6

International research links

• M Tebak, Penn State Cancer Institute, USA
• V Barracos, Edmonton, Canada
• P Buchanan, Dublin City University, Ireland

Keywords

• Cholesterol
• polyunsaturated fatty acids
• mitochondrial bioenergetics.
• Breast cancer
• cell migration
• invasiveness
• Calcium
• membrane transporters
• lipidome
• ion channels
• tumor chemosensitization
• Alkyl-Ether-Lipids
• prostate cancer
• Colon cancer
• invasion
• cell cultures
• Lipid
• migration
• calorimetric chambers
• fluorescence microscopy
• Rodents models of breast cancer
• Organotypic cultures
• clinical trial

Biological Resources

• Metastatic Breast Cancer Patients
• Breast Cancer cell cultures
• Prostate Cancer cell cultures
• Rodent models of mammary tumor
• Biobank of human adipose tissues
• Biobank of human prostate tumor tissues

Research Brief :

The research unit has a long-standing expertise in performing research at the interface between nutrition and cancer, and has received international recognition in this field. The team was the first to link diet-related changes in the breast-associated adipose tissue (lipidome) in relation to breast cancer development and metastasis. This finding is highly consistent with the hypothesis that the western diet plays a pivotal role in the development and the progression of several high incidence and mortality-inducing tumor types, including breast and prostate cancers. UMR1069 has also described the potential benefits of the clinical use of lipid nutrients in order to increase anticancer treatment efficiency. Cancer-induced cachexia, a progressive alteration in the nutritional status of patients that drastically affects their survival, is another association between cancer and nutrition being investigated. Specific dietary and pharmacological lipid interventions may have important beneficial effects and clinical applications.
Our scientific project aims at investigating the cellular mechanisms of action of lipids (ether-lipids, cardiolipins, polyunsaturated fatty acids) to regulate cancer cachexia and tumor progression (bed to bench side). The objective is to facilitate the transfer of of such fundamental knowledge to patients developing chemo-or hormono-resistant cancers and/or metastases and/or cancer-induced cachexia (bench to bedside).

• **Methodologies Used :**

Randomized clinical trial in cancer patients, Analysis of energy metabolism in humans and rodents, Mouse and rat models of breast tumors and metastases, Epithelial cell cultures (proliferation, migration, invasion), Organotypic cultures, Electrophysiology of cancer cells (automated platform in development)and in tissues, Calcium homeostasis, Lipid biochemistry (chromatography, spectrometry) and chemical synthesis, Bioenergetics analysis of mitochondrial functions, Molecular and cellular tools (cloning, siRNA, PCR and Western blotting, lentivirus transfection), Bright field, phase contrast and fluorescence microscopy and Macroscopy. Hypoxia chamber.

Publications

Jaffrès PA, Gajate C, Bouchet AM, Couthon-Gourvès H, Chantôme A, Potier-Cartereau M, Besson P, Bougnoux P, Mollinedo F, Vandier C. (2016). Alkyl ether lipids, ion channels and lipid raft reorganization in cancer therapy, Pharmacology & Therapeutics. S0163-7258(16), 30093-6

Rua C, Guéguinou M, Soubai I, Viel E, Potier-Cartereau M, Chantome A, Barbe C,Bougnoux P, Barin-Le Guellec C, Vandier C. (2018). SK3 Gene Polymorphism Is Associated with Taxane Neurotoxicity and Cell Calcium Homeostasis., Clin Cancer Res. 24(21), 5313-5320

Figiel S, Bery F, Chantôme A, Fontaine D, Pasqualin C, Maupoil V, Domingo I,Guibon R, Bruyère F, Potier-Cartereau M, Vandier C, Fromont G, Mahéo* K (*co-dernier auteurs). (2019). A Novel Calcium-Mediated EMT Pathway Controlled by Lipids: An Opportunity for Prostate Cancer Adjuvant Therapy., Cancers. 11(11),*

Mantha OL, Goupille C, Dumas JF, Robins R, Bougnoux P, Hankard R, De Luca A. (2020). Natural isotopic abundances as markers of compliance in clinical trials., Am J Clin Nutr.. 111(5), 1109-1110

Dolly A, Lecomte T, Bouché O, Borg C, Terrebonne E, Douillard JY, Chautard R, Raoul W, Ternant D, Leger J, Bleuzen A, Dumas JF, Servais S, Baracos VE. (2020). Concurrent losses of skeletal muscle mass, adipose tissue and bone mineral density during bevacizumab / cytotoxic chemotherapy treatment for metastatic colorectal cancer., Clin Nutr. 39(11), 3319-3330

Ferro F, Servais S, Besson P, Roger S, Dumas JF, Brisson L (2020). Autophagy and mitophagy in cancer metabolic remodelling., Semin Cell Dev Biol. 98(), 129-138

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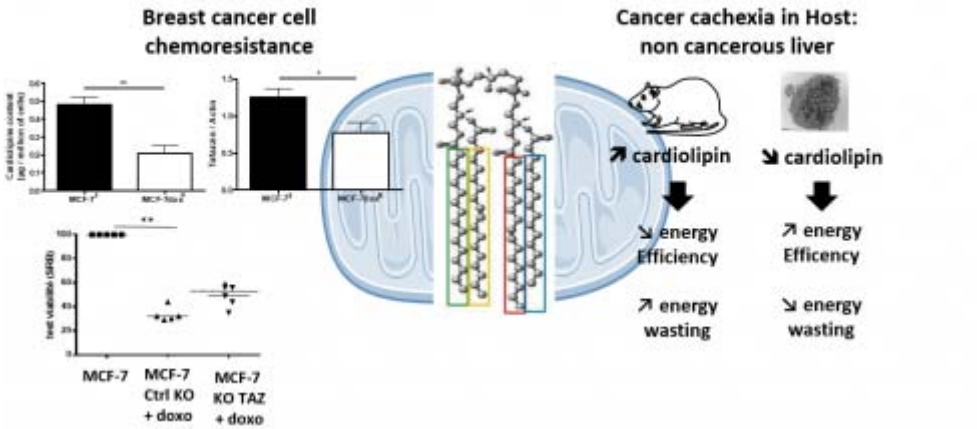
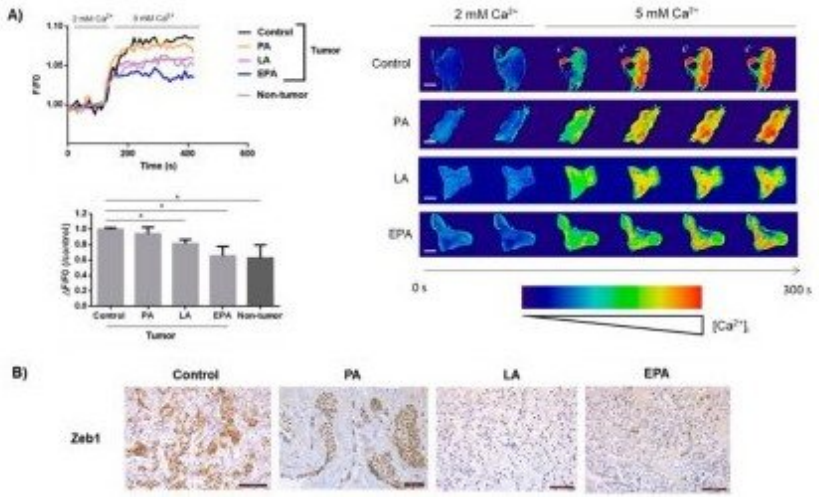
Dual role of cardiolipin in cancer



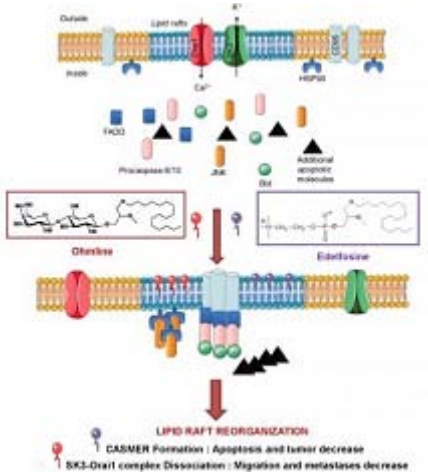
Cardiolipin affect mitochondrial bioenergetics and play a dual role in cancer: chemoresistance and host response to tumor development. CL and tafazzin content were reduced in doxorubicin-resistant breast cancer cells. In cancer cachexia, liver mitochondria display lower oxidative phosphorylation (OXPHOS) efficiency and increased energy wasting processes linked to CL content increase. Direct implication of CL in OXPHOS was confirmed by shRNA interference against cardiolipin synthase.

Linoleic acid (LA) and eicosapentaenoic acid (EPA) reduces calcium entry in human PCa slices



A. The increase in extracellular calcium from 2 to 5 mM induced a higher entry of calcium into human tumours than in non-tumour prostate slices. EPA and LA reduced this entry unlike palmitic acid (PA). B- Contrary to palmitic acid (PA), supplementation with LA and EPA decreased the expression of Zeb1 in these tumor slices. From Figiel et al, Cancers. 2019;11(11).

Proposed mechanism of action of Alkyl-Ether-Lipids (AEL) in tumor cells



SK3 and Orai1 channels are embedded within lipid rafts and form a complex regulating cancer cell migration and metastasis development. CASMER is not formed and cells are resistant to apoptosis. The reorganization of lipid raft induced by AEL allows Orai1-SK3 to move away from lipid rafts and abolishes SK3-dependent constitutive calcium entry. Edelfosine recruits a number of apoptotic signaling molecules in lipid rafts to generate. From Jaffrès et al., Pharmacol Ther. 2016 165:114-31.

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Moïse Coëffier

Nutrition, Inflammation and Microbiota-Gut-Brain axis

University of Rouen Normandy
Inserm U1073
Moïse Coëffier
Rouen

Translational researches on the dysfunction of microbiota-gut-brain axis during eating disorders, irritable bowel syndrome and/or inflammatory bowel diseases to develop rapidely new therapeutics.

Key facts

Team

- Researchers : 25
- Technicians : 8
- Postdoc fellows : 1
- PhD Students : 16

Translational approaches

- Patents : 2
- Clinical research grants : 5
- Industry partnerships : 4

International research links

- Dr L Bindels (Université Catholique de Louvain, Belgique)
- Pr Subrata Ghosh (University College Cork, Cork, Ireland)
- Pr Jonathan Swann (Imperial College of London, London, England)

Keywords

- gut-brain axis
- intestinal inflammation
- eating disorders
- Nutrients
- Microbiota
- visceral sensitivity
- innovative nutrition formulas
- neurostimulation

Biological Resources

- Microbiology
- animal models (ED, IBS, IBD)
- Intestinal models: cell lines (HCT-8, Caco-2, enteroendocrine cells), human intestinal explants, co-culture (bacteria, intestinal cells)
- Cohorts with biobanks (ED, IBS)

Research Brief :

The research of our group, integrated in the IRIB Institute, are mainly dedicated to the study of eating disorders, irritable bowel syndrome (IBS) and inflammatory bowel diseases (IBD). These pathologies share common features of intestinal inflammation and dysregulation of the microbiota-gut-brain axis and offer great opportunities for innovative therapeutic strategies. Our projects explore the underlying mechanisms of these diseases from the molecular level to clinical trials. This broad range of research from the bench to the bedside is the result of our research strategy that brings together basic and clinical sciences, in a tight collaboration between laboratory scientists and health professionals. Our dynamic research team has an active research strategy which also drives the translation of research from the laboratory to patenting and creation of biotech company entrepreneurship.

- **Methodologies Used :**

Intestinal models: epithelial and enteroendocrine cell lines, human intestinal explants
Rodent models for eating disorders (ED), iiritable bowel syndrome (IBS) and inflammatory bowel diseases (IBD)
Proteomics: mass spectrometric analysis and in vivo isotopic studies
Body Composition in rodents and humans
Digestive function investigation platform for rodents and humans (intestinal permeability, motility, sensitivity, endoscopy)
Ussing Chambers for measuring electrical resistance and molecule fluxes
Neurostimulation and neuronavigation systems
Gut microbiota analysis and Host-pathogen interaction in aerobic and anaerobic conditions
qPCR, immunoblotting, immunostaining, flow cytometry
Epidemiological studies (eating-disorders, IBD and IBS)

Publications

Sacleux SC, Sarter H, Fumery M, Charpentier C, Guillon-Dellac N, Coevoet H, Pariente B, Peyrin-Biroulet L, Gower-Rousseau C, and Savoye G; EPIMAD Group. (2018). Post-operative complications in elderly onset inflammatory bowel disease: a population-based study., Aliment Pharmacol Ther. 47(12), 1652-1660

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Amamou A, Rouland M, Yaker L, Goichon A, Guérin C, Aziz M, Savoye G, Marion-Letellier R (2021). Dietary salt exacerbates intestinal fibrosis in chronic TNBS colitis via fibroblasts activation, Sci Rep. 11(), 15055

Tirelle P, Breton J, Keuffmann A, Bahouli W, L'Huillier C, Salameh E, Amamou A, Jarbeau M, Guérin C, Goichon A, do Rego JC, Déchelotte P, Ribet D, Coëffier M (2021). Gut microbiota depletion affects nutritional and behavioral responses to activity-based anorexia model in a sex-dependent manner, Clin Nutr. 40(5), 2734-2744

Ezzine C, Loison L, Montbrion N, Bôle-Feysot C, Déchelotte P, Coëffier M, Ribet D (2022). Fatty acids produced by the gut microbiota dampen host inflammatory responses by modulating intestinal SUMOylation, Gut Microbes. 14(1), 2108280

Grigioni S, Achamrah N, Chan P, Guérin C, Bôle-Feysot C, Delay J, Colange G, Quillard M, Coquard A, Bubenheim M, Jésus P, Tavolacci MP, Déchelotte P, Coëffier M (2022). Intestinal permeability and appetite regulating peptides-reactive immunoglobulins in severely malnourished women with anorexia nervosa., Clin Nutr.. 41(8), 1752-1758

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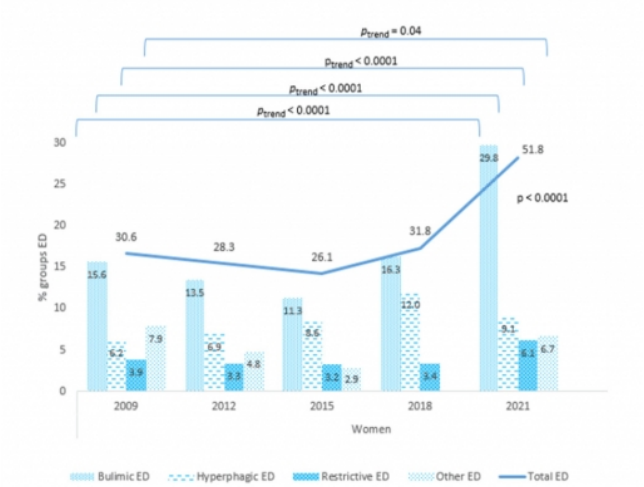
http://recherche.univ-rouen.fr/aden-umr-s-1073-nutrition-inflammation-et-dysfonction-de-l-axe-intestin-cerveau-679066.kjsp



Distribution of ED categories among university female students (2009-2021). Adapted from Tavolacci MP et al, Nutrients 2021;13:3415.

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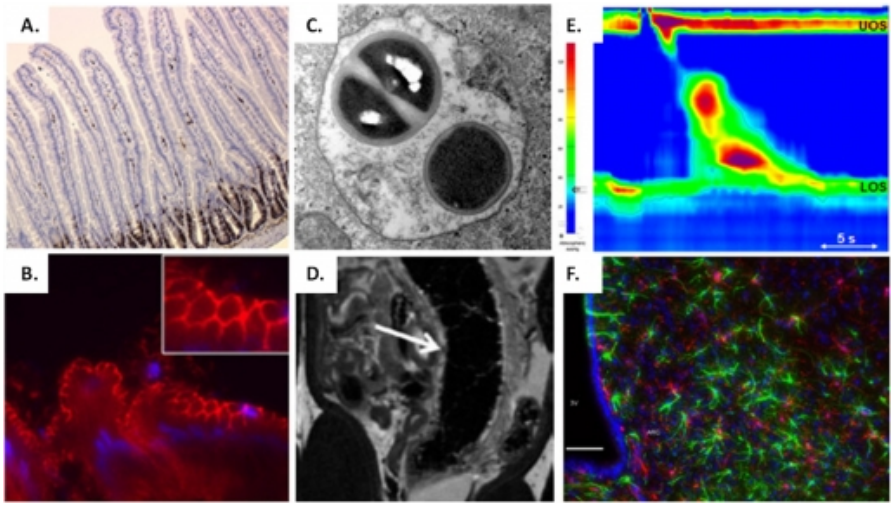

A/ Small Intestinal histology with BrDU labelling
B/ Immunostaining of tight junction protein occludin on human colonic biopsy
C/ Intestinal epithelial cell with intracellular bacteria observed by electronic microscopy
D/ MRI to follow experimenal colitis in rodents
E/ Oesophagal contractility in humans
F/ Immunostaining of microglial cells (Iba1-red) and astrocytes (GFAP-green) in hypothalamus

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Key facts

Team

- Researchers : 6
- Technicians : 5
- Postdoc fellows : 1
- PhD Students : 1

Translational approaches

- Patents : 3
- Clinical research grants : 1
- Industry partnerships : 3

International research links

- UK, Germany, Italy, Denmark, Spain, Ireland, Turkey, USA, Canada

Keywords

- Plant food bioactives, Polyphenols and personalized nutrition
- Vascular function, endothelium, inflammation
- Biomarkers of exposure and health
- Oxylipins and lipid mediators
- Extracellular Vesicles
- Food Metabolome
- Targeted lipidomics
- Nutrigenomics
- Clinical trials
- Cohorts

Biological Resources

- Healthy subjects and patients
- Animal experiments in rodents and minipigs
- Primary human endothelial cells, macrophages and monocytes cell lines

Christine Morand

Nutrivasc - Diet, Plant food bioactives & Vascular Health

Université Clermont Auvergne
INRAE UMR1019
Didier Remond
Clermont Ferrand

Unique expertise in conducting research on the assessment of the exposure to and of the vascular protective effects of dietary plant food bioactives. Special interest in identifying the factors responsible for the interindividual variability in the response to their consumption.

Research Brief :

To preserve cardiometabolic health and healthy aging, it is of great importance to identify innovative and scientifically sound dietary strategies to prevent vascular dysfunctions, themselves closely linked to chronic inflammation. Evidence from large prospective cohort studies have pointed out that some bioactive compounds contribute to the health benefits of diets rich in plant foods. However, the actual impact of most of these compounds in human and their mechanisms of action have not yet been fully evaluated.
Using complementary approaches (human, animal and in vitro) and combining classical and high throughput "omics" methodologies, the research of the NutriVasc team aims to:
1. Develop innovative and effective phenotyping tools (exposure, health) to improve knowledge on the relationship between diet and health. These include (i) the characterization of the complexity of individual exposure to metabolites of plant food bioactives by studying the food metabolome and (ii) the identification of oxylipin signatures characteristic of cardiometabolic and inflammatory disorders.
2. Demonstrate and understand the causality link between polyphenols intake and vascular protection (from clinical to mechanistics studies).
3. Explore and understand inter-individual variability in response to food consumption to move towards science-based personalized nutrition strategies focusing on plant foods rich in specific bioactives.

- **Methodologies Used :**

Randomized controlled trials in humans / Animal and cell experiments/ Non-invasive assessment of vascular function in human (micro and macro-circulation)/ Ex-vivo assessment of vascular reactivity in rodents using myography / Quantification and size-profiling of extracellular vesicles using qNano system / Biological evaluation (immuno-histochemistry, histology, flow cytometry) / Molecular and cellular analysis: gene expression (qPCR, transcriptomics), protein expression (Western blotting, proteomics), chemotaxis, monocyte adhesion, transendothelial migration) / Targeted lipidomics based on LC-MS/MS mass spectrometry to characterize lipid mediators / Metabolomics based on high-resolution mass spectrometry to characterize the food metabolome.

Publications

- Monfoulet LE, Mercier S, Bayle D, Tamaian R, Barber-Chamoux N, Morand C and Milenkovic D (2017). Curcumin modulates endothelial permeability and monocyte transendothelial migration by affecting endothelial cell dynamics, Free Rad Biol Med. 112(), 109-120

- Low D, Lefèvre-Arbogast S, Gonzalez-Dominguez R, Urpi-Sarda M, Micheau P, Pétéra M, Centeno D, Durand S, Pujos-Guillot E, Korosi A, Lucassen PJ, Aigner L, Proust-Lima C, Hejblum BP, Helmer C, Andres Lacueva C, Thuret S, Samieri C and Manach C (2019). Untargeted metabolomics in a prospective cohort to identify diet-related metabolites associated with age-related cognitive decline, Mol Nutr Food Res. 63(18), e1900177

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- Mainka M, Dalle C, Petera M, Dalloux-Chioccioli J, Kampschulte N, Ostermann AI, Rothe M, Bertrand-Michel J, Newman JW, Gladine C and Schebb NH (2020). Harmonized procedures lead to comparable quantification of total oxylipins across laboratories, J lipid Res. 61(), 1424-36

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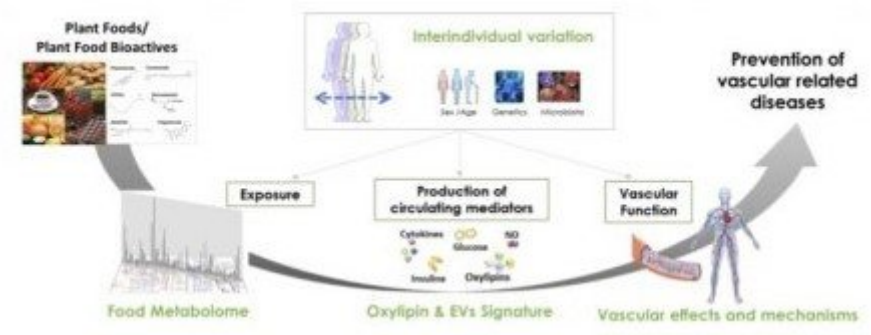
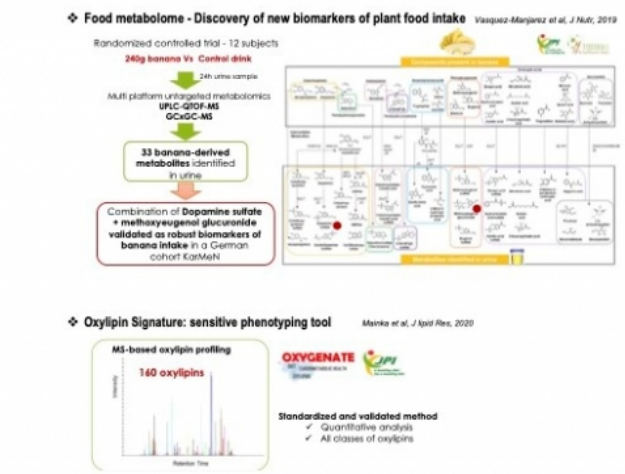
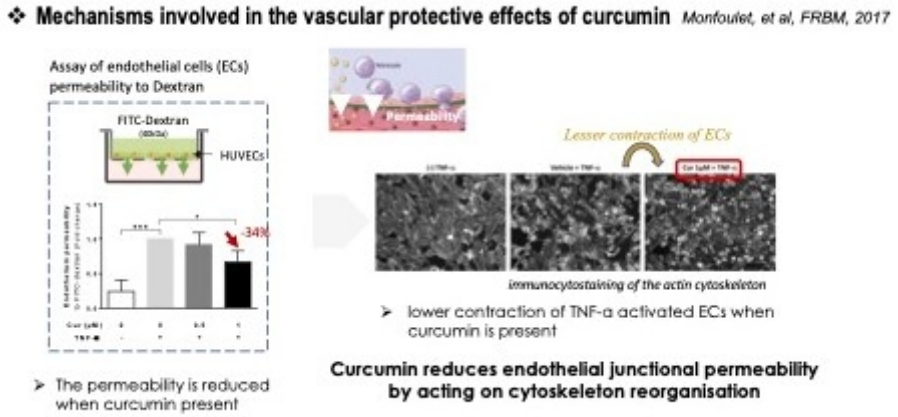
Outlines of the research developed in the NutriVasc Team



Exemples of new phenotyping tools



Exemple of mechanisms involved in vascular protective effects of polyphenols



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Unité de Nutrition Humaine

Pierre Fafournoux

Proteostasis

Université d'Auvergne
Clermont-Ferrand 1
INRA UMR1019
Didier Remond
Clermont-Ferrand

Our team has a strong expertise in studying the mechanisms responsible for the maintenance of protein/amino acid homeostasis during physiological and catabolic states.

Key facts

Team

- Researchers : 13
- Technicians : 5
- Postdoc fellows : 2
- PhD Students : 6

Translational approaches

- Patents : 2
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- Italy, Nederland, Canada, UK, Australia, USA

Keywords

- eIF2a signaling
- metabolism
- Protein
- Amino Acids
- Nutrition
- Molecular Physiology
- Nutrients fluxes
- transgenic mice
- gene expression
- nutritional intervention

Biological Resources

- Human studies on healthy volunteers
- Animal models: transgenic mice, rat, bear(model of resistance to muscle atrophy)
- Cell lines
- Access to human cohorts and human biopsies

Research Brief :

Numerous diseases (cancer, sepsis,) and aging are frequently associated with a dysregulation of amino acid and protein homeostasis. The main consequence is a catabolic state that strongly contributes to the deterioration of patients health and compromises treatments. The main objectives of the team are to understand the mechanisms involved in maintaining protein/amino-acid homeostasis. The endpoint is to develop pharmacological and nutritional strategies to prevent and/or attenuate protein/amino acid homeostasis dysregulations.
Our work focuses on three complementary research themes studying different aspects of the regulation of the metabolism of amino acids and proteins during several physiological and pathological situations (perinatal nutrition, muscle wasting, food intake disorders, aging,):
-Characterization of the molecular mechanisms involved in adaptation to variations in amino acid availability.
-Regulation of tissue protein metabolism: protein synthesis and proteolysis (ubiquitin-proteasome system, autophagy).
-Regulation of inter-organ relationships for the use of amino acids.

- **Methodologies Used :**

Cellular and molecular biology
Gene knock-down and over-expression in vivo and in vitro (electroporation, viral vectors,)
Proteolysis and protein synthesis determination
Gene expression measurement (qPCR, polysome analysis)
Metabolomics / proteomics
In situ hybridization and immunohistochemistry
Recombinant protein production and purification
Biomolecular interaction studies (Surface Plasmon Resonance, Y3H and Y2H, etc.) Nutritional interventions in humans and in animal models
In vivo nutrients fluxes evaluation
Access to human cohorts

Publications

B'chir W, Maurin AC, Carraro V, Averous J, Jousse C, Muranishi Y, Parry L, Stepien G, Fafournoux P, Bruhat A (2013). The eIF2a/ATF4 pathway is essential for stress-induced autophagy gene expression, Nucleic Acids Res. 41(16), 7683

Maurin AC, Benani A, Lorsignol A, Brenachot X, Parry L, Carraro V, Guissard C, Averous J, Jousse C, Bruhat A, Chaveroux C, B'chir W, Muranishi Y, Ron D, Pénicaud L, Fafournoux P (2014). Hypothalamic eIF2a signaling regulates food intake, Cell Reports. 6(3), 438

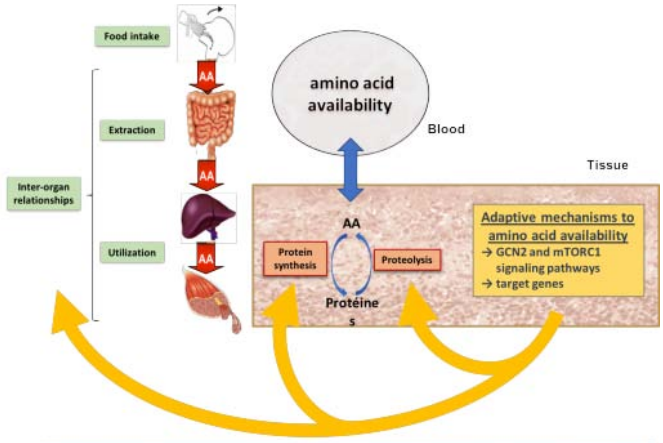
C. Chaveroux, V. Carraro, L. Canaple, J. Averous, A.-C. Maurin, C. Jousse, Y. Muranishi, L. Parry, F. Mesclon, E. Gatti, J. Mallet, P. Ravassard, P. Pierre, P. Fafournoux, and A. Bruhat (2015). In vivo imaging of the spatiotemporal activity of the eIF2a-ATF4 signaling pathway: Insights into stress and related disorders, Science Signaling. 8(374), rs5

Cédric Chaveroux, Alain Bruhat, Valérie Carraro, Céline Jousse, Julien Averous, Anne-Catherine Maurin, Laurent Parry, Florent Mesclon, Yuki Muranishi, Aline Meulle, Patrick Baril, Anh Do Thi, Philippe Ravassard, Jacques Mallet and Pierre Fafournoux (2016). Regulating the expression of therapeutic transgenes by controlled intake of dietary essential amino acids., Nature Biotechnology. 34(7), 746

Deval C, Capel F, Laillet B, Polge C, Béchet D, Taillandier D, Attaix D, Combaret L. (2016). Docosahexaenoic acid-supplementation prior to fasting prevents muscle atrophy in mice, J Cachexia Sarcopenia Muscle. 7(), 587

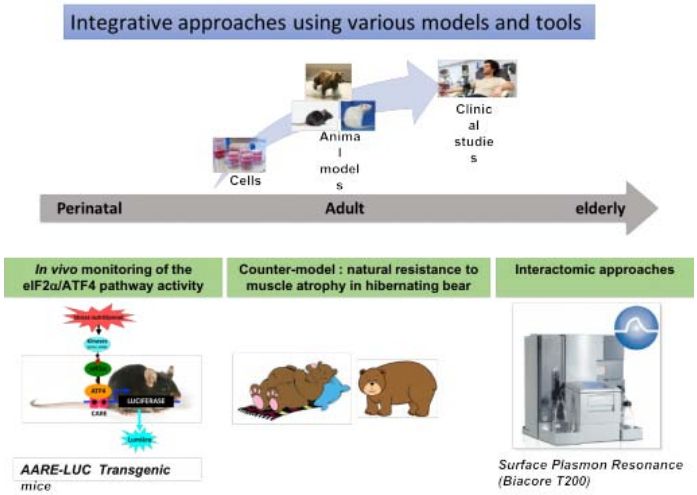
Aniort J, Stella A, Philipponnet C, Poyet A, Polge C, Claustre A, Combaret L, Béchet D, Attaix D, Boisgard S, Filaire M, Rosset E, Burlet-Schiltz O, Heng AE, Taillandier D. (2019). Muscle wasting in patients with end-stage renal disease or early-stage lung cancer: common mechanisms at work., J Cachexia Sarcopenia Muscle. (), 1

Protein/Amino Acid homeostasis

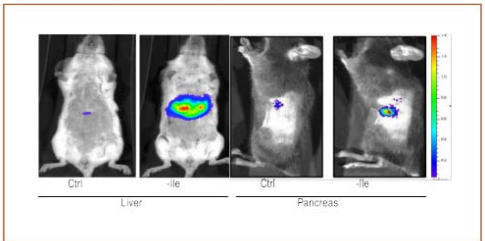


Our goal is to understand the mechanisms responsible for the maintenance of protein/amino acid homeostasis during physiological and catabolic states

Integrative approaches using various models and tools



Regulating the expression of therapeutic transgenes by controlled intake of dietary essential AA



Effective transgene regulation by the AARE*-driven expression system after gene transfer in several organs.
Mice were transduced in liver or pancreas with a vector expressing Luciferase driven by a promoter activated by amino acid starvation. Luciferase activity was measured (biolumiscence imaging) following consumption of a control (Ctrl) or a Ile deficient diet (-Ile). See Chaveroux et al 2016
*Amino Acid Response Element

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Naim Khan

Nutritional Physiology & Toxicology (NUTox)

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(Université de Bourgogne)
Inserm U1231 CHU UMR 1231
Ghiringhelli François
Dijon

Exploration of the molecular and cellular mechanisms responsible for the chemodetection of dietary lipids along the oro-intestinal tract: impacts of estrogenic food contaminants and physiological or pathological consequences on the lipid metabolism, eating behavior and obesity risk

Key facts

Team

• Researchers : 8
• Technicians : 8
• Postdoc fellows : 1
• PhD Students : 6

Translational approaches

• Patents : 2
• Clinical research grants : 2
• Industry partnerships : 4

Keywords

• Small intestine
• Taste buds
• Lipid signalling
• Energy metabolism
• Eating behavior
• Chylomicrons
• Lipid-binding proteins
• Estrogenic contaminants
• Lipid sensing
• Obesity
• Epigenetics
• Genetic polymorphism
• Integrative physiology
• Inflammation

Biological Resources

• Transgenic mice, receptology technical facility
• Caco2, immortalized mouse and
human taste bud cells

Research Brief :

The oro-intestinal tract plays a major role in the regulation of energy balance by controlling nutrient bioavailability and eating behavior. Recent data from our team and other investigations support the existence of a specific sensing system responsible for a real-time detection of lipids in ingested foods both in oral cavity and intestinal lumen. We have shown that the plasma membrane receptor CD36 plays a significant role in this detection as a lipid sensor involved in regulation of the spontaneous fat preference, digestive secretions and quality (size and number) of chylomicrons produced during the post-prandial period. Chemoreception of dietary lipids by the oro-intestinal tract appears to be complex since other lipid sensors candidates (e.g. GPR120) have recently been identified in these tissues. Interestingly, estrogenic contaminants of food contact materials might disturb this lipid sensing system by impairing the function of taste buds and small intestine. Our objective is to determine the respective role(s) of these lipid sensors and explore whether dysfunction in this oro-intestinal lipid sensing system leads to physio-pathological states increasing obesity risk and prevalence of associated plethora diseases. A better understanding of these mechanisms might leads to the development of novel therapies.

• **Methodologies Used :**

Metabolic and behavioral phenotyping (indirect calorimetry, Echo MRI, lickometers)
Micro-surgery in the mouse
In situ isolated intestinal loop (intestinal lipid absorption)
Postprandial triglyceridemia, CD36 methylation,
Organ and cell cultures, genetic polymorphism
Molecular and cellular biology
Cell signalling
Clinical studies in humans

Publications

Dramane G, Abdoul-Azize S, Hichami A, Vögtle T, Akpona S, Chouabe C, Sadou H, Nieswandt B, Besnard P, Khan NA. (2012). STIM1 regulates calcium signaling in taste bud cells and preference for fat in mice., The Journal of clinical investigation. 22(2267), 2282

Ozdener MH, Subramaniam S, Sundaresan S, Sery O, Hashimoto T, Asakawa Y, Besnard P, Abumrad NA, Khan NA. (2014). CD36- and GPR120-mediated Ca2+ Signaling in Human Taste Bud Cells Mediates Differential Responses to Fatty Acids and is Altered in Obese Mice., Gastroenterology. 146(995), 1005

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Besnard P, Passilly-Degrace P, Khan NA. (2016). Taste of Fat: A Sixth Taste Modality?, Physiol Rev.. 96(151), 176

Buttet M, Poirier H, Traynard V, Gaire K, Tran TT, Sundaresan S, Besnard P, Abumrad NA, Niot I. (2016). Deregulated Lipid Sensing by Intestinal CD36 in Diet-Induced Hyperinsulinemic Obese Mouse Model., PLoS One. 11(e014), 5626

Karmous I, Plesník J, Khan AS, ?erý O, Abid A, Mankai A, Aouidet A, Khan NA. (2018). Orosensory detection of bitter in fat-taster healthy and obese participants: Genetic polymorphism of CD36 and TAS2R38, Clin Nutr. 37(313), 320

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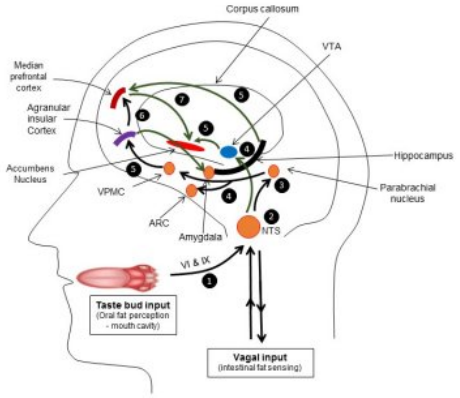
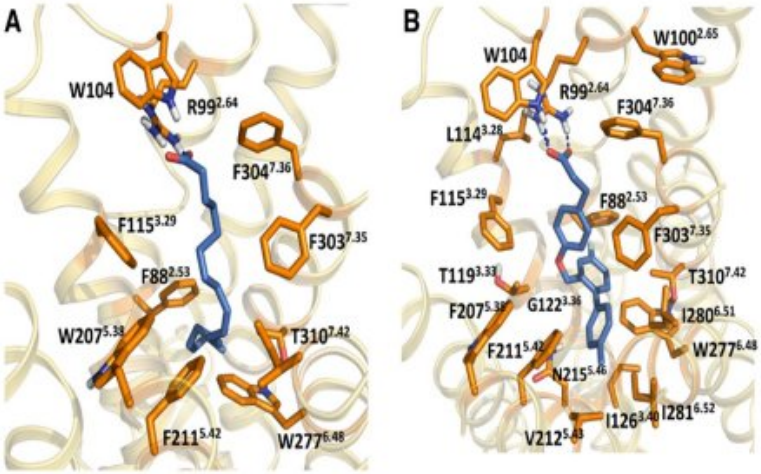
Brain gustatory and reward circuit



Activation of different brain areas by dietary lipids. The lipid lingual gustatory message is transmitted to brain by chorda tympani (VII) and glossopharyngeal (IX) nerves via NTS, the relay of peripheral and central regulatory pathways connecting the physiologic regulation of food behavior with gastro-intestinal tract (GIT). The results shown here are derived from the experiments conducted on mic, but for the simplification, we have tried to transpose them on human brain circuits.

A non-caloric GPR120 agonist binds to lipid taste sensor



Docking studies show orthosteric binding (in blue color) of linoleic acid, LA (A) and TUG891 (B) to GPR120.

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Key facts

Team

- Researchers : 9
- Technicians : 3
- Postdoc fellows : 2
- PhD Students : 2

Translational approaches

- Patents : 1
- Clinical research grants : 3
- Industry partnerships : 3

International research links

- USA
- Norway

Keywords

- Apolipoprotein
- Lipids
- Diabetes
- Obesity
- endocannabinoid
- HDL
- Liver fat
- Kinetic study
- Stable isotopes
- Lipidomic
- cell culture
- animal studies

Biological Resources

- plasma samples from patients
- mice and rats obesitymodels
- cell cultures
- liver tissue explants
- fat tissue explants

Bruno Vergès

Pathophysiology of dyslipidemia (PADYS)

Université de Dijon
(Université de Bourgogne)
Inserm U1231 CHU UMR-1231
François Ghiringhelli
Dijon

The work of our team is dedicated to the study of the pathophysiology of dyslipidemia in humans, mostly dyslipidemia associated with diabetes and insulin-resistance.

Research Brief :

For more than 10 years, our team has been working on the pathophysiology of dyslipidemia in humans, mostly dyslipidemia associated with diabetes and insulin-resistance. Our team includes scientists and also physicians who are working on both sides (clinic and research). This allows performing many translational studies "from bed to bench". Our main research activities within the field of "pathophysiology of dyslipidemia in humans" are built in 3 axes: 1) dysfunction of lipid metabolism in diabetes and insulin resistance (including in vivo human lipoprotein kinetic studies); 2) study of HDL in diabetes and insulin resistance; 3) involvement of the endocannabinoid system in diabetes and insulin resistance.
During the 4 previous years we have shown:
?a close relationship between HDL-apoA-II catabolism and VLDL1 catabolism in the Metabolic Syndrome (MS).
?reduction of ApoB48 production and increase in ApoB48 catabolism with the GLP-1 agonist
?a direct inhibitory effect of liraglutide on chylomicron production.
?significant modification of the sphingophospholipidome of HDL from non-diabetic obese patients: depletion in sphingosine-1-phosphate (S1P), sphingomyelins and some plasmalogens.
?that S1P depletion of HDL is responsible for decreased activation of endothelium NO synthase by HDL, in individuals with the MS.
?that peripheral Endocannabinoïd system impairs the inhibitory function of insulin on the hormone sensitive lipase in the adipose tissue, in the fed state.

• Methodologies Used :

In vivo kinetic studies in humans with stable isotopes
HDL function studies
Animal studies
Cell culture
Hepatic tissue explants
Lipidomic studies

Publications

Vergès, Bruno; Duvillard, Laurence; Pais de Barros, Jean Paul; Bouillet, Benjamin; Baillot-Rudoni, Sabine; Rouland, Alexia; Sberna, Anne-Laure; Petit, Jean-Michel; Degrace, Pascal; Demizieux, Laurent (2018). Liraglutide Reduces Postprandial Hyperlipidemia by Increasing ApoB48 (Apolipoprotein B48) Catabolism and by Reducing ApoB48 Production in Patients With Type 2 Diabetes Mellitus, Arteriosclerosis, Thrombosis, and Vascular Biology. 38(9), 2198-2206

Roger, Célia; Buch, Chloé; Muller, Tania; Leemput, Julia; Demizieux, Laurent; Passilly-Degrace, Patricia; Cinar, Resat; Iyer, Malliga R.; Kunos, George; Vergès, Bruno; Degrace, Pascal; Jourdan, Tony (2020). Simultaneous Inhibition of Peripheral CB1R and iNOS Mitigates Obesity-Related Dyslipidemia Through Distinct Mechanisms, Diabetes. 69(10), 2120-2132

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Buch, Chloé; Muller, Tania; Leemput, Julia; Passilly-Degrace, Patricia; Ortega-Deballon, Pablo; Pais de Barros, Jean-Paul; Vergès, Bruno; Jourdan, Tony; Demizieux, Laurent; Degrace, Pascal (2021). Endocannabinoids Produced by White Adipose Tissue Modulate Lipolysis in Lean but Not in Obese Rodent and Human, Frontiers in Endocrinology. 12(), 716431

Vergès, Bruno; Duvillard, Laurence; Pais de Barros, Jean Paul; Bouillet, Benjamin; Baillot-Rudoni, Sabine; Rouland, Alexia; Petit, Jean Michel; Degrace, Pascal; Demizieux, Laurent (2021). Liraglutide Increases the Catabolism of Apolipoprotein B100-Containing Lipoproteins in Patients With Type 2 Diabetes and Reduces Proprotein Convertase Subtilisin/Kexin Type 9 Expression, Diabetes Care. 44(4), 1027-1037

Cinar, Resat; Park, Joshua K.; Zawatsky, Charles N.; Coffey, Nathan J.; Bodine, Steven P.; Abdalla, Jasmina; Yokoyama, Tadafumi; Jourdan, Tony; Jay, Lindsey; Zuo, Mei Xing G.; O'Brien, Kevin J.; Huang, Junfeng; Mackie, Ken; Alimardanov, Asaf; Iyer, Malliga R.; Gahl, William A.; Kunos, George; Gochuico, Bernadette R.; Malicdan, May Christine V. (2021). CB1 R and iNOS are distinct players promoting pulmonary fibrosis in Hermansky-Pudlak syndrome, Clinical and Translational Medicine. 11(7), e471

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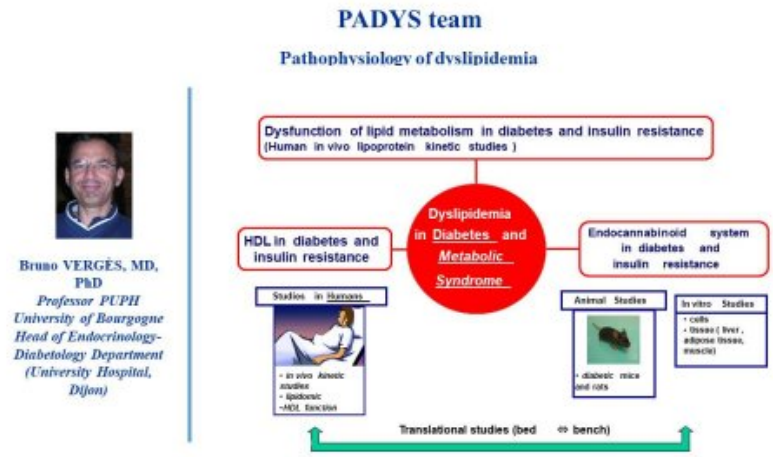
Presentation of the PADYS Team (Inserm-u1231, Dijon)



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Key facts

Team

• Researchers : 6
• Technicians : 2
• Postdoc fellows : 0
• PhD Students : 2

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 0

International research links

• RIVM, Bilthoven (Netherlands), National Research Institute of the Working Environment (Denmark)
• Ecole vétérinaire de Liège (Belgium)
• ETH and EMPA (Switzerland)

Keywords

• DOHaD
• placenta
• nutrition, metabolism, pollutantss
• long-term effects
• maternal environment
• animal model
• culture
• physiological approach

Biological Resources

• Biomedical models (rabbit, mouse, sheep)
• Cultures of trophoblastic stem cells and cell lines
• Models for the livestock (equine and ovine)

Anne Couturier-Tarrade

PEPPS (Placenta, Environment and Phenotype Programming)

Université Paris-Saclay
INRAE UMR1198
Pascale Chavatte-Palmer
Jouy-en-Josas

The team studies the role of the placenta on the establishment of fetal, post-natal and intergenerational phenotypes in relation to peri-conceptional and/or gestational disturbances of the maternal environment (nutrition, metabolic status, pollution, nanoparticles, food contaminants).

Research Brief :

Intrauterine life imposes specific constraints on the conceptus that affect the expression of its genetic potential. As a result, the maternal environment will influence the health of the offspring up to adulthood. These observations has led to the DOHaD concept, based on the existence of a memory of the factors presents in early environment, which molecular basis is the apposition of epigenetic marks that will regulate genome expression. The regulation of gene expression leads to structural and functional changes in tissues during development that, in adults, will be at the origin of individual variability of the phenotype and adaptation to new environmental stimuli. They are also capable of inducing predisposition to non-communicable diseases. The placenta is formed after the attachment of the embryo to the uterine mucosa and derives from complex cellular and molecular interactions between uterine and embryonic tissues. This organ is involved in nutritional, endocrine and immunological exchange functions. The team studies the role of the placenta on the establishment of fetal, post-natal and intergenerational phenotypes in relation to periconception and/or gestation disturbances of the maternal environment. The objective is to characterize the window(s) of vulnerability and to understand the adaptive phenomena, in order to propose recommendations for the mother and to determine whether placental biomarkers can be used to identify and predict the long-term phenotype.

• **Methodologies Used :**

- Physiology : Placental function, Glucose metabolism (IVGTT, OGTT, FSIVGTT, euglycemic hyperinsulinemic clamps), cardiovascular function (blood pressure, heart rate)
- Animal handling : gavage, inhalation exposure, reproduction, collection and dissection of embryos, organs and fluids
- In vivo imaging : ultrasound-Doppler 2D and 3D GE, Visualsonics micro-ultrasound, Cellvizio, osteodensitometry, iDEXA GE (https://www6.jouy.inrae.fr/mima2)
- Histology: classical histology, stereology, immunodetection
- Ultrastructure : MET, MEB
- Gene Expression : RT-qPCR, transcriptome analysis (en collaboration)
- Lipidology : fatty acid profiling by gas chromatography
- Biochemistry: endocrinology by Alphalisa and Elisa, clinical biochemistry

Publications

Valentino SA, Tarrade A, Aioun J, Mourier E, Richard C, Dahirel,M, Rousseau-Ralliard D, Fournier N, Aubrière MC, Lallemand MS, Camous S, Guinot M, Charlier M, Aujean E, Al Adhami H, Fokkens PH, Agier L, Boere JA, Cassee FR, Slama R, Chavatte-Palmer P. (2016). Maternal exposure to diluted diesel engine exhaust alters placental function and induces intergenerational effects in rabbits., Part Fibre Toxicol. 13(1), 39

Peugnet P, Robles M, Mendoza L, Wimel L, Dubois C, Dahirel M, Guillaume D, Camous S, Berthelot V, Toquet MP, Richard E, Sandersen C, Chaffaux S, Lejeune JP, Tarrade A, Serteyn D, Chavatte-Palmer P. (2016). Correction: Effects of Moderate Amounts of Barley in Late Pregnancy on Growth, Glucose Metabolism and Osteoarticular Status of Pre-Weaning Horses., PloS One. 11(12), e0167604

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Rousseau-Ralliard D., Couturier-Tarrade A., Thieme R., Brat R., Rolland A., Boileau P., Aubrière M.-C., Daniel N., Dahirel M., Derisoud E., Fournier N., Schindler M., Duranthon V., Fischer B., Santos A. N., and Chavatte-Palmer P. (2018). A short periconceptional exposure to maternal type-1 diabetes is sufficient to disrupt the feto-placental phenotype in a rabbit model., Molecular and Cellular Endocrinology. 480(), 42-53

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Rousseau-Ralliard, D., Valentino, S.A., Aubriere, M-C., Dahirel, M., Lallemand, M-S., Archilla, C., Jouneau, L., Fournier, N., Richard, C., Aioun, J., Vitorino Carbalho, A., Lecardonnel, J., Slama, R., Duranthon, V., Cassee, F.R., Chavatte-Palmer, P., Couturier-Tarrade, A. (2019). Effects of first-generation in utero exposure to diesel engine exhaust on second-generation placental function, fatty acid profiles and f?tal metabolism in rabbits: preliminary results., Sci Rep. 9(1), 9710

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Alexandre Benani

Plasticity of brain feeding circuits

Université de Dijon
(Université de Bourgogne) AgroSup Dijon
CNRS INRA
Loïc Briand
Dijon

Coupling state-of-the-art molecular analysis, histology and gene manipulation to investigate the neurobiological bases of feeding behaviour.

Key facts

Team

- Researchers : 3
- Technicians : 2
- Postdoc fellows : 0
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- Hypothalamus
- Obesity
- Food intake
- Neurobiology
- Vulnerability
- Feeding behaviour
- Molecular biology
- Histology
- Stereotaxy
- Tolerance tests

Biological Resources

- AgRP-cre mice
- POMC-cre mice
- RiboTag mice
- St8sia4 KO mice

Research Brief :

The team aims at a better understanding of the neurobiological basis of feeding behaviour.
First, we want to provide details about the structure of neuronal circuits that control food intake.
Second, we want to characterize the morphological plasticity of these networks (i.e. synaptic remodeling, modification of neuro-glial interactions, neurogenesis). We have shown that the structural plasticity of these networks is an essential element in the adaptive control of food intake. Indeed, reduced ability to structural plasticity in these networks could be a risk factor in obesity and related disorders.
Third, we want to characterize the influence of various internal and external factors on the feeding behaviour, such as the metabolic state (effect of overeating), the nutritional history (perinatal imprinting, food experience in adulthood), and pathological context (metabolic diseases, major depression, cachexia).

- **Methodologies Used :**

Use of standard and transgenic murine models.
Behavioral analysis (food intake, size and frequency of meals, satiety, preferences) and functional investigation (metabolic performance).
Molecular biology (gene regulation, chromatin remodeling, epigenetic).
Histology (neuroanatomy, neuronal tracing, cFos detection, immunohistochemistry).
Targeted intracranial manipulations (stereotactic injections of drugs and viral tools, shRNA-mediated silencing, pharmacogenetic).

Publications

Matarazzo V, Schaller F, Nédélec E, Benani A, Pénicaud L, Muscatelli F, Moyse E, Bauer S (2012). Inactivation of Socs3 in the hypothalamus enhances the hindbrain response to endogenous satiety signals via oxytocin signaling., The Journal of neuroscience : the official journal of the Society for Neuroscience. 32(48), 17097-107

Benani A, Hryhorczuk C, Gouazé A, Fioramonti X, Brenachot X, Guissard C, Krezymon A, Duparc T, Colom A, Nédélec E, Rigault C, Lemoine A, Gascuel J, Gerardy-Schahn R, Valet P, Knauf C, Lorsignol A, Pénicaud L (2012). Food intake adaptation to dietary fat involves PSA-dependent rewiring of the arcuate melanocortin system in mice., The Journal of neuroscience : the official journal of the Society for Neuroscience. 32(35), 11970-9

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Maurin AC, Benani A, Lorsignol A, Brenachot X, Parry L, Carraro V, Guissard C, Averous J, Jousse C, Bruhat A, Chaveroux C, B'chir W, Muranishi Y, Ron D, Pénicaud L, Fafournoux P (2014). Hypothalamic eIF2a signaling regulates food intake., Cell reports. 6(3), 438-44

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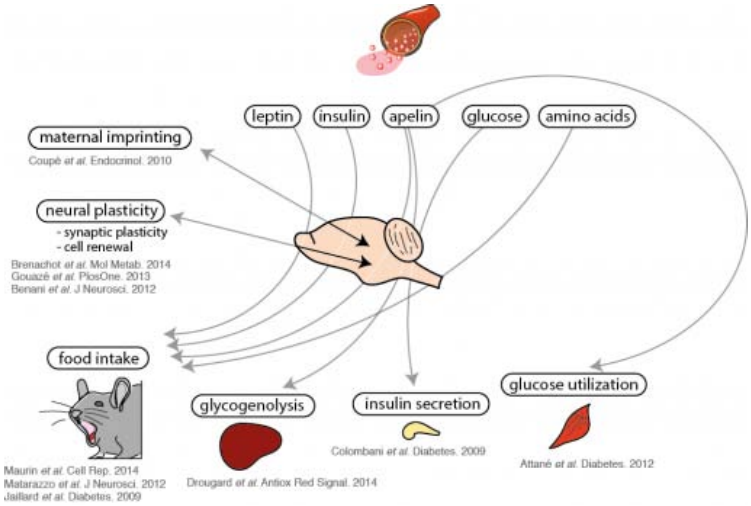
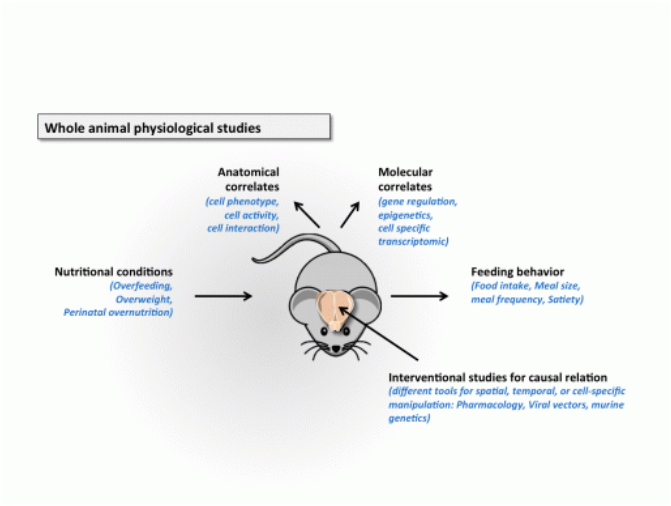
Benani Alexandre - alexandre.benani@u-bourgogne.f r - https://www2.dijon.inra.fr/csga/site_fr/equipe_15.php

New insight into the mode of action of some metabolic cues



Models and skills



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Key facts

Team

• Researchers : 21
• Technicians : 5
• Postdoc fellows : 2
• PhD Students : 6

Translational approaches

• Patents : 2
• Clinical research grants : 6
• Industry partnerships : 6

International research links

• Canada
• Netherlands
• USA

Keywords

• Lipid
• Intestinal absorption
• Hypertriglyceridemia
• Lipoprotein
• Nutrition
• Clinical trial
• Lipidomics
• Cell culture
• Animal model
• Endotoxemia

Biological Resources

• rodent models
• in vitro models: Caco-2 cells, endothelial cells...

Marie-Caroline Michalski
Philippe Moulin

Postprandial Lipids and Lipoproteins: Regulations and Functional Impacts

Université Claude Bernard Lyon
1 INSA-Lyon
Inserm U1060 INRA UMR1397
Hubert VIDAL
VILLEURBANNE

To facilitate and accelerate translational research by combining genetics, lipidomics and both in vitro and clinical experiments in order to explore lipid metabolism in patients and in healthy controls. To consider the molecular and supramolecular structures of dietary lipids in their effects.

Research Brief :

The main scientific objectives are to understand the mechanisms and the consequences of hypertriglyceridemia by studying both primary and secondary hypertriglyceridemia as well as postprandial hyperlipidemia. The team will focus on:1) How dietary lipids, through their structure and oxidation, can metabolically impact on intestinal absorption, TGRL composition and lipolysis, and the metabolic fate of lipids in the postprandial phase. The role of specific lipids present in the gut on LPS coabsorption and biology of the gut cell lienage will be considered. 2) How TGRL modified by nutrition and/or altered by abdominal obesity/diabetes or malabsorption play a role in atherothrombotic and inflammatory processes both in the fasting and postprandial phase. The role of oxygenated species derived from DHA on ischemic cardiovascular disease will be studied.3) How new genetic and epigenetic regulations interfere with TGRL lipolysis. Interactions between LPL/AV/GPIHBP1 on endothelial cells will be studied. Association studies in extreme phenotypes and segregation studies in families with unexplained familial chylomicronemia syndrome will be conducted to identify new genes involved in TG metabolism. Studies considering the role of miRNA in the regulation of lipolysis gene expression will be expended.This project will provide new dietary strategies to prevent the alterations of postprandial lipemia and identify new therapeutic targets for improving treatment of hypertriglyceridemia.

• **Methodologies Used :**

- Nutritional interventions in humans and in animal models (mice and rats).
- Cell cultures Cell biology (transwell inserts).
- Next generation sequencing (386 gene chips) applied in the field of dyslipoproteinemia
- Lipoprotein isolations and platelet aggregation.
- Endotoxemia analysis.
- Lipidomic platform analyses (HPLC, GC, GC-MS/MS, LC-MS/MS).

Publications

Colas R, Sassolas A, Guichardant M, Cugnet-Anceau C, Moret M, Moulin P, Lagarde M, Calzada C. (2011). LDL from obese patients with the metabolic syndrome show increased lipid peroxidation and activate platelets., Diabetologia. 54(11), 2931

Vors C, Pineau G, Gabert L, Drai J, Louche-Pélissier C, Defoort C, Lairon D, Désage M, Danthine S, Lambert-Porcheron S, Vidal H, Laville M, Michalski MC. (2013). Modulating absorption and postprandial handling of dietary fatty acids by structuring fat in the meal: a randomized crossover clinical trial., Am J Clin Nutr. 97(1), 23

Caussy C, Charrière S, Marçais C, Di Filippo M, Sassolas A, Delay M, Euthine V, Jalabert A, Lefai E, Rome S, Moulin P. (2014). An APOA5 3' UTR variant associated with plasma triglycerides triggers APOA5 downregulation by creating a functional miR-485-5p binding site., Am J Hum Genet.. 94(1), 129

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Lê QH, El Alaoui M, Véricel E, Ségrestin B, Soulère L, Guichardant M, Lagarde M, Moulin P, Calzada C. (2015). Glycoxidized HDL, HDL enriched with oxidized phospholipids and HDL from diabetic patients inhibit platelet function., J Clin Endocr Metab. 100(5), 2006

Véricel E, Colas R, Calzada C, Lê QH, Feugier N, Cugnet C, Vidal H, Laville M, Moulin P, Lagarde M. (2015). Moderate oral supplementation with docosahexaenoic acid improves platelet function and oxidative stress in type 2 diabetic patients., Thromb Haemost.. 114(2), 289

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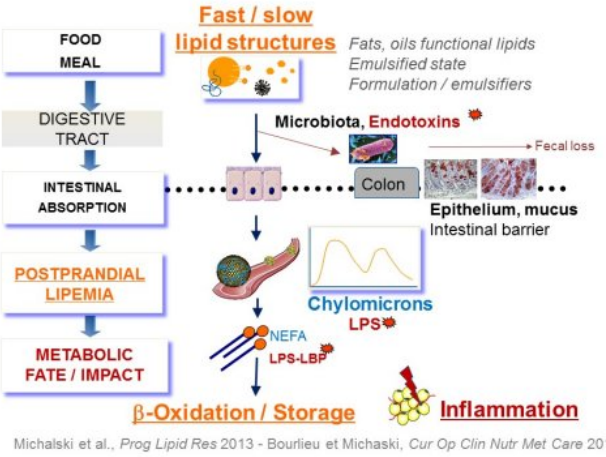
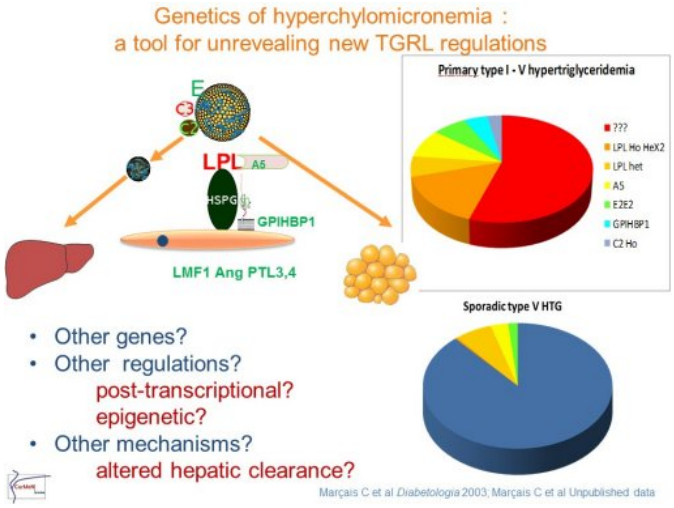
Impact of dietary lipid structures on postprandial lipemia and metabolism



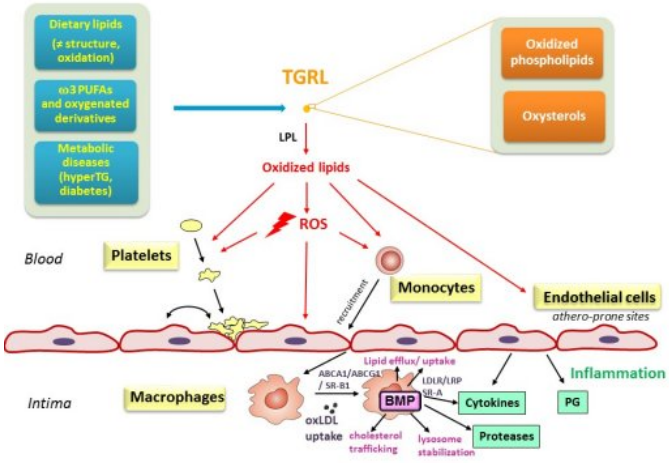
Michalski et al., *Prog Lipid Res* 2013 - Bourlieu et Michaski, *Cur Op Clin Nutr Met Care* 2015

Genetics of hyperchylomicronemia : a tool for unraveling new TG-rich lipoprotein regulations



Marçais C et al *Diabetologia* 2003; Marçais C et al Unpublished data

Functional impact of TGRL as vector of oxidized lipids on circulating cells and endothelium



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Key facts

Team

- Researchers : 7
- Technicians : 3
- Postdoc fellows : 1
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 3
- Industry partnerships : 7

International research links

- Wageningen University
- St John Insititute, Bangalore, India
- Helsinki University

Keywords

- Animal protein
- Plant protein
- Amino acid requirement
- Energy metabolism
- Protein digestion and metabolism
- Humans
- Rodents
- Indirect calorimetry
- Stable isotopes
- Molecular biology

Biological Resources

- Human volunteers
- Primary cell culture
- Rodent models

Dalila Azzout-Marniche

Protein Intake and Metabolic Regulation

Paris-Saclay AgroParisTech
INRAE UMR0914
Gaudichon Claire
Palaiseau

Our team addresses the influence of quality and quantity of protein intake on digestive, metabolic and physiologicalresponses, using a large panel of approaches (metabolic fluxes by the way of tracers and calorimetry, molecular biology, indirect calorimetry, metabolomic) in rodents and humans.

Research Brief :

Protein intake plays an important role in protein and energy homeostasis. Quantity and quality of protein influence the regulation of protein pathways in different tissues (intestine, liver, muscle, kidney, brain, ..) and also interact with glucose and lipid homeostasis, subsequently affecting lean and adipose tissue distribution. Dietary proteins are also involved in different signals interfering with dietary intake, either directly through homeostatic centers or indirectly through food reward. Our team studies the different pathways by which protein intake interacts with caloric intake and with protein and energy metabolism to achieve homeostasis.
In the past years, we provided important integrative knowledge on the adaptive responses to high protein diets that had been proposed as strategies in weigh management. We currently address the consequences of low protein intake on energy homeostasis, given that protein resources are worldwide a main concern for food insecurity.
Moreover, our team is recognized for its strong expertise in the in vivo assessment of protein quality depending on the protein source as well as technological treatments.
Clinical studies are mostly realized in the Research Human Nutrition Center, in Bobigny. Rodent studies are realized in our own animal care facility.

- **Methodologies Used :**

*In vivo exploration of protein digestion and metabolism as well as energy metabolism, using isotopic tracers, gastrointestinal tubes and indirect calorimetry
* Exploration of signaling pathways, especially in intestine, liver and brain, using classical molecular approaches and genetic models
* Phenotyping of ingestive behavior and metabolism using multiscale criteria in rodents
* Development of obesity resistant and prone rodent models

Publications

Tessier R, Calvez J, Airinei G, Khodorova N, Kapel R, Quinsac A, Galet O, Piedcoq J, Benamouzig R, Tomé D, Gaudichon C.entin G, Airinei G, Pedersen C, Léonil J, Piedcoq J, Rémond D, Benamouzig R, Tomé D, Gaudichon C. (2014). The true amino acid digestibility of 15N-labelled sunflower biscuits determined with ileal balance and dual isotope methods in healthy humans., J Nutr. doi(),

Guillin FM, Gaudichon C, Guérin-Deremaux L, Lefranc-Millot C, Airinei G, Khodorova N, Benamouzig R, Pomport PH, Martin J, Calvez J. (2015). Real ileal amino acid digestibility of pea protein compared to casein in healthy humans, a randomized trial., Am J Clin Nutr. doi: 10.1093/ajcn/nqab354(),

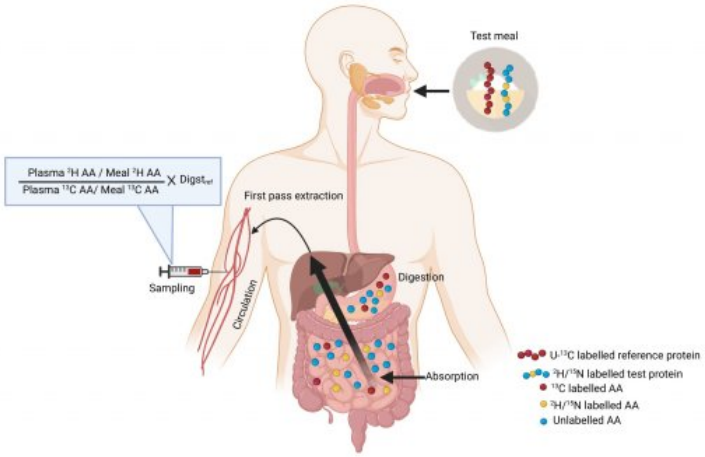
Tessier R, Ribeiro-Parenti L, Bruneau O, Khodorova N, Cavin JB, Bado A, Azzout-Marniche D, Calvez J, Le Gall M, Gaudichon C. (2016). Effect of different bariatric surgeries on dietary protein bioavailability in rats., Am J Physiol Gastrointest Liver Physiol. 317(5), G592

Moro J, Chaumontet C, Even PC, Blais A, Piedcoq J, Gaudichon C, Tomé D, Azzout-Marniche D.D, Chalvon-Demersay T, Pimentel G, Chaumontet C, Nadkarni NA, Piedcoq J, Fromentin G, Tome D, Gaudichon C, and Even PC (2021). Severe protein deficiency induces hepatic expression and systemic level of FGF21 but inhibits its hypothalamic expression in growing rats., Sci Rep. 11(1), 12436

Bandyopadhyay S, Kashyap S, Calvez J, Devi S, Azzout-Marniche D, Tomé D, Kurpad AV, Gaudichon C. (2021). Evaluation of Protein Quality in Humans and Insights on Stable Isotope Approaches to Measure Digestibility - A Review., Adv Nutr. doi: 10.1093/advances/nmab134.(),

Gehring J, Azzout-Marniche D, Chaumontet C, Gaudichon C, Even PC. (2021). Plasma FGF21 concentrations and spontaneous self-selection of protein suggest that 15% protein in the diet may not be enough for male adult rats., Am J Physiol Endocrinol Metab.. doi: 10.1152/ajpendo.00204.2021.(),

Une méthode peu invasive pour déterminer la biodisponibilité des acides aminés alimentaires



Principe de la méthode double traceur: La protéine test (bleu) est marquée au 2H (ou à défaut au 15N). La protéine de référence (rouge) est de digestibilité connue et marquée au 13C. Pour chaque acide aminé, le ratio 2H/13C est mesuré dans le repas et le sang, ce qui donne un indice d'absorption de la protéine test par rapport à la protéine de référence. La digestibilité des acides aminés de la protéine de référence permet au final de calculer ceux de la protéine test.

Azzout-Marniche Dalila - dalila.azzout-marniche@agropar istech.fr - 33 1 44 08 72 44 - http://www6.jouy.inra.fr/pnca/Presentation-de-l-Unite

Key facts

Team

- Researchers : 4
- Technicians : 0
- Postdoc fellows : 0
- PhD Students : 6

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 1

International research links

- USA
- Germany

Keywords

- protein
- nutritional transition
- Nutritional security
- Cardiometabolic risk
- diet quality
- Algorithm-based simulations
- Diet modelling
- Metabolic and functional explorations
- Multicriteria approaches

Francois Mariotti

Protein intake, nutritional security, and cardiometabolic risk.

AgroParisTech Université Paris Saclay
INRAE UMR0914
Claire Gaudichon
Paris

We are combining models of dietary changes (algorithm/scenario-based simulation and optimization models) and an in depth assessment of the impact of the diets on nutritional adequacy/security and morbimortality. We are now widening the scope to sustainabiliy. We are specialist of dietary protein.

Research Brief :

We are studying the relationships between food consumption of animal and plant proteins, nutritional security and prevention of cardiometabolic risk. Our studies are thus set in the general context of the transition from dietary protein sources to less animal protein and more vegetable protein in Western (energy-rich) diets.
The effects of a differential intake of plant and animal proteins are addressed at several levels to address several complementary issues. We are thus implementing two types of studies: (1) metabolic studies, with nutritional interventions in animals and humans to study the impact of protein transitions on cardiometabolic risk, and (2) consumption analysis studies at the individual and population level, with observational and simulation/optimization studies to guide nutritional recommendations.

- **Methodologies Used :**

Metabolism/Physiology: tracer-based method for amino acid metabolism; physiological/biomarker assessment of cardiometabolic health; clinical trials

In silico epidemiological approach: modelling nutrient absorption and requirements; diet changes models (simulation, optimization); diet quality assessment; nutritional adequacy assessment; comparative risk assessment.

Publications

Dussiot A, Fouillet H, Perraud E, Salomé M, Huneau JF, Kesse-Guyot E, Mariotti F. (2022). Nutritional issues and dietary levers during gradual meat reduction - a sequential diet optimization study to achieve progressively healthier diets., Clin Nutr. 41(12), 2597-2606

Salomé M, Mariotti F, Nicaud MC, Dussiot A, Kesse-Guyot E, Maillard MN, Huneau JF, Fouillet H. (2022). The potential effects of meat substitution on diet quality could be high if meat substitutes are optimized for nutritional composition - a modeling study in French adults (INCA3)., Eur J Nutr. 61(4), 1991-2002

Lépine G, Huneau JF, Rémond D, Mahé V, David J, Hermier D, Guérn-Deremaux L, Lefranc-Millot C, Poupin N, Mariotti F, Polakof S, Fouillet H. (2022). Compared to milk protein, a wheat and pea protein blend reduces high-fat high sucrose induced metabolic dysregulations while similarly supporting tissue protein anabolism in rats., J Nutr in press. (),

Perraud E, Wang J, Salomé M, Huneau JF, Lapidus N, Mariotti F (2022). Plant and animal protein intakes largely explain the nutritional quality and health value of diets higher in plants - a path analysis in French adults., Front Nutr. (), 28 June 2022

Dussiot A, Fouillet H, Wang J, Salomé M, Huneau JF, Kesse-Guyot E, Mariotti F. (2022). odeled healthy eating patterns are largely constrained by currently estimated requirements for bioavailable iron and zinc - a diet optimization study in French Adults., Am J Clin Nutr. 115(3), 958-969

Key facts

Team

• Researchers : 5
• Technicians : 1
• Postdoc fellows : 1
• PhD Students : 1

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 1

International research links

• Denmark
• United States
• Singapore

Keywords

• Ion transporter
• Intracellular pH
• Reactive O and N species
• Intracellular compartments
• Ischemia-Reperfusion
• Kinetics
• Nanodosages
• Fluorescence
• Functional exploration

Biological Resources

• in vivo/in vitro models
• biobanks from patients

Laurent Counillon

Transport and metabolism

Université Côte d'Azur
CNRS UMR7370
Laurent COUNILLON
Nice

> ***Interdisciplinary topic that connects key physicochemical parameters with molecular mechanisms, physiology and pathology***

Research Brief :

Our team is focused on ion transport, from the molecular mechanisms to the physiological and pathological implications, with a particular focus the relations between transport and metabolism and with oxidative stress and its consequences in physiology and pathology.
We are interested in particular in the chemical modifications due to oxygen and nitrogen reactive species and their impact on the regulation of transporters. A special attention is given to Na+/H+ exchangers of the SLC9 family that are essential to control cellular pH, volume, proliferation, organism salt balance. While their activity is involved in ischemia-reperfusion injury and cancer cell survival, the loss of functions of endosomal Na+/H+ exchangers is linked to neurodevelopmental and neurodegenerative disorders.
In another part of our activity, we develop strategies to fight oxidative stress by decreasing its onset through the identification of new pharmacological targets. This includes for example the newly identified eIF5A pathway, that is able to enhance the ischemic tolerance in brain or kidney.

• **Methodologies Used :**

- Protein biochemistry
- Kinetics
- Ions and metabolites nanomeasurements
- Fluorescence
- Mathematical Modelling
- In vivo models
- Functional exploration
- Preclinical studies

Publications

Milosavljevic N, Monet M, Léna I, Brau F, Lacas-Gervais S, Feliciangeli S, Counillon L, Poët M (2014). The intracellular Na(+)/H(+) exchanger NHE7 effects a Na(+)-coupled, but not K(+)-coupled proton-loading mechanism in endocytosis, Cell Reports. 7(1-8), 689-696

Stine F Pedersen and Laurent Counillon (2019). The SLC9A-C Mammalian Na+/H+ Exchanger Family: Molecules, Mechanisms, and Physiology, Physiological Reviews. 99(4), 2015-2113

Cougnon M, Carcy R, Melis N, Rubera I, Durantopn C, Dumas K, Tanti JF, Pons C, Soubeiran N, Shkreli M, Hauet T, Pellerin L, Giraud S, Blondeau N, Tauc M, Pisani DF (2020). Inhibition of eIF5A hypusination reprograms metabolism and glucose handling in mouse kidney, Cell Death Dis. 12(4), 283

Giraud S, Kerforne T, Zely J, Ameteau V, Couturier P, Tauc M, Hauet T (2020). The inhibition of eIF5A hypusination by GC7, a preconditioning protocol to prevent brain death-induced renal injuries in a preclinical porcine kidney transplantation model, Am J Transplant. 20(12), 3326-3340

Bourourou M, Gouix E, Melis N, Friard J, Heurteaux C, Tauc M, Blondeau (2020). Inhibition of eIF5A hypusination pathway as a new pharmacological target for stroke therapy, J Cereb Blood Flow Metab. DOI: 10.1177/0271678X20928882(),

Michala G. Rolver, Line O. Elingaard-Larsen, Anne P. Andersen, Laurent Counillon & Stine F. Pedersen (2020). Pyrazine ring-based Na+/H+ exchanger (NHE) inhibitors potently inhibit cancer cell growth in 3D culture, independent of NHE1, Scientific Reports. 10(), 5800

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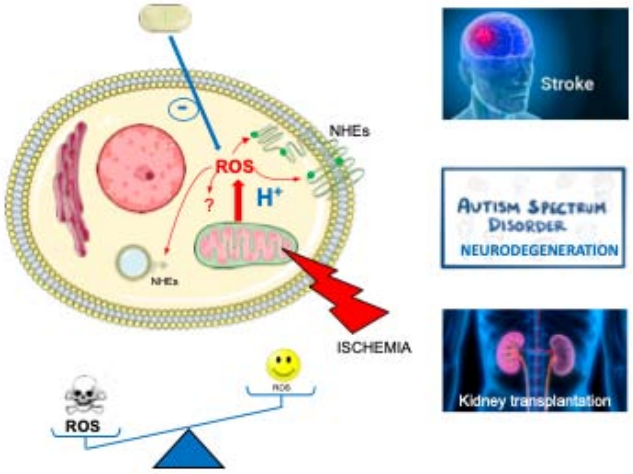
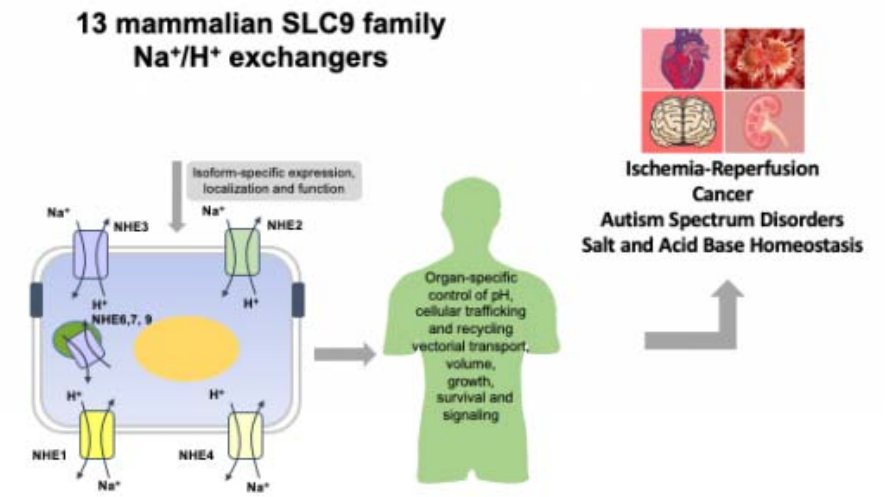
ROS and Transport



Relation between ROS production and Na+/H+ exchange in ischemia-reperfusion

The SLS9A Family of Na/H Exchangers



The mammalian SLC9 Family of Na+/H+ exchangers contains 13 members expressed in all cells and tissues and contributing differently to physiological and pathological situations.

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Hervé Blottière

UMR 1280 PhAN "Physiopathologie des Adaptations Nutritionnelles"

Nantes Université
INRAE UMR 1280
Hervé Blottière
Nantes

PhAN is a unique structure that performs translational and clinical research on the role played by nutrition in the first 1000 days of life in human, thanks to the collaborative work between obstetricians and pediatricians of CHU de Nantes, professors at Nantes University, and researchers at INRAE.

Key facts

Team

- Researchers : 24
- Technicians : 9
- Postdoc fellows : 1
- PhD Students : 5

Translational approaches

- Patents : 0
- Clinical research grants : 5
- Industry partnerships : 4

International research links

- Mexico, Brazil, Canada
- USA : The University of Colorado Boulder; Monell Institute - Philadelphia

Keywords

- Nutrition and Neonatology
- Microbiota-Gut-Brain Axis
- Gastrointestinal Physiology
- Obstetrics
- Lipid metabolism
- Omics
- Cohorts
- Translational research

Biological Resources

- Lactomics biobank of human milk
- CEMAFOER cohort of high risk-pregnant women

Research Brief :

Focusing on the first 1000 days of life as a determinant of health and well-being, our research aims to understand how exposure to various risk factors could be determinant in the development of chronic diseases and how nutrition could be a lever to reduce such risk. Our research follows 4 strongly interconnected axes. The first one is dedicated to improving our understanding of the role of nutrition and the metabolic status of the mother on placenta function and milk composition with consequence on baby's growth, cognitive development and metabolic health ; the second one aims at understanding how the establishment of intestinal functions including its microbiota is impacted by malnutrition and what are the long term consequences. A third axis focus on brain functions with similar aims. In a fourth axis, we propose projects which are at the interface of the other 3 axes but which clearly put the microbiota at the heart of the question.
Our objectives can be reached through tight connections between basic, translational, and clinical research. Our work will associate in vitro work, preclinical animal models, and clinical studies.

- **Methodologies Used :**

- Translational Research, Cohorts
- Animal models
- Omics
- Epigenetic
- Cell and molecular biology

Publications

Le Dréan G, Pocheron AL, Billard H, Grit I, Pagniez A, Parnet P, Chappuis E, Rolli-Derkinderen M, Michel C. (2019). Neonatal Consumption of Oligosaccharides Greatly Increases L-Cell Density without Significant Consequence for Adult Eating Behavior, Nutrients. 11(9), 1967

Rozé JC, Ancel PY, Marchand-Martin L, Rousseau C, Montassier E, Monot C, Le Roux K, Butin M, Resche-Rigon M, Aires J, Neu J, Lepage P, Butel MJ; EPIFLORE Study Group. (2020). Assessment of Neonatal Intensive Care Unit Practices and Preterm Newborn Gut Microbiota and 2-Year Neurodevelopmental Outcomes, JAMA Netw Open. 3(9), e2018119

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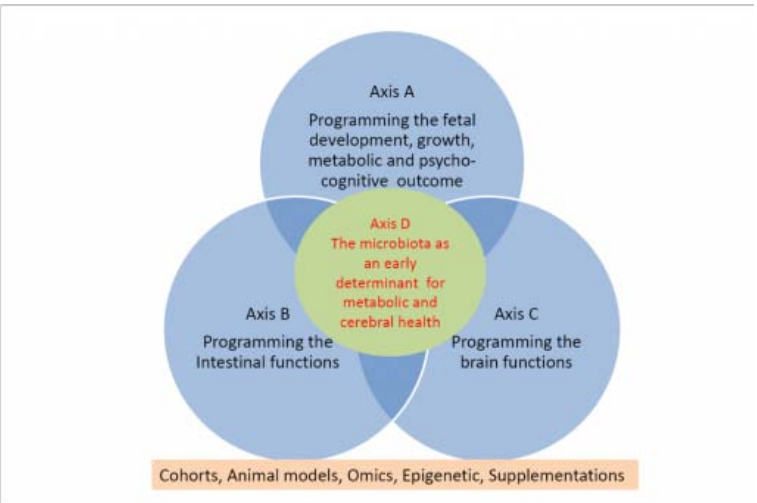
Pocheron AL, Le Dréan G, Billard H, Moyon T, Pagniez A, Heberden C, Le Chatelier E, Darmaun D, Michel C, Parnet P. (2021). Maternal Microbiota Transfer Programs Offspring Eating Behavior, Front Microbiol. 12(), 672224

Blottière Hervé - herve.blottiere@inrae.fr - 0619322872 - https://www6.angers-nantes.inrae.fr/phan/

The research axis at UMR 1280 PhAN



The PhAN team

Blottière Hervé - herve.blottiere@inrae.fr - 0619322872 - https://www6.angers-nantes.inrae.fr/phan/

Key facts

Team

- Researchers : 3
- Technicians : 1
- Postdoc fellows : 1
- PhD Students : 4

Translational approaches

- Patents : 3
- Clinical research grants : 1
- Industry partnerships : 3

International research links

- Spain
- italy
- switzerland

Keywords

- Cytotoxic lymphocytes
- dichloroacetate
- immunotherapy
- ERK5
- Tolerance
- bone marrow transplantation
- in vivo models
- in vitro lymphocyte expansion

Biological Resources

- HEMODIAG: cohort from hematological neoplasias

Martin Villalba Gonzalez

Lymphocytes differentiation, tolerance and metabolism: basis for immunotherapy

University of Montpellier
INSERM 1183
Christian Jorgensen
montpellier

We have been the first to link tumor cell metabolism to tumor immune escape. We have developed an unique protocol to expand NK cells. We have identified antitumor cells in patients.

Research Brief :

We are interested on understanding how tumor cell metabolism affects tumor immune escape. The mostly glycolytic tumor metabolism generate the activation of intracellular signalling pathways that induces expression on the membrane of ligands for immune receptors. Therefore, it is possible to modulate tumor immune recognition by altering tumor metabolism. We also develop specific protocols to produce large numbers of cytotoxic lymphocytes, in particular natural killer (NK) cells. We use these cells to develop clinical trials.

- **Methodologies Used :**

Lymphocyte expansion
in vivomodels for lymphocyte infiltration
FACs 20 colors

Publications

Seyma Charni, Geoffroy de Bettignies, Moeez Ghani Rathore, Juan I. Aguiló, Peter J. van den Elsen, Delphine Haouzi, Robert A. Hipskind, José Antonio Enriquez, Margarita Sanchez-Beato, Julián Pardo, Alberto Anel and Martin Villalba (2010). Oxidative Phosphorylation induces de novo expression of the Major Histocompatibility Complex-I in tumor cells through de ERK5 pathway., J Immunol. S. 185(6), 3498

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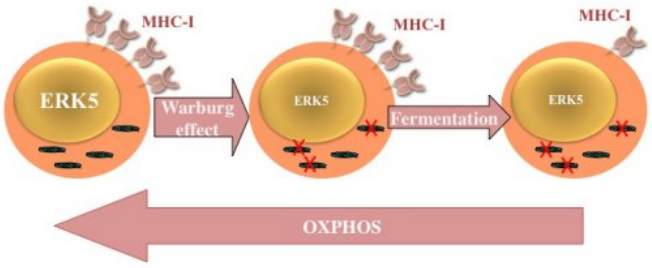
Nerea Allende-Vega, Ewelina Krzywinska, Stefania Orecchioni, Nuria Lopez-Royuela, Francesca Reggiani, Giovanna Talarico, Jean-François Rossi, Rodrigue Rossignol, Yosr Hicheri, Guillaume Cartron, Francesco Bertolini and Martin Villalba (2015). The presence of wild type p53 in hematological cancers improves the efficacy of combinational therapy targeting metabolism., Oncotarget. 6(22), 19228

Elena Catalán, Seyma Charni, Juan Ignacio Aguiló, José Antonio Enríquez, Javier Naval, Julián Pardo, Alberto Anel & Martín Villalba (2015). MHC-I modulation due to metabolic changes regulates tumor sensitivity to CTL and NK cells., Oncoimmunology. 4(1),*

Abrar Ul Haq Khan, Moeez G. Rathore, Nerea Allende-Vega, Dang-Nghiem Vo, Sana Belkhala, Stefania Orecchioni, Giovanna Talarico, Francesco Bertolini, Guillaume Cartron, Charles-Henri Lecellier and Martin Villalba. (2016). Human leukemic cells performing oxidative phosphorylation (OXPHOS) generate an antioxidant response independently of reactive oxygen species (ROS) generation., EBioMedicine. 3(1), 43

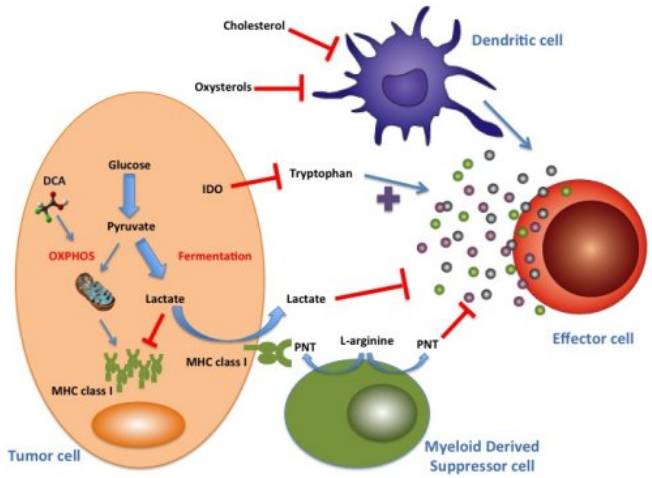
Tumor metabolism controls MHC-I expression.



Tumor metabolism controls MHC-I expression. Tumor cells choose glycolysis metabolism to generate ATP rather than mitochondrial metabolism even in the presence of oxygen (Warburg effect). The pyruvate generated in the glycolysis is reduced to lactate (fermentation). Surface expression of MHC-I is often reduced in tumor cells to avoid the immune attack. Oxidative phosphorylation (OXPHOS) induces expression of ERK5, which increases MHC-I expression at the transcription level.

Tumor cells choose glycolysis metabolism to generate ATP rather than mitochondrial metabolism even in the presence of oxygen (Warburg effect). The pyruvate generated in the glycolysis is reduced to lactate (fermentation). Surface expression of MHC-I is often reduced in tumor cells to avoid the immune attack. Oxidative phosphorylation (OXPHOS) induces expression of ERK5, which increases MHC-I expression at the transcription level.

Tumor cell metabolism protect them from immune cells



Co-regulation of metabolism and immune function to kill tumor cells.

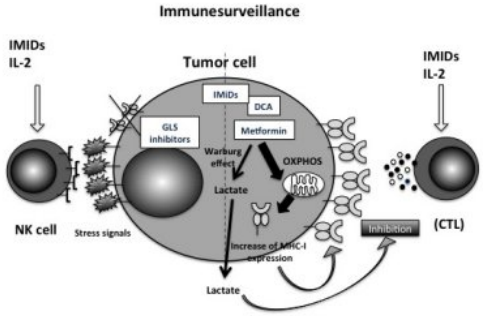


Figure 1. Co-regulation of metabolism and immune function to kill tumor cells. Metabolic drugs such as DCA and Metformin induce OXPHOS that up-regulate the MHC-I expression, immunomodulators (IMiDs) and IL-2 stimulate the anti-tumor activity of effector immune cells (CTL and NK cells). This strategy will help the CTLs to recognize and bind to the MHC-I complex. In contrast, inhibition of OXPHOS reduces MHC-I expression and Natural Killer cells (NK) will recognize the absence of MHC-I and the stress signals. GLS inhibitors could induced NK activation by these means.

Metabolic drugs such as DCA and Metformin induce OXPHOS that up-regulate the MHC-I expression, immunomodulators (IMiDs) and IL-2 stimulate the anti-tumor activity of effector immune cells (CTL and NK cells).

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Research teams with secondary association to PMN Institute

Unité de Nutrition Humaine

Florence CALDEFIE-CHEZET

ECREIN- micro-Environnement CellulaiRE, Immunomodulation et Nutrition

Université Clermont Auvergne
(UCA)
INRA UCA UMR1019
André MAZUR
CLERMONT-FERRAND

Key facts

Team

• Researchers : 17
• Technicians : 6
• Postdoc fellows : 3
• PhD Students : 5

Translational approaches

• Patents : 1
• Clinical research grants : 3
• Industry partnerships : 5

International research links

• African countries (Algeria, Congo, Mali) - projects on bioactive plant compouds
• Sweden (Uppsala ; Karolinska Institute)
• United Kingdom (Leeds, Dr J Torne)

Keywords

• Immunocompetent cells, adipocytes, endothelial; Inflammation, immunity, oxidative stress, microenvironment
• Cancer, therapy/prevention
• Obesity, physical activity
• Plant food and Bioactives / Vit D/ pré-probiotics
• Phytochemistry
• Cell polarization (in vitro models of induced polarization Th1/2, M1/M2; phenotyping, flow and image cytometry)
• Co-cultures; 3D-cultures (adipocytes, cancer, immune cells; spheroïds)
• Plant selection; Extraction; Purification; Structural determination; Metabolite identification
• Obesity, breast cancer, physical activity experimental (cell and animal) models
• Screening (inflammation, immunity, cancer)

Biological Resources

• 2D and 3D models ; experimental animal model of obesity, cancer and physical activity

Research Brief :

The main objective of our team is to characterize the response of immunocompetent cells (ICCs) to their microenvironment variations. It is part of the field of immunonutrition with two major objectives:

1) Identify the relationships between immune / inflammatory alterations and metabolic disorders related to nutritional and immune status in physio-pathological conditions (notably aging, cancer). In this context, our research focuses more specifically on interactions between mammary epithelial cells (immunocompetent barrier cells) and their microenvironment (adipocyte, immune and inflammatory) with obesity, considered as a risk factor for breast cancer.

2) Maintain / optimize the response of ICCs through nutritional interventions with preventive and / or therapeutic approach. For this, modulation of the interaction between the ICCs and the other cells (breast, intestine, muscles) is developed using immunomodulatory food bioactives (pre and probiotics, vitamin D, plant bioactives), in order to prevent the risk of chronic pathology associated with aging.

Our work is conducted with a transversal approach using both experimental original cell (2 and 3D) and animal models (hypercaloric regime, enriched environment) and clinical research protocols.
Keywords

Publications

Bingula R, Dupuis C, Pichon C, Berthon JY, Filaire M, Pigeon L, Filaire E. (2016). Study of the Effects of Betaine and/or C-Phycocyanin on the Growth of Lung Cancer A549 Cells In Vitro and In Vivo., Journal of Oncology.. (),

Bougaret L, Delort L, Billard H, Lequeux C, Goncalves-Mendes N, Mojallal A, Damour O, Vasson MP, Caldefie-Chezet F. (2017). Supernatants of Adipocytes From Obese Versus Normal Weight Women and Breast Cancer Cells: In Vitro Impact on Angiogenesis., J Cell Physiol.. 232(7), 1808-1816

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Fraisse D, Degerine-Roussel A, Bred A, Ndoye SF, Vivier M, Felgines C, Senejoux F. (2018). A novel HPLC method for direct detection of nitric oxide scavengers from complex plant matrices and its application to Aloysia triphylla leaves., Molecules. 23(7),

Bougaret L, Delort L, Billard H, Le Huede C, Boby C, De la Foye A, Rossary A, Mojallal A, Damour O, Auxenfans C, Vasson MP, Caldefie-Chezet F. (2018). Adipocyte/breast cancer cell crosstalk in obesity interferes with the anti-proliferative efficacy of tamoxifen., PLoS ONE.. 13:(e0191571),

Lécuyer L, Victor Bala A, Deschasaux M, Bouchemal N, Nawfal Triba M, Vasson MP, Rossary A, Demidem A, Galan P, Hercberg S, Partula V, Le Moyec L, Srour B, Fiolet T, Latino-Martel P, Kesse-Guyot, Savarin P, Touvier M. (2018). NMR metabolomic signatures reveal predictive plasma metabolites associated with long-term risk of developing breast cancer., Int J Epidemiol.. 47(2), 484-494

Gladys Mirey

Genotoxicity Signaling

Université Paul Sabatier -
Toulouse III
INRA UMR1331
Oswald Isabelle
Toulouse

Association of DNA damage and DNA repair assays to study genotoxicity mechanisms, particularly after exposure to food contaminants.

Key facts

Team

- Researchers : 4
- Technicians : 4
- Postdoc fellows : 0
- PhD Students : 1

Translational approaches

- Patents : 1
- Clinical research grants : 0
- Industry partnerships : 1

International research links

- Europe (Sweden, Italy, Germany, etc), United States (National Institute on Aging - NIH)

Keywords

- Signaling
- Metabolism
- Genotoxicity/DNA damage
- Contaminants
- DNA repair
- Genotoxicity assays
- Cell engineering
- Biotracers/Biosensors
- Repair systems/Biochemistry
- Biomonitoring

Biological Resources

- In vivo/in vitro genotoxic assays

Research Brief :

Our team studies the effects of various chemical (pesticides, nanoparticules) or biological (such as bacterial genotoxins) compounds present as contaminants in food, on the integrity of our DNA. We develop in particular cell assays and biotracers to characterize the genotoxicity mechanisms.

- **Methodologies Used :**

Molecular biology, Cell Biology, Biochemistry, Cell imaging & Cytometry (DNA damage, cell cycle, apoptosis), Genotoxicity assays (comet assay, micronucleus,...).

Publications

Fedor Y, Vignard J, Nicolau-Travers ML, Boutet-Robinet E, Watrin C, Salles B, Mirey G. (2013). From single-strand breaks to double-strand breaks during S-phase: a new mode of action of the Escherichia coli Cytolethal Distending Toxin., Cell Microbiol.. 15(1), 1-15

Bezine E, Malaisé Y, Loeuillet A, Chevalier M, Boutet-Robinet E, Salles B, Mirey G, Vignard J. (2016). Cell resistance to the Cytolethal Distending Toxin involves an association of DNA repair mechanisms., Scientific Reports. (6), 36022

Graillot V, Dormoy I, Dupuy J, Shay JW, Huc L, Mirey G, Vignard J. (2016). Genotoxicity of Cytolethal Distending Toxin (CDT) on Isogenic Human Colorectal Cell Lines: Potential Promoting Effects for Colorectal Carcinogenesis., Front Cell Infect Microbiol.. (6), 34

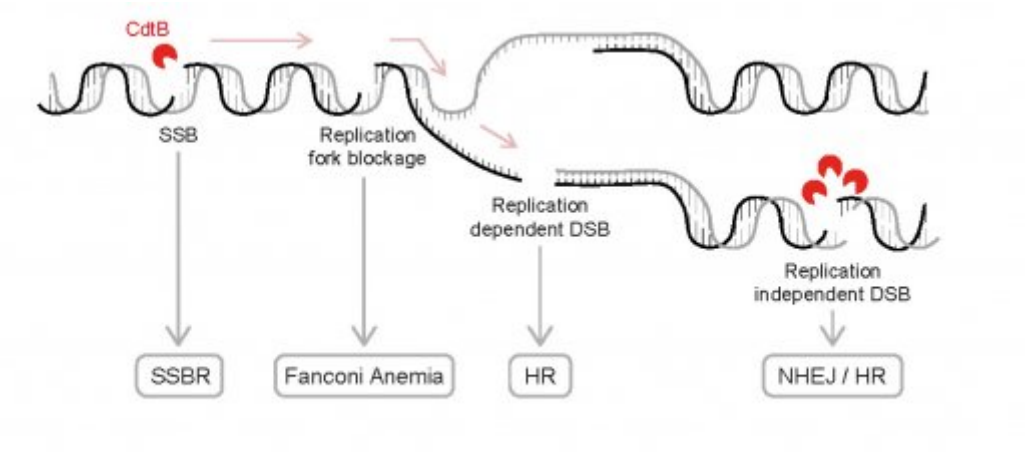
Jullien D, Vignard J, Fedor Y, Béry N, Olichon A, Crozatier M, Erard M, Cassard H, Ducommun B, Salles B, Mirey G. (2016). Chromatibody, a novel non-invasive molecular tool to explore and manipulate chromatin in living cells., J Cell Science. 129(13), 2673-83

Kopp B, Vignard J, Mirey G, Fessard V, Zalko D, Le Hgarat L, Audebert M. (2018). Genotoxicity and mutagenicity assessment of food contaminant mixtures present in the French diet., Environ Mol Mutagen.. 59(8), 742-754

He Z, Gharaibeh RZ, Newsome RC, Pope JL, Dougherty MW, Tomkovich S, Pons B, Mirey G, Vignard J, Hendrixson DR, Jobin C. (2019). Campylobacter jejuni promotes colorectal tumorigenesis through the action of cytolethal distending toxin., Gut. 68(2), 289-300

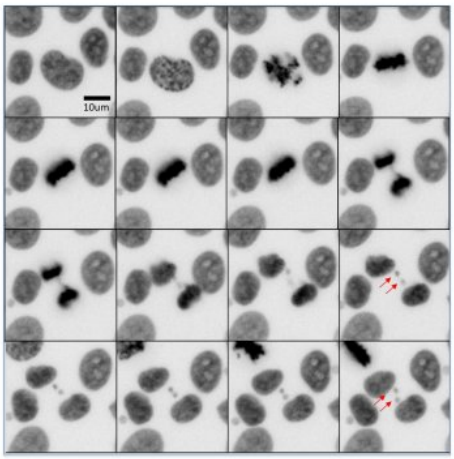
Mirey Gladys - gladys.mirey@inrae.fr - +33 5 82 06 63 38 -
https://www6.toulouse.inra.fr/toxalim_eng/Research-Teams/E8-GS-Genotoxicity-Signaling/Research

A new mode of action for the Cytolethal Distending Toxin.



We used an association of DNA damage and DNA repair assays to revisit the Cytolethal Distending Toxin mode-of-action and showed the importance of replicative stress to generate DNA double-strand breaks (Fedor et al., Graillot et al., Bezine et al.).

Real-time observation of micronuclei assay in metabolic-competent cells.



We are using metabolic-competent cells, expressing a chromatin biotracer (Jullien et al.), to study genotoxicity and micronucleus formation.

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https://www6.toulouse.inra.fr/toxalim_eng/Research-Teams/E8-GS-Genotoxicity-Signaling/Research

Oncogenesis Stress Signaling

Eric Chevet

Protein Homeostasis and Cancer (PROSAC)

Université Rennes 1
Inserm U1242
Eric Chevet
Rennes

Key facts

Team

- Researchers : 5
- Technicians : 3
- Postdoc fellows : 1
- PhD Students : 8

Translational approaches

- Patents : 3
- Clinical research grants : 0
- Industry partnerships : 2

International research links

- Ireland
- Chile
- Canada

Keywords

- endoplasmic reticulum
- stress
- protein misfolding
- cancer
- screening
- cell and molecular biology
- integrated approaches

Integrated study of Endoplasmic reticulum functions in health and disease.

Research Brief :

Our team focuses on the study of Endoplasmic Reticulum (ER) functions in health and disease. In particular we are interested in better understanding two major molecular machines of the ER, namely the stress signalling machinery and the quality control machinery. The first research axis developed in the laboratory aims at characterizing ER stress signalling actors important for tumour development. Indeed in solid tumours, cells are subjected to major environmental challenges that condition their growth and fate. Under those circumstances, protein folding in the ER is affected and ER stress signalling is activated (the Unfolded Protein Response pathway). Our studies focus mainly on IRE1, the most conserved ER stress signal transducer, in various cancers including hepatocellular carcinoma and glioblastoma. The second research axis developed in the laboratory aims at characterizing novel component of the ER quality control whose expression is regulated upon IRE1 activation. We focus on proteins which specifically participate to the control of misfolded proteins secretion in the liver. Our third research axis focuses on the identification of IRE1 activity modulators through automated screening using the AlphaScreen® technology. These approach provide an integrated framework to better characterize and perturb ER biology in health and disease.

- **Methodologies Used :**

Cell and molecular biology
In vitro and cell-based assays
Automated analases, alphascreen

Publications

Higa A, Taouji S, Lhomond S, Jensen D, Fernandez-Zapico ME, Simpson JC, Pasquet JM, Schekman R, Chevet E. (2014). Endoplasmic reticulum stress-activated transcription factor ATF6? requires the disulfide isomerase PDIA5 to modulate chemoresistance., Mol Cell Biol.. (),

Negroni L, Taouji S, Arma D, Pallares-Lupon N, Leong K, Beausang LA, Latterich M, Bossé R, Balabaud C, Schmitter JM, Bioulac-Sage P, Zucman-Rossi J, Rosenbaum J, Chevet E (2014). Integrative quantitative proteomics unveils proteostasis imbalance in human hepatocellular carcinoma developed on nonfibrotic livers., Mol Cell Proteomics.. (),

Marza E, Taouji S, Barroso K, Raymond AA, Guignard L, Bonneu M, Pallares-Lupon N, Dupuy JW, Fernandez-Zapico ME, Rosenbaum J, Palladino F, Dupuy D, Chevet E (2015). Genome-wide screen identifies a novel p97/CDC-48-dependent pathway regulating ER-stress-induced gene transcription., EMBO Rep.. (),

Chevet E, Hetz C, Samali A. (2015). Endoplasmic reticulum stress-activated cell reprogramming in oncogenesis., Cancer Discov.. (),

Fessart D, Domblides C, Avril T, Eriksson LA, Begueret H, Pineau R, Malrieux C, Dugot-Senant N, Lucchesi C, Chevet E, Delom F. (2016). Secretion of protein disulphide isomerase AGR2 confers tumorigenic properties., Elife. (),

Le Reste PJ, Avril T, Quillien V, Morandi X, Chevet E. (2016). Signaling the Unfolded Protein Response in primary brain cancers., Brain Res. (),

Chevet Eric - eric.chevet@inserm.fr - http://oss-clcc-rennes.com/index.html

Key facts

Team

• Researchers : 7
• Technicians : 3
• Postdoc fellows : 1
• PhD Students : 3

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 0

Keywords

• membrane biology
• traffic
• lipid transfer
• membrane curvature
• polyunsaturated lipids
• biochemistry
• liposomes
• cell biology
• molecular dynamics

Bruno Antonny

Dynamics of lipid membranes and protein coats

Université de Nice - Sophia
Antipolis
CNRS UMR7275
Jean-Louis Nahon
Valbonne

Molecular approaches

Research Brief :

Various proteins remodel the membranes of organelles involved in intracellular transport. Protein coats deform membranes to promote the budding of vesicles. Golgins, sort of molecular strings, tether vesicles to restrict their diffusion. Lipid transporters adjust the membrane composition. Although very different, most of these mechanisms are controlled by small G proteins of the Arf family and by the physical chemistry of membranes.

We study these mechanisms through molecular, cellular and in silico approaches. With original assays based on fluorescence and light scattering, we follow elementary reactions such as the assembly cycle of protein coats, the tethering of liposomes by a golgin or the transfer of lipids. With fluorescence light microscopy and electron microscopy, we visualize these events in cells and in reconstituted systems. With molecular dynamics, we describe at the atomic level how specific protein motifs sense the chemistry and curvature of lipid membranes.

Recent findings
- Intracellular transport of cholesterol through the counter exchange of a phosphoinositide and its hydrolysis.
- Phospholipids with omega 3 acyl chains boost membrane deformation and fission
- Atomic description of the packing of lipids in membranes of various curvature and composition

• **Methodologies Used :**

Combination of molecular, cellular and in silico approaches.

Reconstitution experiments with liposomes to study and understand elementary reactions
Molecular dynamics simulations to understand the behavior of lipids in membranes

Publications

Mesmin B, Bigay J, Moser von Filseck J, Lacas-Gervais S, Drin G, Antonny B. (2013). A four-step cycle driven by PI(4)P hydrolysis directs sterol/PI(4)P exchange by the ER-Golgi tether OSBP, Cell. 155(), 830-43

Vanni S, Hirose H, Barelli H, Antonny B, Gautier R (2014). A sub-nanometre view of how membrane curvature and composition modulate lipid packing and protein recruitment, Nat Commun. 5(), 4916

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Antonny Bruno - antonny@ipmc.cnrs.fr - https://www.ipmc.cnrs.fr/cgi-bin/ipmcx.cgi

Key facts

Team

• Researchers : 4
• Technicians : 4
• Postdoc fellows : 1
• PhD Students : 2

Translational approaches

• Patents : 2
• Clinical research grants : 0
• Industry partnerships : 3

International research links

• Allemagne
• Chine
• Italie

Keywords

• gut microbiota, metabolic diseases, brain diseases, nutrition
• germ-free animal models, metagenomicsUMR

Biological Resources

• germ-free mice and rats

Philippe Gérard

Amipem

Université Paris Saclay
INRAE UMR1319
Philippe Noirot
Jouy-en-Josas

Thanks to the unique tool constituted by the germfree facilities of the MICALIS institute, we developed strategies based on microbiota transfer (from animal models or human patients) to germfree rodents in order to prove the causal role played by the gut microbiota in metabolic and brain diseases.

Research Brief :

There is growing evidence that the gut microbiota and its bacterial genome (the microbiome), affect host physiology. These findings raise the possibility that the gut microbiota plays a role in the susceptibility to develop pathologies.
In the AMIPEM team, our projects concern the study of the interaction between food and gut microbiota as a factor involved in the development of human pathologies. Thanks to the unique tool constituted by the germfree facilities of the MICALIS institute, we developed strategies based on microbiota transfer (from animal models or human patients) to germfree rodents in order to prove the causal role played by the gut microbiota in these pathologies. Using molecular analysis (including metagenomics) of the gut microbiota, analytical biochemistry and metabolomics, we also aim at identifying bacterial species, genes and metabolites associated with patho-physiological parameters. We also assess the effects of a microbiota modulation using pro or prebiotics on the considered pathologies. Our current projects more specifically target the role of the gut microbiota in the development of the metabolic diseases and in brain disorders.

• **Methodologies Used :**

. gnotobiology (germ-free animal models)
. metagenomics
. transcriptomics

Publications

Le Roy T, Llopis M, Lepage P, Bruneau A, Rabot S, Bevilacqua C, Martin P, Philippe C, Walker F, Bado A, Perlemuter G, Cassard-Doulcier AM, Gérard P. (2013). Intestinal microbiota determines development of non-alcoholic fatty liver disease in mice., Gut. (),

Crumeyrolle-Arias M, Jaglin M, Bruneau A, Vancassel S, Cardona A, Daugé V, Naudon L, Rabot S. (2014). Absence of the gut microbiota enhances anxiety-like behavior and neuroendocrine response to acute stress in rats., Psychoneuroendocrinology. (),

Llopis M, Cassard-Doulcier AM, Wrosek L, Boschat L, Ferrere G, Bruneau A, Puchois V, Martin JC, Lepage P, Le Roy T, Lefèvre L, Langelier B, Cailleux F, González-Castro AM, Rabot S, Gaudin F, Agostini H, Prévot S, Berrebi D, Ciocan D, Jousse C, Naveau S, Gérard P, Perlemuter G (2016). Intestinal microbiota contributes to individual susceptibility to alcoholic liver disease, Gut. (),

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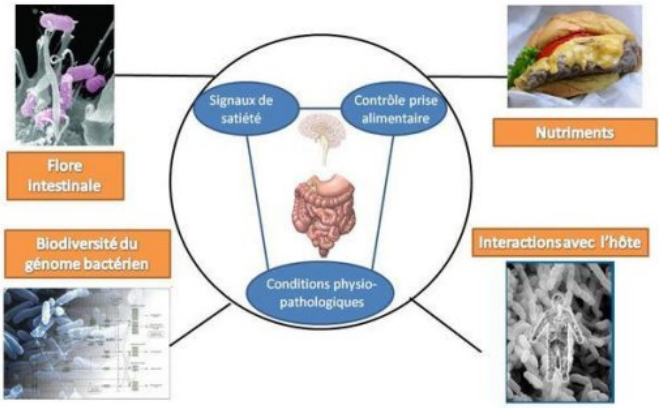

Gérard Philippe - philippe.gerard@inra.fr - 0134652428 - https://www.micalis.fr/Poles-et-Equipes/Pole-Ecosystemes/Amipem-Gerard

Arnaud Mourier

BioDynaMit

Université de Bordeaux
CNRS UMR5095
Isabelle Sagot
Bordeaux

The BioDynaMit team gathers great levels of expertise focused on mitochondria (physiology, cell biology, genetics and bioenergetics). Our goal is to elucidate molecular defects underpinning mitochondrial and metabolic disorders to open new diagnostic and therapeutic avenues.

Key facts

Team

- Researchers : 2
- Technicians : 1
- Postdoc fellows : 0
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- Prof. Nils-Göran Larsson (Karolinska Institute - Sweden)
- Prof. Chan Bae Park (Seoul - South Korea)

Keywords

- mitochondria
- Energy metabolism
- Bioenergetics
- mitochondrial dynamics
- Oxidative phosphorylation
- Oxygraphy
- membrane potential
- redox and phosphate potential
- Supercomplexes -BN-PAGE

Biological Resources

- Transgenic mouse models
- Yeast (Sacharomyces Cerevisae)

Research Brief :

Mitochondria are double membrane organelles, which hold a central role in cell metabolism as they produce the bulk part of the energy currency ATP through the oxidative phosphorylation (OXPHOS) system. The localization of mitochondria at intracellular sites of high-energy demand is crucial to maintain cell energy metabolism. In muscle, mitochondria are embedded between myofibrils that consume ATP during contraction. Likewise, in neurons, mitochondria are transported and accumulate in synapses to provide the energy required to maintain and regulate neurotransmission. Due to their key energetic role, mitochondrial dysfunction is a common cause of disease in both children and adults. During the past few years our group has made significant breakthrough deciphering the interplay between OXPHOS supramolecular organisation, bioenergetics and mitochondrial dynamics and genetics.

Scientific goals of the BioDynaMit group
* To unravel molecular mechanism mediating mitochondrial fusion, and developing tools allowing in vivo quantification of these processes.
* To decipher the link between mitochondrial morphology, mitochondrial genetics and bioenergetics.
* To elucidate physiopathological mechanisms underpinning mitochondrial dynamics-related diseases.
* To investigate modulation of OXPHOS system structure and composition allowing mitochondria to adapt to various tissues specific energy demands under physiological or pathological conditions.

• **Methodologies Used :**

* Isolation of metabolically active mitochondria from different mammalian cell types and other organisms (yeast, drosophila, trypanosoma, C.elegans). Organelles immuno-isolation using magnetic beads.
* Bioenergetic characterization (oxygen consumption rate using High resolution respirometry (O2K oxygraphs), membrane potential measurement, H2O2 and ATP production rate)
* Coupled bioenergetics and metabolomic approches correlating, proteome changes to metabolic and energetic changes.
* Combined native and denaturing electrophoreses (BN-PAGE, 2D SDS electrophoreses)

Publications

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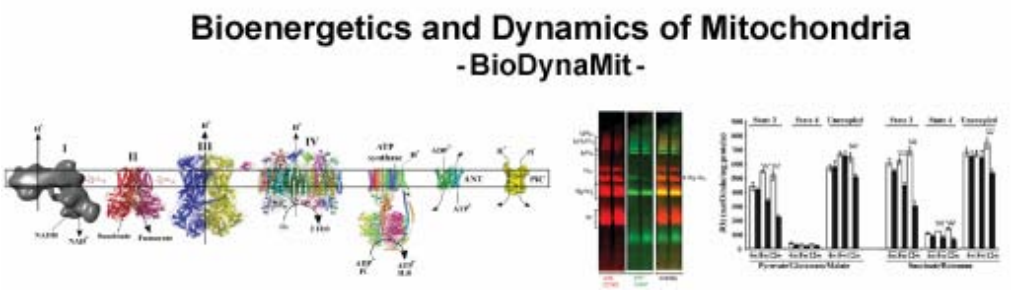
Brandt T, Mourier A, Tain LS, Partridge L, Larsson NG, Kühlbrandt W. (2017). Changes of mitochondrial ultrastructure and function during ageing in mice and Drosophila., Elife. 12(6),

Silva Ramos E, Motori E, Brüser C, Kühl I, Yeroslaviz A, Ruzzenente B, Kauppila JHK, Busch JD, Hultenby K, Habermann BH, Jakobs S, Larsson NG, Mourier A. (2019). Mitochondrial fusion is required for regulation of mitochondrial DNA replication., PLoS Genetics. 15(6),

Molinié T, Cougouilles E, David C, Cahoreau E, Portais JC, Mourier A. (2022). MDH2 produced OAA is a metabolic switch rewiring the fuelling of respiratory chain and TCA cycle., BBA Bioenergetics. (),

Mourier Arnaud - arnaud.mourier@ibgc.cnrs.fr - +33556999040 - http://ibgc.cnrs.fr/?page=equipe&eq=biodynamit

Mitochondrial Morphology, Dynamics and OXPHOS supercomplexes and Bioenergetics



Mourier Arnaud - arnaud.mourier@ibgc.cnrs.fr - +33556999040 - http://ibgc.cnrs.fr/?page=equipe&eq=biodynamit

Key facts

Team

- Researchers : 1
- Technicians : 2
- Postdoc fellows : 4
- PhD Students : 1

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- antibiotics
- metallo-enzymes
- natural products
- Enzyme
- RiPP
- Crystallogenesis
- Mass spectrometry
- Biochemistry

Olivier Berteau

ChemSyBio

Université Paris Sud : Paris 11
INRA UMR1319
Olivier Noirot
Jouy en Josas

Our team uses biochemical and chemical approaches to solve the mechanism of novel enzymes.

Research Brief :

The ChemSyBio team is investigating novel enzymes catalysing unprecedented post-translational modifications. These enzymes use radical chemistry notably to produces various antibiotics, anti-cancer agents and toxins.

- **Methodologies Used :**

Mass spectrometry, structural biology.

Publications

Pierre, S., Guillot, A., Benjdia, A., Sandstrom, C., Langella, P., and Berteau, O. (2012). Thiostrepton tryptophan methyltransferase expands the chemistry of radical SAM enzymes, Nature Chemical Biology. 8(), 957

Philmus, B., Decamps, L., Berteau, O., and Begley, T. P. (2015). Biosynthetic versatility and coordinated action of 5'-deoxyadenosyl radicals in deazaflavin biosynthesis, J Am Chem Soc. 137(), 5406

Benjdia, A., Pierre, S., Gherasim, C., Guillot, A., Carmona, M., Amara, P., Banerjee, R., and Berteau, O. (2015). The thiostrepton A tryptophan methyltransferase TsrM catalyses a cob(II)alamin-dependent methyl transfer reaction, Nature Communincations. 6(), 8377

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Parent, A., Guillot, A., Benjdia, A., Chartier, G., Leprince, J., and Berteau, O (2016). The B12-Radical SAM Enzyme PoyC Catalyzes Valine Cbeta-Methylation during Polytheonamide Biosynthesis, J Am Chem Soc. 138(), 15515

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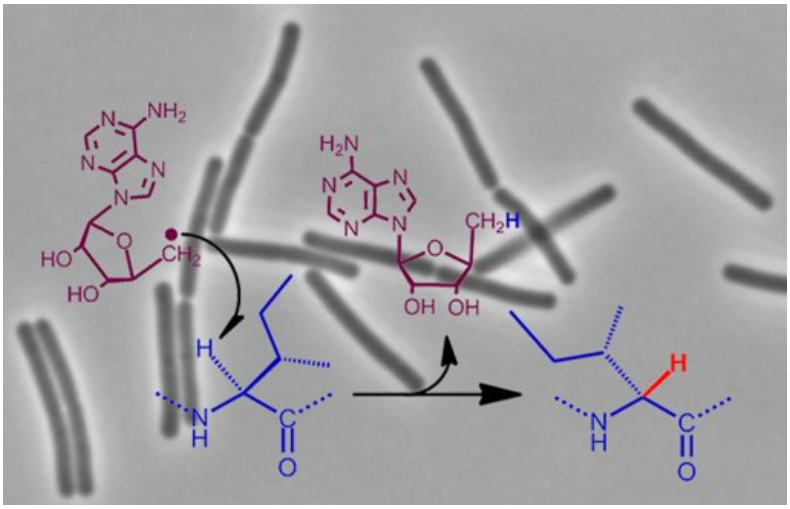
Novel synthesis of post-translationally modified peptides



Key facts

Team

- Researchers : 3
- Technicians : 1
- Postdoc fellows : 1
- PhD Students : 2

Translational approaches

- Patents : 1
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- non-coding RNAs
- gene expression
- RNA metabolism
- inflammatory disorders
- epigenetics
- in vivo models
- high throughput sequencing
- bioinformatics
- mass-spectrometry
- epidemiology

Biological Resources

- mouse lines

Michele Trabucchi

CONTROL OF GENE EXPRESSION

Université de Nice
Sophia-Antipolis
Inserm 1065
Patrick Auberger
NICE

combination of biochemistry and bioinformatics approaches in the investogation of non-coding RNA in gene expression control

Research Brief :

we focused on discovering novel mechanisms of post-transcriptional events controlling gene expression. Particularly, since its creation the team has utilized several newly-emerging technologies to investigate the importance of the expression control and the mode of action of small RNAs in development and physiopathological events of metabolic disorders. We use different high-throughput experimental approaches, including mass-spectrometry and deep sequencing analysis coupled with bioinformatics, mouse models and epidemiological approaches. We have developed a series of important and complex stories to the point that they stand scrutiny at rigorous and prestigious journals, including Nature, Plos Genetics, BMC Medicine, Nucleic Acids Research, Cell Death & Disease, Nature Structural & Molecular Biology, and Nucleic Acids Research. In these papers, we described novel aspects of small RNA-dependent gene expression control, which shed a light of their central role in physiopathological events.

- **Methodologies Used :**

Mass-spectrometry; high-throughput sequencing; in vivo models; bioinformatics, epidemiology

Publications

E. Repetto, L. Lichtenstein, Z. Hizir, N. Tekaya, M. Benahmed, J.B. Ruidavets, L.E. Zaragosi, B. Perret, L. Bouchareychas, A. Genoux, R. Lotte, R. Ruimy, J. Ferrières, P. Barbry, L.O. Martinez, M. Trabucchi (2015). RNY-derived small RNAs as a signature of Coronary Artery Disease, BMC Medicine. 13(1), 259

S. Bottini, N. Hamouda-Tekaya, R. Mategot, L.E. Zaragosi, S. Audebert, S. Pisano, V. Grandjean, C. Mauduit, M. Benahmed, P. Barbry, E. Repetto, M. Trabucchi (2017). Post-transcriptional gene silencing mediated by microRNAs is controlled by nucleoplasmic Sfpq, Nature Communications. 8(1), 1189

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M. Trabucchi (2019). Subcellular heterogeneity of the microRNA machinery, Trends in Genetics. 35(1), 15

Trabucchi Michele - mtrabucchi@unice.fr

Matthieu Jules

Systems Biology for bacterial Engineering and Redesign

AgroParisTech Université Paris-Saclay
INRAE UMR1319
Philippe Noirot
Jouy-en-Josas

Key facts

Team

- Researchers : 7
- Technicians : 3
- Postdoc fellows : 1
- PhD Students : 4

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- Synthetic Biology
- Minimal genome
- Gene expression
- Resource allocation
- Orthogonal machineries
- Genome Engineering
- Adaptive Laboratory Evolution
- Cell free

The SyBER group aims at understanding the overall functionning of the fundamental cellular processes (replication, transcription and translation), from single-cell to cell population, using synthetic biology approaches (genome engineering, metabolic engineering, etc.)

Research Brief :

The SyBER group aims at understanding the overall functionning of the fundamental cellular processes (replication, transcription and translation), from single-cell to cell population. Members of SyBER apply quantitative and systemic experimental approaches in combination with mathematical modeling and exploit the newly acquired knowledge using synthetic biology approaches (genome engineering, metabolic engineering, etc.) to:

rationally modify B. subtilis, and at midterm Escherichia coli, to generate efficient cell factories (for the production of proteins and metabolites of interest).
conceive synthetic biological systems possessing novel functions, i.e. not found in nature (new metabolic activities, biosensors, etc.).

- **Methodologies Used :**

Genome engineering (CRISPR/Cas, in-yeast assembly, in vitro assembly, pop in /out, etc.),
Adaptive laboratory evolution (Phage-assisted continuous evolution, chemostat, etc),
etc.

Publications

Borkowski O, Goelzer A, Schaffer M, Calabre M, Mäder U, Aymerich S, Jules M$ and Fromion V$ (2016). Translation elicits a growth-rate-dependent, genome-wide, differential protein production in Bacillus subtilis, Mol. Syst. Biol.. (),

Guiziou S, Sauveplane V, Chang HJ, Clerté C, Declerck N, Jules M and Bonnet J (2016). A part toolbox to tune genetic expression in Bacillus subtilis, Nucleic Acids Research. (),

Charbonnier T, Le Coq D, McGovern S, Calabre M, Delumeau O, Aymerich S and Jules M$ (2017). Molecular and Physiological Logics of the Pyruvate-Induced Response of a Novel Transporter in Bacillus subtilis, MBio. (),

Deloupy A, Sauveplane V, Robert J, Aymerich S, Jules M$ and Robert L$. (2020). Extrinsic noise prevents the independent tuning of gene expression noise and protein mean abundance in bacteria, Science Advances. (),

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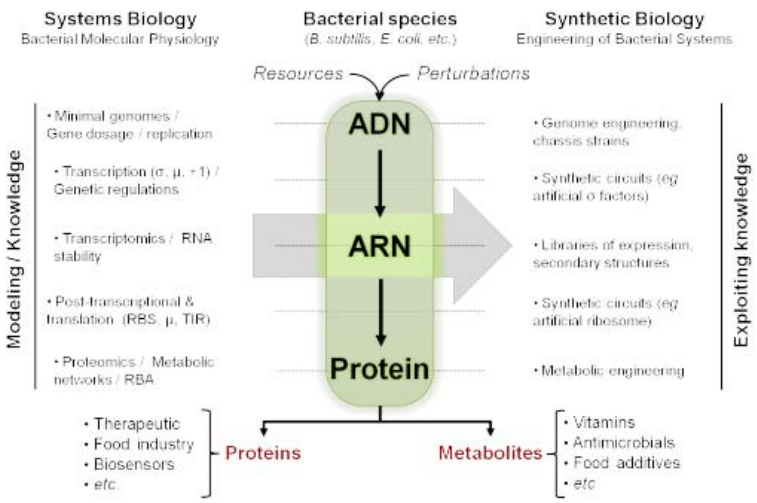
SyBER research activities



Yaël Grosjean

Sensory Perception, Interactions between Glia and Neurons

Institut Agro Université de Bourgogne-Franche Comté
CNRS UMR6265 INRAE UMR1324
Loïc Briand
Dijon

We try to understand how chemicals (food odors and amino acids) are detected and processed into the brain to lead to a specific behavioral and/or physiological response, mainly focusing on glia/Neuron interaction through the study of a family of amino acid transporters.

Key facts

Team

- Researchers : 4
- Technicians : 4
- Postdoc fellows : 0
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- drosophila
- glia/neuron interaction
- SLC7A amino acid transporters
- olfaction
- metabolism
- immunohistology
- molecular genetics
- calcium imaging
- biochemistry
- behavior

Biological Resources

- S2 cells
- Drosophila melanogaster

Research Brief :

Our surrounding environment is bathed in chemicals. They can be tasted, smelled and eaten. They represent vital information for the cells and the organism. Our team "Sensory Perception, Glia/Neuron Interactions" explores the molecular and cellular mechanisms allowing the perception of these chemical signals, and their effects on physiology and metabolism.

- **Methodologies Used :**

Basic research (molecular genetics, biochemistry, immunohistology, developmental assays, behavioral analyses) using Drosophila melanogaster as a biological model.

Publications

Ziegler A.B., Ménagé C., Grégoire S., Garcia T., Ferveur J.-F., Bretillon L. & Grosjean Y. (2015). Lack of Dietary Polyunsaturated Fatty Acids Causes Synapse Dysfunction in the Drosophila Visual System., PLoS One. 10(), e0135353

Manière G., Ziegler A.B., Geillon F., Featherstone D.E. & Grosjean Y. (2016). Direct Sensing of Nutrients via a LAT1-like Transporter in Drosophila Insulin-Producing Cells., Cell Reports. 17(), 137-148

Depetris-Chauvin A, Galagovsky D, Chevalier C, Maniere G & Grosjean Y. (2017). Olfactory detection of a bacterial short-chain fatty acid acts as an orexigenic signal in Drosophila melanogaster larvae., Scientific Reports. 7(), 14230

Galagovsky D, Depetris-Chauvin A, Manière G, Geillon F, Berthelot-Grosjean M, Noirot E, Alves G, Grosjean Y. (2018). Sobremesa L-type Amino Acid Transporter Expressed in Glia Is Essential for Proper Timing of Development and Brain Growth., Cell Reports. 24(), 3156-3166

Ziegler A.B., Manière G.* & Grosjean Y. (2018). JhI-21 plays a role in Drosophila insulin-like peptide release from larval IPCs via leucine transport., Scientific Reports. 8(), 1908*

Masuzzo A, Manière G, Viallat-Lieutaud A, Avazeri É, Zugasti O, Grosjean Y, Kurz CL, Royet J. (2019). Peptidoglycan-dependent NF-?B activation in a small subset of brain octopaminergic neurons controls female oviposition., Elife. 8(), e50559

Mathilde Touvier

Nutritional Epidemiology Research Team (EREN-CRESS)

University Sorbonne Paris Nord
(Paris 13) University Paris Cité
Inrae U1125 Cnam -
Philippe Ravaud
Bobigny

EREN is one of the most strategic epidemiological research teams at the international level to study health impact of dietary behaviors and emerging nutritional exposures.

Key facts

Team

- Researchers : 24
- Technicians : 24
- Postdoc fellows : 7
- PhD Students : 22

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- https://eren.univ-paris13.fr/index.php/en/projects-and-collaborations.html

Keywords

- Nutrition
- Chronic diseases
- Epidemiology
- Public Health

Biological Resources

- NutriNet-Santé: https://etude-nutrinet-sante.fr/ - https://info.etude-nutrinet-sante.fr/node/2
- Other studies coordinated by EREN: https://eren.univ-paris13.fr/index.php/en/epidemiological-studies.html

Research Brief :

Objectives of EREN are to study the impact of nutrition on human and planetary health, underlying mechanisms and the determinants of dietary behaviors. Its purpose is to provide health authorities and agencies with scientific evidence to guide the development of public health nutritional policies. The team studies a large array of health outcomes, such as cardiometabolic pathologies, cancers, obesity, etc. EREN is the only French research team and one of the few internationally to be fully dedicated to nutritional epidemiology in all its dimensions. The dynamism of the team has been acknowledged and rewarded over the past years through, for instance, the Inserm Research Prize 2019, an ERC Consolidator Grant 2020-2025, a Bettencourt Schueller Prize 2021, 3 articles in the top 100 Altmetric in 2019, a Chair of Professor at Collège de France 2022-2023, and an important public health impact nationally and internationally. EREN's work on nutritional labelling, with the development of the Nutri-Score now selected as the official nutritional label in France and 6 other European countries, but also on ultraprocessed foods, organic food and diet sustainability have directly impacted and shaped the nutritional recommendations in France (PNNS, Programme National Nutrition Santé) and at the international level (WHO-FAO, etc.), and have led to a Parliamentary inquiry into the industrial food offer with regular auditions of EREN's researchers at the Senate and National Assembly.

- **Methodologies Used :**

EREN coordinates NutriNet-Santé, a web-based cohort study launched in 2009, now comprising >173,000 participants, among which 20,000 participated in a clinical/biological component (clinical measurements, blood and urine samples). A microbiota component with a collection of stool samples is also ongoing for n=8000-10000. NutriNet-Santé is characterized by a very detailed assessment of nutritional exposures both current and emerging, with a repeated collection over time through validated dietary questionnaires: consumption of >3500 generic food items + the brand for industrial food products, quantitative data on organic food consumption or dietary supplement intakes, etc. NutriNet-Santé has already led to >250 publications.

Publications

Chaltiel D, Julia C, Adjibade M, Touvier M, Hercberg S, Kesse-Guyot E (2019). Adherence to the 2017 French dietary guidelines and adult weight gain: A cohort study, PLoS Med. 16(12), e1003007

Chazelas E, Srour B, Desmetz E, Kesse-Guyot E, Julia C, Deschamps V, Druesne-Pecollo N, Galan P, Hercberg S, Latino-Martel P, Deschasaux M, Touvier M (2019). Sugary drink consumption and risk of cancer: results from NutriNet-Santé prospective cohort, BMJ. 366(), l2408

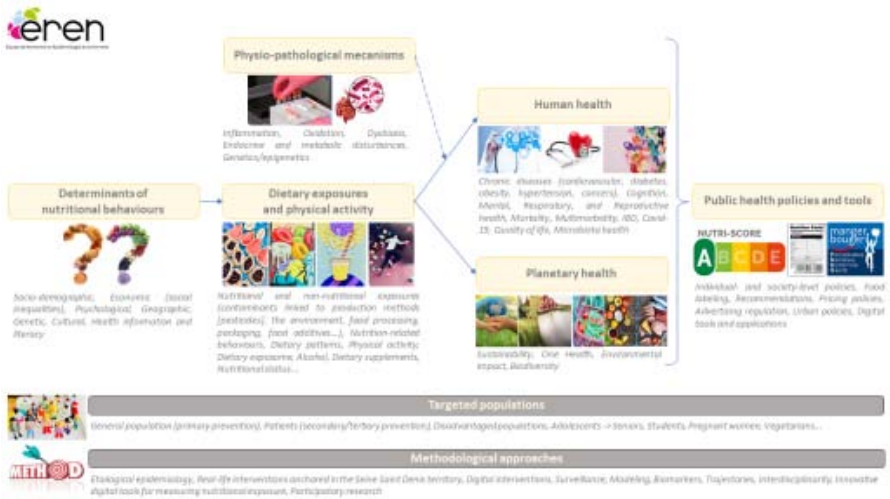
Srour B, Fezeu LK, Kesse-Guyot E, Allès B, Debras C, Druesne-Pecollo N, Chazelas E, Deschasaux M, Hercberg S, Galan P, Monteiro CA, Julia C, Touvier M (2020). Ultraprocessed Food Consumption and Risk of Type 2 Diabetes Among Participants of the NutriNet-Santé Prospective Cohort, JAMA Intern Med. 180(2), 283-291

Deschasaux M, Huybrechts I, Julia C, Hercberg S, Egnell M, Srour B, Kesse-Guyot E, Latino-Martel P, Biessy C, Casagrande C, Murphy N, Jenab M, Ward HA, Weiderpass E, Overvad K, Tjønneland A, Rostgaard-Hansen AL, Boutron-Ruault MC, Mancini FR, Mahamat-Saleh Y, Kühn T, Katzke V, Bergmann MM, Schulze MB, Trichopoulou A, Karakatsani A, Peppa E, Masala G, Agnoli C, De Magistris MS, Tumino R, Sacerdote C, Boer JM, Verschuren WM, van der Schouw YT, Skeie G, Braaten T, Redondo ML, Agudo A, Petrova D, Colorado-Yohar SM, Barricarte A, Amiano P, Sonestedt E, Ericson U, Otten J, Sundström B, Wareham NJ, Forouhi NG, Vineis P, Tsilidis KK, Knuppel A, Papier K, Ferrari P, Riboli E, Gunter MJ, Touvier M (2020). Association between nutritional profiles of foods underlying Nutri-Score front-of-pack labels and mortality: EPIC cohort study in 10 European countries, BMJ. 370(), m3173

Debras C, Chazelas E, Sellem L, Porcher R, Druesne-Pecollo N, Esseddik Y, Szabo de Edelenyi F, Agaësse C, De Sa A, Lutchia R, Fezeu L, Julia C, Kesse-Guyot E, Allès B, Galan P, Hercberg S, Deschasaux-Tanguy M, Huybrechts I, Srour B, Touvier M (2022). Artificial sweeteners and risk of cardiovascular diseases: results from the prospective NutriNet-Santé cohort, BMJ. 378(e071204),

o Kesse-Guyot E, Allès B, Brunin J, Fouillet H, Dussiot A, Berthy F, Perraud E, Hercberg S, Mariotti F, Deschasaux-Tangui M, Srour B, Lairon D, Pointereau P, Baudry J, Touvier M (2022). Environmental impacts along the value chain from consumption of ultra-processed foods, Nature Sustainability. https://doi.org/10.1038/s41893-0(),

EREN Team - Objectives



NutriScore

NutriNet-Santé

Touvier Mathilde - m.touvier@eren.smbh.univ-paris 13.fr - https://eren.univ-paris13.fr/index.php/en/

Endocrinology Reproduction

Key facts

Team

- Researchers : 6
- Technicians : 3
- Postdoc fellows : 3
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- central control of metabolism
- neurogenesis
- cognition
- endocrine disruptions
- life history
- gene expression
- immunohistochemistry
- transgenic mice
- transcriptomics

Marie-Stéphanie Clerget-Froidevaux Nicolas Narboux-Nême

BBC Brain-body crosstalk during adaptive processes

Muséum National d'Histoire Naturelle
MNHN/CNRS UMR 7221
Laurent Sachs
Paris 05

Our team studies the brain-body interactions and their modulations by internal and external influences, to understand the cellular and molecular mechanisms which assure the maintenance of homeostasis throughout life, from development to aging through reproductive maturity.

Research Brief :

We study the links between genetic diversity (allelic variations and gene expression) and plasticity (morphological, metabolic, behavioral or cognitive) to elucidate adaptive processes in response to environmental constraints. Our research has implications for increasing societal threats such as metabolic and neurodegenerative diseases.
Our work is articulated around three main axes:
- Central control of metabolism
- Cognition, neurogenesis and aging
- Development and life history

In this context, the main research thematics developed within the BBC team are:
- Influence of key gene expression on cognition and central control of metabolism: consequences for adaptation to the environment, aging and neurological pathologies.
- Interactions between thyroid hormone levels, metabolic defects, neuroinflammation and neurodegeneration
- Involvement of thyroid signaling in neural stem cell fate choice: molecular, cellular and behavioral responses under normal and pathological conditions at all ages.
- Interactions between genetic background, oxidative stress, metabolism and environmental conditions in young and adult individuals: consequences for life history and reproductive success.
- Study of the genetic and cellular developmental processes that regulate the formation of an integrated and functional musculoskeletal system: evolution of the morphological innovations implicated in the water-to-land transition of vertebrates.

Methodologies Used :

- Generation of targeted mutations in mice
- neurospheres
- wild-derived mouse strains
- Single cell and spatial transcriptomics
- behaviour studies

Publications

De Lombares Camille, Heude Eglantine, Alfama Gladys, Fontaine Anastasia, Hassouna Rim, Vernochet Cécile, deChaumont Fabrice, Olivo-Marin Christophe, Ey Elodie, Parnaudeau Sébastien, Tronche François, Bourgeron Thomas, Luquet Serge, Levi Giovanni & Narboux-Nême Nicolas (2019). Dlx5 and Dlx6 expression in GABAergic neurons controls behavior, metabolism, healthy aging and lifespan., Aging (Albany NY). 11(17), 6638-6656

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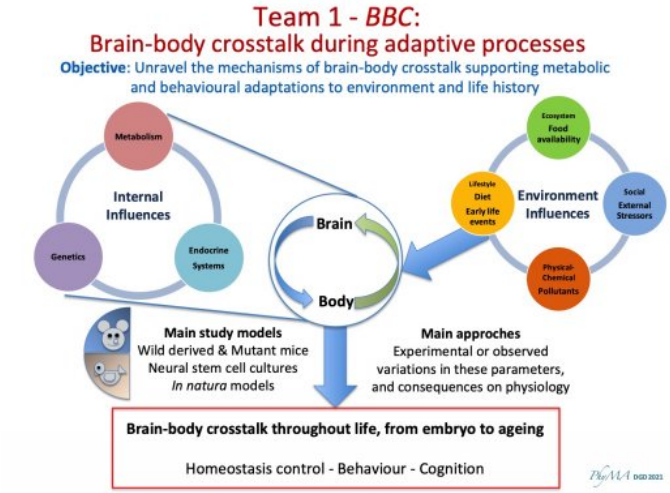
https://phyma.mnhn.fr/en/bbc-brain-body-cross-talks-during-adaptive-processes-7178



We study the consequences of variations in internal (metabolism, genetic background, hormonal levels) and external (stress, food availability, exposure to pollutants,..) events in body homeostasis, throughout life, and the influence of perinatal events on the adulthood. We seek to understand the influence of experimental observed variations of these factors on brain-body crosstalk, in particular on the hypothalamic control of homeostasis, and on behavior and cognition.

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https://phyma.mnhn.fr/en/bbc-brain-body-cross-talks-during-adaptive-processes-7178

Key facts

Team

• Researchers : 5
• Technicians : 3
• Postdoc fellows : 0
• PhD Students : 2

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 0

International research links

• America : USA and Chile
• EU: Belgium, Germany, Denmark,
Sweden, England, Spain.

Keywords

• thyroid hormone
• Adaption
• Endocrine disruption
• Cell fate
• functional genomic
• bioinformatic
• genetically modified organisms
• Xenopus embryonic thyroid signalling assay
• histology

Laurent Sachs

Molecular and cellular responses to environmental challenges

Museum Nationale d'Histoire
Naturelle
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Laurent Sachs
Paris

Our objective is to determine at the molecular, cellular and whole-body levels, the physiological consequences of exposure to endocrine disruptors and environmental changes related to stress and life cycle transitions.

Research Brief :

We will develop two axes of research to understand the regulations that control development and tissue homeostasis in normal and perturbed conditions (stress or endocrine disruptors). The first axis is the evolution of molecular control of life cycle transitions with a special emphasis on amphibian metamorphosis, a post-embryonic developmental process that is linked to change of environment and controlled by environmental challenges. Metamorphosis in Anuran is essential in their life cycle and spectacular. However, metamorphosis in Urodele is facultative and morphologically less dramatic. We will study the control of cell fate plasticity during life cycle transitions resulting from a diversity of gene regulatory programs. The second axis focuses on the impact of changes in ecosystems during life cycle transitions. First, because life cycle transitions are controlled by hormonal signaling, where thyroid hormones play an essential role, we will analyze the impact of endocrine disruptors on development addressing jointly the adverse effects of these chemicals on environment and their potential adverse effects on human health. Second, the interaction between thyroid and glucocorticoid signaling will be analyzed because glucocorticoids play a pivotal role in the response to stressful challenges and environmental changes can be seen as stressful events. Again, we will pay attention to gene regulatory programs and control of cell fate plasticity.

• **Methodologies Used :**

Transversals approaches addressing the regulatory programs and molecular mechanisms induced by adaptation (effects on transcriptome, epigenome and 3D organization of the genome in the nucleus) and the organism plasticity with tissues remodelling and cell fate consequences of adaptation (effects on cell proliferation / differentiation / death, stemness, morphology, metabolism, comportment and locomotion). Our work will focus on a class of vertebrate close to mammals: The Amphibians

Publications

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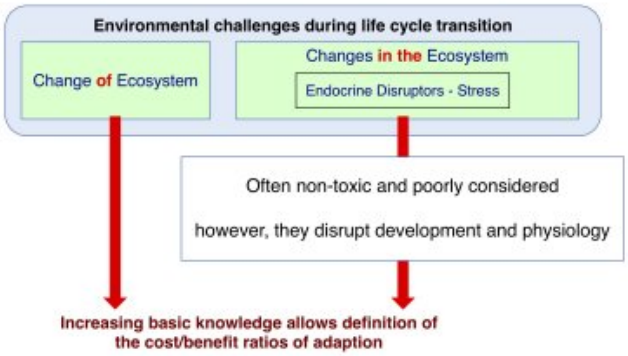
Context of research



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Marseille Medical Genetics

Thierry Brue

DIfferentiation and Proliferation of NeuroEndocrine Tissues (DIPNET)

Aix-Marseille Université
Inserm UMR1251
Nicolas Lévy
Marseille

Key facts

Team

- Researchers : 10
- Technicians : 5
- Postdoc fellows : 2
- PhD Students : 3

Translational approaches

- Patents : 0
- Clinical research grants : 10
- Industry partnerships : 2

International research links

- Canada
- USA

Keywords

- Endocrinology
- Pituitary
- endocrine tumors
- transcription factors
- signalling pathways
- induced pluripotent stem cells
- primary cell culture
- kinomics

Biological Resources

- Genhypopit Cohort

> ***Translational research in endocrine tumors and pituitary diseases***

Research Brief :

As nervous and endocrine systems often act together to regulate physiologic processes of the human body, the branch of medicine concerned with the interactions between both systems is called Neuroendocrinology. The neuroendocrine system includes endocrine glands such as the pituitary as well as endocrine islets within glandular tissues (e.g. pancreatic tissue) or cells dispersed between exocrine cells such as endocrine cells of the digestive tract.
Our main objectives are to identify key factors (from receptors to transcription factors) involved in differentiation and proliferation mechanisms of neuroendocrine cells and to improve our understanding of the physiological molecular pathways and their abnormalities involved in hormone deficiencies or neuroendocrine hypersecretion and proliferation syndromes in order to identify new therapeutic strategies.
Human cells are poorly available due to their localization while murine models display a number of discrepancies with human neuroendocrine physiology and pathology. Therefore our experimental strategy is to develop human cellular models from induced pluripotent stem cells(iPS) differentiated into neuroendocrine cells of interest such as pituitary cells.
Overall the ultimate goal of our research is to develop new therapeutic strategies for neuroendocrine diseases based on a better understanding of their mechanisms.
509

- **Methodologies Used :**

Unique model of differentiated human pituitary cells derived from iPSc

Publications

Cuny T, Zeiller C, Bidlingmaier M, Défilles C, Roche C, Blanchard MP, (). In vitro impact of pegvisomant on growth hormone-secreting, Endocrine Related Cancer. 2016(23), 7

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Key facts

Team

- Researchers : 17
- Technicians : 5
- Postdoc fellows : 1
- PhD Students : 5

Translational approaches

- Patents : 3
- Clinical research grants : 4
- Industry partnerships : 2

International research links

- Canada
- Colombie
- Germany

Keywords

- Endocrine tumorigenesis
- Pituitay tumors and adrenal lesions
- Gonadal pathology
- Hypogonadotropic Hypogonadism
- Biosynthesis and corticosteroid signaling in newborns
- Translational medecine and clinical research
- Mouse models
- Genomics (NGS, SNP, qPCR)
- Gene expression (transcription, post-transcription)
- Development of cellular models

Biological Resources

- Biological Resource Center (BRC) of the University Hospitals of Paris South

Peter Kamenický

Endocrine Physiology and Pathophysiology

Université Paris Sud : Paris 11
Inserm U1185
Peter Kamenický
Le Kremlin Bicêtre

A long tradition of basic research in molecular endocrinology and a close relationship to the hospital with access to cohorts of patients with rare endocrine disorders, favor translational efficiency and create an environment of excellence: ERN Endo-Rare, ERN Bond, CMR HYPO.

Research Brief :

Our project is centered on endocrine physiology and pathophysiology. It is based on translational research using the clinical-biological-fundamental tripod, which associates clinicians, biologists and scientists entirely dedicated to cellular and molecular endocrinology in relation to medical concerns.

We address fundamental aspects of hormone signaling describing fine mechanisms of regulation of signal transduction or transcription, characterizing hormonal or genetic abnormalities and performing clinical investigations on animal models or exceptional cohorts of patients.

Our scientific strategy focuses on three selected questions in the field of endocrine physiology and pathophysiology:

1) "Endocrine tumorigenesis" addresses two unresolved and clinically relevant questions regarding the pathophysiology of somatotroph adenomas without responsible mutations in the GNAS gene and the molecular mechanisms of their invasive behavior.

2) "Gonadal pathophysiology", studies endocrine diseases that affect hypothalamic-pituitary-gonadal function, which are responsible for abnormalities of puberty and fertility in humans. The objectives of this theme will be to discover new neuroendocrine control factors of gonadal diseases.

3) "Corticosteroid signaling in the perinatal period" will study the regulation of corticosteroid signaling pathways during the perinatal period: from their biosynthesis to the activation of their receptors (mineralocorticoid receptor and glucocorticoid).

- **Methodologies Used :**

Cellular imaging analysis,
Animal models
Genetic analyses
Hormone assays
Mass spectrocopy
Gene expression analyses
Molecular and cellular biology

Publications

Hage M, Chaligné R, Viengchareun S, Villa C, Salenave S, Bouligand J, Letouzé E, Tosca L, Rouquette A, Tachdjian G, Parker F, Lombès M, Lacroix A, Gaillard S, Chanson P, Kamenický P. (2019). Hypermethylator Phenotype and Ectopic GIP Receptor in GNAS Mutation-Negative Somatotropinomas, J Clin Endocrinol Metab. 104(5), 1777

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Key facts

Team

• Researchers : 3
• Technicians : 2
• Postdoc fellows : 1
• PhD Students : 1

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 0

International research links

• Switzerland
• USA

Keywords

• Reproduction
• Metabolisme
• Signalisation (Recepteurs nucléaires)
• Cancer
• Endocrine disruptors
• Rodent models
• C elegans
• Stem cell transplatation
• RNAseq
• Crispr/CAS9

David Volle

Environment, Metabolism, spermatogenesis, pathophysiology and inheritance

Université Clermont Auvergne
Inserm U 1103 CNRS UMR 6293
Krzysztof JAGLA
Clermont-Ferrand

Our project is located at the interface of reproductive biology and liver metabolism. It relies on the hypothesis that Csignalling pathway could alter liver and reproductive functions acting either within testis or liver directly or through bi-directional hepato-testis dialog leading to pathologies.

Research Brief :

Our aim is to elucidate the cellular and molecular mechanisms that support the harmful effects of BAs and EMs with an impact on male reproductive functions. This is a main issue to tackle since it would contribute to understand how changes in the local SSC niche environment due to EM exposures and/or altered BA metabolism could affect SSC biology and identity - to promote pathologies such as infertility, testicular germ cell tumors (TGCT), or alter germ cell quality associated with paternal transgenerational transmission of diseases. Regarding the BA signaling pathways we do analyze the involvement of the known BA receptors such as FXRa, TGR5, PXR and CAR.

• **Methodologies Used :**

* Transgenic rodent models
* Primary cell culture
* Testicular explants
* Lentivirus infection
* Spermatogonial stem cell transplantation
* Crispr/CAS9
* RNAseq
* Single Cell

Publications

Martinot E, Sèdes L, Baptissart M, Holota H, Rouaisnel B, Damon-Soubeyrand C, De Haze A, Saru JP, Thibault-Carpentier C, Keime C, Lobaccaro JA, Baron S, Benoit G, Caira F, Beaudoin C, Volle DH. (2017). The Bile Acid Nuclear Receptor FXR? Is a Critical Regulator of Mouse Germ Cell Fate., Stem Cell Reports. 9(1),

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Key facts

Team

- Researchers : 1
- Technicians : 1
- Postdoc fellows : 3
- PhD Students : 2

Translational approaches

- Patents : 2
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- Memory
- neuronal plasticity
- aging
- Energy balance
- Hormones
- behavioral tests
- stereotactic injections
- lentiviral based gene downregulation
- primary hippocampal neurons
- dendritic analysis

Franck Oury

Hormonal regulation of brain development and functions

Paris Cité University
Inserm U1151 CNRS UMR8253
Fabiola Terzi
Paris

Hormonal regulation of brain development and cognitive functions

Research Brief :

Hormones are essential factors ensuring proper regulation of our physiological functions by mediating dialogue between organs. Their broad spectrum of actions is not limited to the peripheral organs. Some hormonal factors, such as leptin, insulin, thyroid hormones, steroid hormones reach the central nervous system (CNS) where they modulate the central regulation of whole-body metabolism. Recently, it has been shown that they can also influence more intrinsic functions of the CNS, such as brain development, adult neurogenesis and cognitive functions. Importantly, increasing evidence suggests that changes in their circulating levels may contribute to age-related cognitive decline, as well as to the development of neurodegenerative diseases.
While the functional importance of hormonal factors on brain activities is undeniable, their cellular and molecular mechanisms of action are unclear. Moreover, although the brain expresses receptors for most, if not all, hormonal factors, the role(s) of many hormones in the CNS remain unexplored. Characterizing the influence of hormonal homeostasis during aging may open up new roads for therapeutic intervention to ameliorate age- and disease-related cognitive impairments, and reverse/prevents age-related memory decline.

• **Methodologies Used :**

We are currently using an interdisciplinary approach that combines
- mouse genetics
- behavioral/metabolic analyses
- Local brain stereotactic injections
- cellular and molecular methodologies
- lentiviral-based gene downregulation
- Hormonal measurements
- Primary neuronal cells-based assays
- Dendritic morphology and activity
- Collaborative translational studies

Publications

Oury, F., Sumara G, Sumara O, Ferron M, Chang H, Smith C.E, Hermo I, Suarez S, Roth B.L, Ducy P, Karsenty G (2011). Endocrine regulation of male fertility by skeleton, Cell. (),

Oury F, Khrimian L, Gardin A, Chamouni A, Goeden N, Huang Y, Lee H, Srinivas P, Gao XB, Suyama S, Mann JJ, Horvath T, Bonnin A, Karsenty G (2013). Maternal and offspring pools of osteocalcin influence brain development and functions, Cell. (),

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Oury Franck - franck.oury@inserm.fr - 0172606541 - https://www.institut-necker-enfants-malades.fr/

Key facts

Team

- Researchers : 7
- Technicians : 3
- Postdoc fellows : 0
- PhD Students : 3

Translational approaches

- Patents : 1
- Clinical research grants : 8
- Industry partnerships : 3

International research links

- USA
- Canada
- GB

Keywords

- GHRH
- Growth
- Imprinting disorders
- Insulin-Like Growth Factors
- Nutrition-metabolism
- alelespecific methylated multiplex RTQPCR
- exome sequencing
- hormone signaling
- animal experimentation
- in vitro arcuate explant cultures

Yves Le Bouc Irene Netchine

IGF system and foetal and postnatal growth

Sorbonne Université -
Université Pierre et Marie
Curie Paris 6
INSERM UMRS 938
Yves LE BOUC
Paris

Analyses of imprinting anomalies of exceptional cohorts of foetal growth disorders : Beckwith-Wiedemann Syndrome and Silver Russell Syndrome

Research Brief :

In recent years, we have identified the epigenetic mechanisms involved in abnormal fetal growth and dissected the molecular mechanisms underlying the excessive growth observed in Beckwith-Wiedemann Syndrome, which is associated with a high risk of tumor development during childhood. In this context, our patented molecule, IGF Trap, has provided proof-of-concept for the inhibition of cancer cell proliferation, raising possibilities for treatment. We have identified the primary molecular lesion responsible for intrauterine growth retardation in Russell-Silver Syndrome, mirroring the abnormality of Beckwith-Wiedemann syndrome in the IGF2 gene region. In some cases, we have identified the genetic causes (mutation, deletion, duplication at the 2 centers of the 11p1.5 imprinted region, as well as others imprinted regions) of the epigenetic abnormalities underlying these syndromes. We have also investigated the impact of the IGF system on fetal and postnatal growth and metabolism in mice and particularly the role of the impact of nutrition, which is one of the major factors stimulating IGF-I biosynthesis, in growth and in the development of the GH hypothalamic-pituitary axis during the perinatal period. Early neonatal denutrition results in a definitive retardation of postnatal growth associated with the development of cardiometabolic diseases in adult. This is associated with a delayed axon growth of the GHRH neuron, a hypomethylation of the SRIH promoter and an insulin resistance.

- **Methodologies Used :**

Imprinting genomic analysis, Allele-specific methylated multiplex RTQPCR, exome sequencing, signaling analysis, nutritional experiments in mice, arcuate explants culture, IHC, HIS

Publications

Abi Habib W, Azzi S, Brioude F, Steunou V, Thibaud N, Das Neves C, Le Jule M, Chantot-Bastaraud S, Keren B, Lyonnet S, Michot C, Rossi M, Pasquier L, Gicquel C, Rossignol S, Le Bouc Y, Netchine I. (2014). Extensive investigation of the IGF2/H19 imprinting control region reveals novel OCT4/SOX2 binding site defects associated with specific methylation patterns in Beckwith-Wiedemann syndrome., Hum Mol Genet. 23(21), 5763-73

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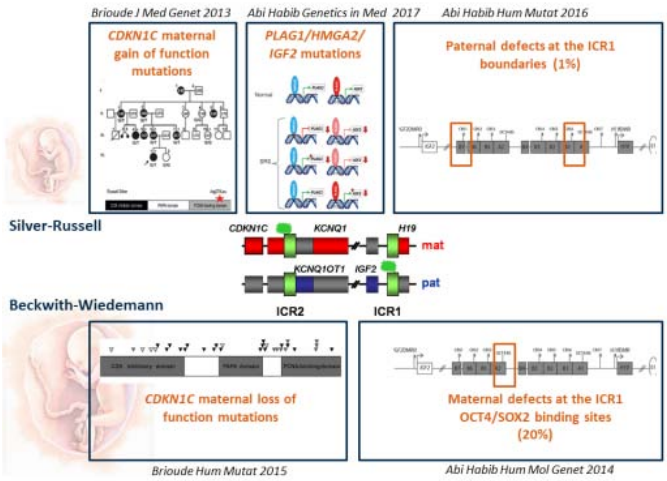
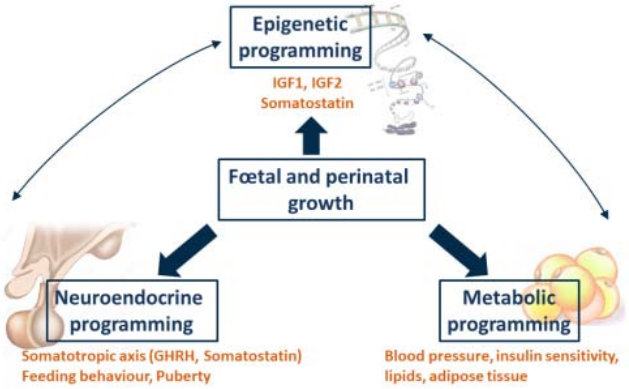
Fetal growth disorders and Imprinting abnormalities



Long term consequences of perinatal growth



Team IGF system and foetal and postnatal growth

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UMR 1011
Récepteurs Nucléaires Maladies métaboliques et Cardiovasculaires

Philippe Lefebvre

Integrated molecular analysis of gene expression in liver diseases

Université de Lille
Inserm UMR1011 Institut Pasteur UMR1011
Bart Staels
Lille

A long term, proven expertise in the field of transcriptional regulation by nuclear receptors in pathology enabling the discovery of novel regulatory mechanisms and the design of new screening tools for the pharmaceutical/biotech companies

Key facts

Team

- Researchers : 2
- Technicians : 4
- Postdoc fellows : 5
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 1

International research links

- Belgium
- Canada
- Danmark

Keywords

- Nuclear receptors
- Molecular endocrinology
- Transcription
- Epigenetics
- Molecular biology
- Cellular biology
- Biochemistry
- Epigenetics
- Molecular pharmacology

Research Brief :

Our project is focused on the investigation of molecular mechanisms controlling nuclear receptor (NR) activity in cardiometabolic diseases, in which metabolic dysregulations and inflammation play an important role. NRs are transcription factors whose transcriptional activity is regulated mostly through either small lipophilic ligands and/or post-transcriptional modifications. A significant subset of members of the NR superfamily is regulated by dietary lipids or by those originating from metabolic conversions, hence constituting central signaling nodes relaying metabolic signals to the cell genome to fine-tune cellular responses to an altered environment. NRs are thus considered as molecular relays of either deleterious or beneficial adaptative responses to metabolic inputs and, importantly, as therapeutic targets usable to decrease or at best to normalize metabolic and/or inflammatory parameters in humans. Three research areas are thus investigated, aiming at identifying (i) how RNs fulfill their role of transcriptional rheostats with respect to varying metabolic fluxes, (ii) how these functions are modified in pathological conditions and (iii) how epigenomic events, which shape the transcriptional properties of each cell, alter RN-regulated events. The translational aspect of our research involves the characterization of (dys)regulated transcriptional networks in cardiometabolic diseases, involving the interaction with several clinical teams.

- **Methodologies Used :**

*Molecular biology: mutagenesis, recombinant proteins, protein-DNA interactions; protein-protein interactions, siRNA and shRNA-mediated gene knockdown
*Transcriptional studies: reporter genes, Q-PCR, microarrays
*Epigenetic regulation: ChIP, ChIP-Seq, RNA-Seq
*Cellular Biology: Immunofluorescence, confocal microscopy, adenovirus transduction, retroviral and lentiviral transduction
*Animal models: AAV-based hepatocyte transduction; exivo bioluminescence monitoring, precision-cut liver slices
*Development of bioinformatic tools

Publications

Montaigne, D.; Marechal, X.; Modine, T.; Coisne, A.; Fayad, G.; Mouton, S.; Berthier, A.; Gheeraert, C.; Potelle, C.; Debry, N.; Souissi, Z.; Alexandre, J. , Duez, H.; Koussa, M.; Edme, J.-L.; Lefebvre, P. and Staels, B. (2017). Time-of-the day and REV-ERB alpha clock gene impact myocardial ischemic tolerance., The Lancet. 391(), 59-69

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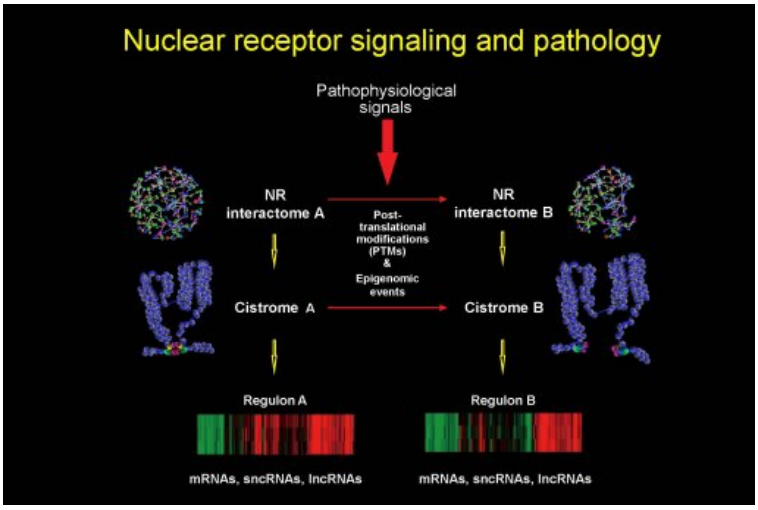
https://u1011.pasteur-lille.fr/lunite/theme-4-analyse-moleculaire-de-la-regulation-des-genes-dans-le-syndrome-cardiometabolique/

Mechanistic investigation of nuclear receptor pathophysiology



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https://u1011.pasteur-lille.fr/lunite/theme-4-analyse-moleculaire-de-la-regulation-des-genes-dans-le-syndrome-cardiometabolique/

Enzo Lalli

Mechanisms of gene expression regulation in physiopathology

Université de Nice - Sophia
Antipolis
CNRS UMR7275
Jean-Louis Nahon
Valbonne

Using an integrated approach including cell biology methods, protein structure analysis, genomics, transgenic animals and clinical studies, we aim to understand the molecular mechanisms implicated in adrenal physiopathology and to develop novel therapeutic tools.

Key facts

Team

• Researchers : 3
• Technicians : 1
• Postdoc fellows : 1
• PhD Students : 1

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 0

International research links

• USA - CNRS International Research Project (EXPOGEN-CANCER)
• Brazil - CNRS International Research Project (EXPOGEN-CANCER)
• Germany

Keywords

• endocrinology
• regulation of gene expression
• transcription factors
• cancer
• genetics
• mouse models
• cell biology
• molecular biology
• clinical studies
• pharmacology

Biological Resources

• Access to large Brazilian cohort of carriers of the germline R337H TP53 mutation
• Adrenocortical cell lines with doxycycline-inducible SF-1 overexpression
• Transgenic mice overexpressing Sf-1 in steroidogenic tissues

Research Brief :

We aim to understand the mechanisms of gene expression in endocrine physiopathology, focusing on both transcriptional and post-transcriptional regulations. Particularly, in the field of adrenocortical cancer we have described the critical role of the dosage of transcription factor SF-1 in triggering tumourigenesis, characterized genomic alterations and the patterns of mRNA and miRNA deregulation, identified critically perturbed signalling pathways and demonstrated the efficacy of novel therapeutic agents in the preclinical setting. Our most recent studies have identified the pituitary hormone prolactin as an important regulator of adrenocortical growth and hormone production in a sexually dimorphic fashion.

• **Methodologies Used :**

- cell culture
- transcriptome analysis
- ChIP-seq
- transgenic mice
- protein expression in bacterial and eukaryotic systems

Publications

Doghman-Bouguerra M, Granatiero V, Sbiera S, Sbiera I, Lacas-Gervais S, Brau F, Fassnacht M, Rizzuto R, Lalli E (2016). FATE1 antagonizes calcium- and drug-induced apoptosis by uncoupling ER and mitochondria, EMBO Rep.. 17(), 1264-1280

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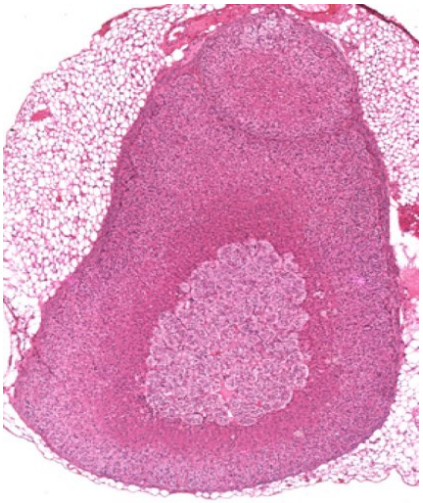
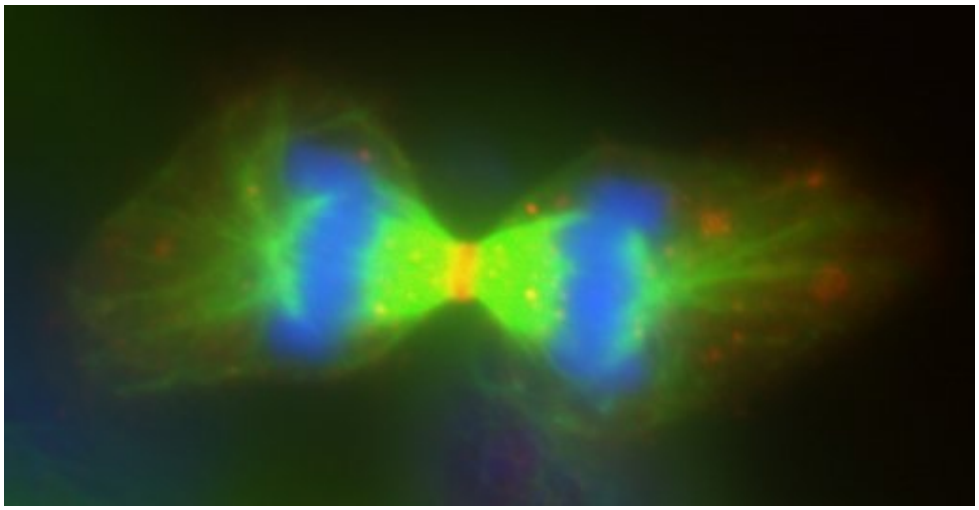
SF-1 overexpression triggers adrenocortical tumourigenesis



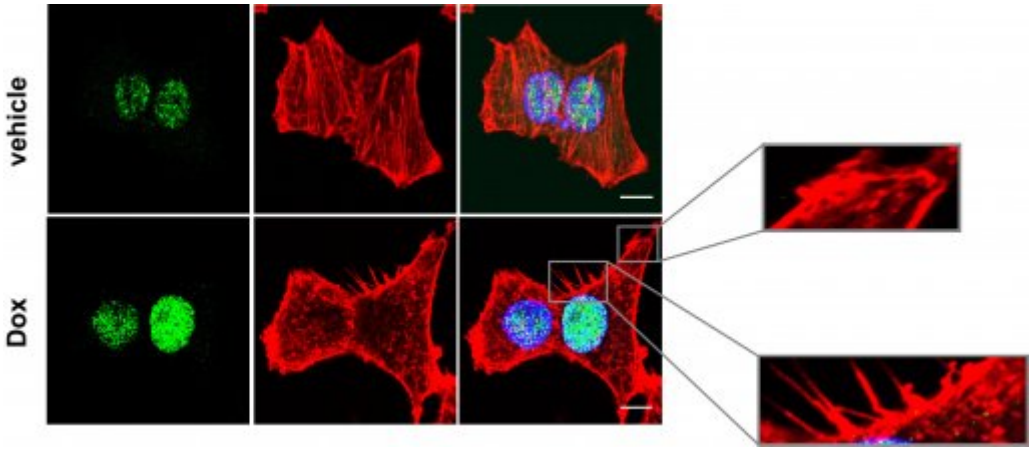
Nodule developing in the adrenal cortex of a transgenic mouse overexpressing rat Sf-1. Neoplastic cells express gonadal markers (Gata4, AMH) and are probably derived from undifferentiated adrenogonadal precursors.

Subcellular localization of phospho(Ser2448)-mTOR in mitotic adrenocortical cancer cells



The IGF-1R - mTOR pathway has a critical role in regulating proliferation of adrenocortical cancer cells. Drugs inhibiting this pathway significantly inhibit their proliferation. The specific localization of activated (Ser2448-phosphorylated) mTOR in the midbody of telophase mitotic cells suggests a role of this protein in the process of cytokinesis. Green, beta-tubulin; red, phospho(Ser2448)-mTOR; blue, DAPI staining of DNA.

Increased SF-1 dosage in adrenocortical cancer cells induces cytoskeleton remodeling



SF-1 (green) and actin cytoskeleton labeled by phalloidin (red) in H295R-TR SF-1 cells treated with either vehicle or doxycycline (Dox). SF-1 overexpression is heterogeneous in cells treated with Dox. Figure enlargements show filopodia and lamellipodia-ruffles present only in the cell with the highest SF-1 expression level.

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Patrice Mollard

NETWORKS AND RHYTHMS IN ENDOCRINE GLANDS

University of Montpellier
Inserm U1191 CNRS UMR 5203
Jean-Philippe Pin
Montpellier

Our research deals with a paramount challenge of Physiology research in the 21st century which is to understand the endocrine dialogue between the brain and peripheral organs

Key facts

Team

- Researchers : 5
- Technicians : 4
- Postdoc fellows : 1
- PhD Students : 3

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- Israel
- United Kingdom
- Germany

Keywords

- Endocrinology
- Hypothalamus-pituitary system
- Pancreas
- Hormone rhythms
- Cell networks
- Cellular in vivo imaging
- hormone Elisa assays
- genetically-modified animals
- multi-photon microscopy
- optogenetic manipulation

Biological Resources

- transgenic mouse models expressing fluorescent proteins in distinct cell types
- Cre mouse models
- ROSA26 floxed mouse models
- constitutive Cas9 mouse line
- Cre-dependent Cas9 mouse line

Research Brief :

Over the last years the research objectives of our team have converged on a long-standing yet fundamental question in endocrinology: how is the production and release of peptide hormones controlled?. Whilst in vitro studies have provided important insight into these physiological processes and the mechanisms that are dysregulated in pathology, understanding how this translates into the living organism has been challenging, especially where cell-cell interaction and dynamics have key functional roles. This is particularly relevant for the hypothalamus-pituitary system which controls reproduction, body growth and metabolism as well as pancreatic islets and their key roles in diabetes. In addition to ex vivo studies, we have engaged a multi-disciplinary in vivo approach in animal models to explore the tissue integration of individual neuron/endocrine cell function and its relationship with the vasculature in health and disease. Our strategy has been based on the development/adaptation of cellular in vivo imaging and cell activity manipulation techniques combined with newly-developed hormone assays, electrophysiological and functional studies in tractable animals with genetically-encoded fluorescent proteins/opsins, and data analysis/modelling.

- **Methodologies Used :**

Cellular in vivo imaging, longitudinal intravital imaging studies in conscious animal models, in vivo imaging in freely-moving animals with miniscopes, optogenetic manipulation, CRISPR-Cas9 technics in mouse models, selective viral infection of neuroendocrine/endocrine tissues, high-resolution mono/multiphoton microscopy, ultra-sensitive hormone Elisa assays, electrophysiology, amperometry, 3D-imaging of cleared tissues, data analysis, custom-made software, data and network modeling, biomathematics

Publications

Hodson DJ, Schaeffer M, Romano N, Fontanaud P, Lafont C, Birkenstock J, Molino F, Christian H, Lockey J, Carmignac D, Fernandez-Fuente M, Le Tissier P, Mollard P (2012). Existence of long-lasting experience-dependent plasticity in endocrine cell networks, Nat Commun.. 3(), 605

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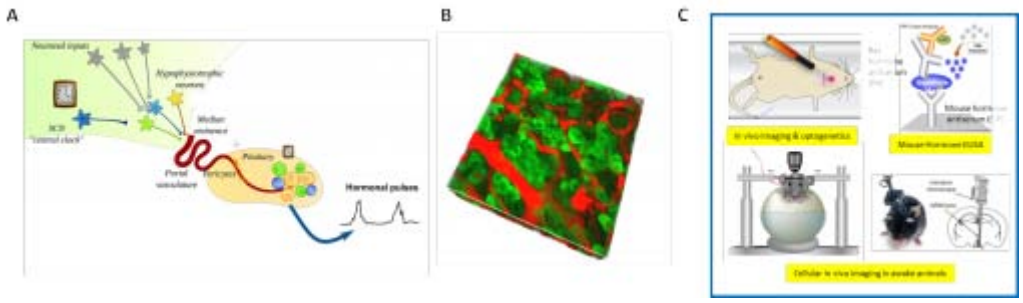
Aims and experimental strategies of the team



A. To decipher the hypothalamus-pituitary control of pituitary hormone pulses. B. To elucidate the function of the endocrine-vascular unit in health and disease. C. Techniques and tools which have been adapted/developed by the team to explore in vivo signal-transduction at single-cell resolution in combination with monitoring of hormonal outputs.

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Institut de recherche en santé, environnement et travail

Nathalie Dejucq-Rainsford

Physiology and Physioathology of the Uro-Genital Tract (UrGenT)

Université de Rennes
Inserm U1085
Michel Samson
Rennes

Key facts

Team

• Researchers : 15
• Technicians : 5
• Postdoc fellows : 2
• PhD Students : 9

Translational approaches

• Patents : 0
• Clinical research grants : 5
• Industry partnerships : 0

International research links

• European countries: Germany, Denmark, Norway...
• Switzerland/ United Kingdom
• USA

Keywords

• Uro-genital tract physiology and development
• Viral and Chemical (environmental, pharmaceutical & drugs) exposures
• Kidney and Testis Cancer
• Emerging viruses & Sexual Transmission
• Reproduction
• Ex vivo models: Organ cultures & Microfluidic
• In situ analyses & 3D microscopy
• Genomics & Single cell RNA seq
• Cellular and Molecular Biology

Biological Resources

• Collection of human uro-genital organs, adult and foetal, healthy or pathological

Our team articulates unique ex vivo models of human organs, single-cell genomics and classic biology, as well as in vivo and in silico approaches in both human and animal models to answer major public urogenital health concerns related to viral infections and chemical exposures

Research Brief :

Our scientific objectives are to address issues related to the uro-genital health, such as sexually transmissible infectious diseases and the impact of our biological and chemical environment on reproduction and uro-genital cancers (testis and kidney cancers mainly). We articulate unique ex vivo models of human fetal and adult uro-genital organs, classic biology, bulk and single-cell genomics with in vivo approaches in human cohorts and animal model and in silico approaches, to answer major public urogenital health concerns. Our team is internationally renowned as a leader for the study of the effect of urogenital viral and chemical exposures, as attested by its publications, invitations and participation to international consortiums. The team takes its strength from the combined expertise of its members in the physiology/physiopathology of the human uro-genital tract and in virology, toxicology, genomics and oncology. The efficient network of clinicians and international collaborators allows privileged access to human samples and grants.

• **Methodologies Used :**

- Culture of human uro-genital organs: adult and fetal testis, ovary and kidney; adult epididymis, prostate, seminal vesicles and colon
- In situ detection techniques: immunohistochemistry/confocal/3D microscopy; in situ hybridization (RNAscope)
- Classic cellular and molecular techniques: cell cultures; Western-Blot; flow cytometry; RT-qPCR...
- Genomics: single cell RNAseq, BRBseq, ATACseq...
- In silico approaches: developement of tools and softwares

Publications

Giulia Matusali 1 , Laurent Houzet 1 , Anne-Pascale Satie 1 , Dominique Mahé 1 , Florence Aubry 1 , Thérèse Couderc 2 3 , Julie Frouard 1 , Salomé Bourgeau 1 , Karim Bensalah 4 , Sylvain Lavoué 5 , Guillaume Joguet 6 , Louis Bujan 7 , André Cabié 8 , Gleide Avelar 9 , Marc Lecuit 2 3 10 , Anna Le Tortorec 1 , Nathalie Dejucq-Rainsford 1 (2018). Zika virus infects human testicular tissue and germ cells, J Clin Invest. (),

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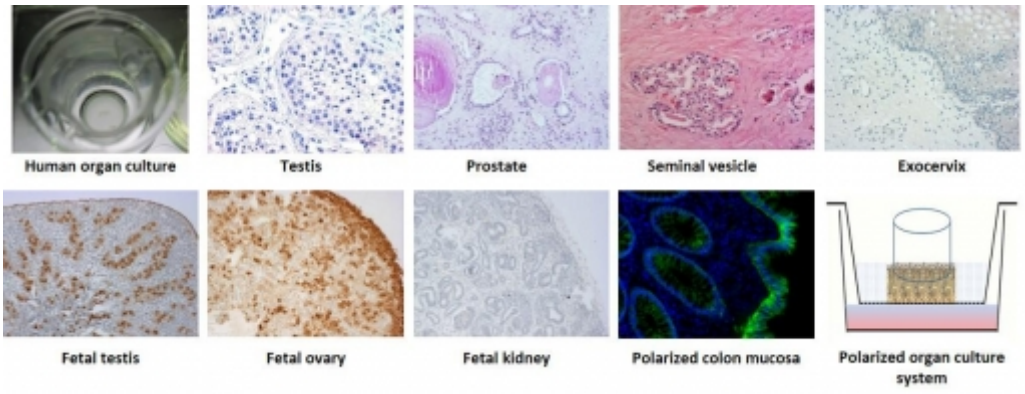
Research themes and models

Development of innovative bio-informatic softwares

Developmemt of human fetal & adult uro-genital organs ex vivo models



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Vincent Goffin

PRL/GH Pathophysiology: Translational Approaches

Université Paris Cité
Inserm U1151
Fabiola Terzi
Paris

Key facts

Team

• Researchers : 3
• Technicians : 2
• Postdoc fellows : 0
• PhD Students : 1

Translational approaches

• Patents : 1
• Clinical research grants : 1
• Industry partnerships : 4

International research links

• Austria
• Australia
• USA

Keywords

• Breast and prostate cancer
• STING/IFN signaling
• Calcium signaling and nutrition
• Stem cells
• Prolactin signaling
• recombinant proteins
• In vitro cell assays
• Signaling
• IHC
• Transgenic mice
• Gene expression studies
• FACS

Biological Resources

• Recombinant proteins of the PRL/GH family (agonists, antagonists)
• Transgenic mouse models of prostate tumorigenesis (benign, malignant)

Our lab is internationally recognized for its expertise on prolactin (all aspects)

Research Brief :

We use translational approaches to identify, understand and target cellular and molecular mechanisms responsible for the progression and/or resistance to treatment of hormone-dependent cancers (breast and prostate cancers).
Aim #1. Determine the identity of castration-tolerant prostate cell(s), decipher their regulation by/downstream of PRLR signaling, and identify new actionable targets to prevent cancer relapse leading to lethal disease.
Aim #2. Elucidate the vicious circle involving calcium signaling and tissue inflammation in prostate cancer progression, in relationship with nutritional behaviors.
Aim #3. Decipher cell-autonomous IFN-related responses to treatment of breast cancer cells to develop strategies preventing/delaying cancer relapse.

• **Methodologies Used :**

- Protein engineering (production/purification of recombinant proteins, mutagenesis)
- Cell bioassays designed for basic studies and pre-clinical studies of therapeutic compounds (proliferation, reporter genes, intracellular signaling, transcriptomic profiling)
- Phenotyping of genetically-modified mouse models, focused on prostate tumors (morphology, tissue anatomy/histology, immunohistochemistry, xenografts, stem cells, gene expression)
- Clinical studies (cohorts, genotyping, immunohistochemistry)

Publications

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Sackmann Sala, L., Boutillon, F., Menara, G., De Goyon-Pelard, A., Leprevost, M., Codzamanian, J., Lister, N., Pencik, J., Clark, A., Cagnard, N., Bole-Feysot, C., Moriggl, R., Risbridger, G. P., Taylor, R. A., Kenner, L., Guidotti, J. E., Goffin, V. (2017). A rare castration-resistant progenitor cell population is highly enriched in Pten-null prostate tumors, Journal of Pathology. 243(), 54

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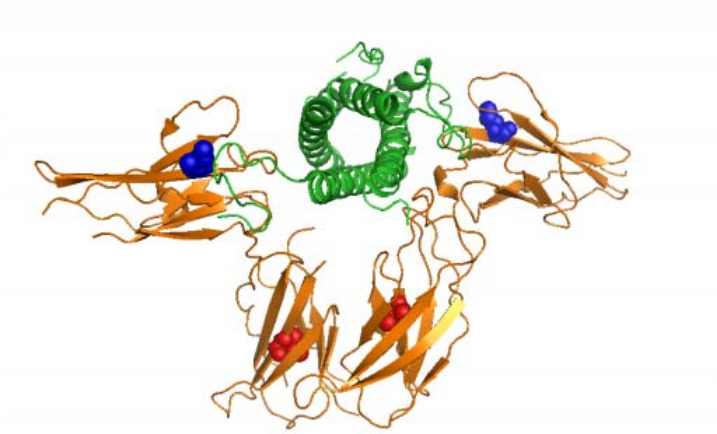
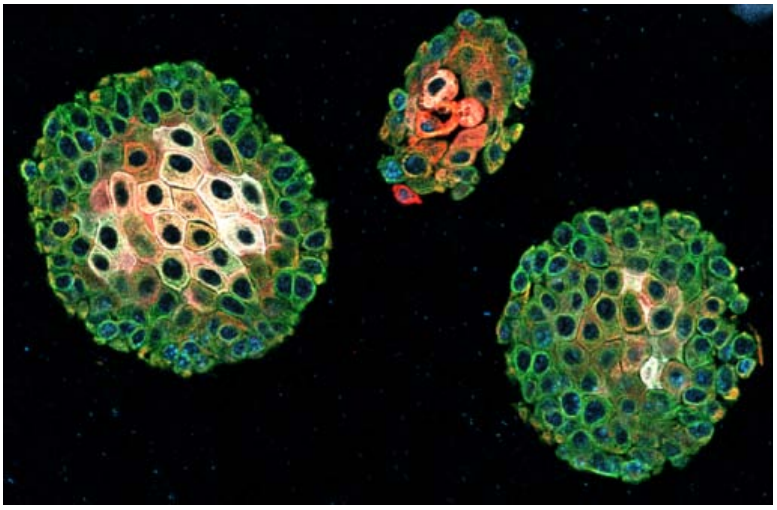
Structure of the PRL-PRL receptor complex



The crystal structure of PRL bound to its homodimerized receptor was obtained using recombinant proteins produced in the lab. On each receptor, Ile76 (blue) and Ile146 (red) are represented. Mutations of these residues confer ligand-independent receptor signaling activity. These positions correspond to natural SNPs found in the human PRL receptor.

Prostasphere generated from mouse stem cells



Sphere generation in low adherence culture media reflects the stem properties of a cell population. Each stem/progenitor cell gives rise to one sphere in which cells at various stages of differentiation can be visualized using cell-specific phenotypic markers. This figure shows prostaspheres generated after plating a population of epithelial cells dissociated from a mouse prostate. Basal cells, luminal progenitors and mature luminal cells exhibit different colors in immunoflourescence.

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Research teams with secondary association to PMN Institute

UMR Biologie du Developpement et Reproduction

Eric Pailhoux

DGP: Gonad Differentiation and its Perturbations

Universite Paris Saclay
INRA UMR1198
Corinne Cotinot
Jouy en Josas

Key facts

Team

- Researchers : 6
- Technicians : 4
- Postdoc fellows : 0
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- Sex reversal
- Gonad differentiation
- Sex determination
- Farm ruminants
- Rabbits
- Molecular biology
- Epigenetic
- Genome editing

The main originality of our team resides in the mammalian models we studied appearing quite divergent from mice according to gonadal differentiation and sexual development.

Research Brief :

The DGP team studied the genes involved in sex determination and sexual development in mammals. One of the aim of the team is to decipher the genetic pathways sustaining the main steps of gonadal differentiation (i.e.: early switch of the gonad toward testicular or ovarian development; germ cell meiosis; ovarian follicles formation; spermatogenesis) in different species of agronomical interest (mainly domestic ruminants and rabbits). Another aim of the team is to understand how these genetic pathways could be influenced by different environmental factors such as endocrine disruptors, diesel particles or maternal nutrition. The team had previously demonstrated that gonad differentiation in farm mammals used genetic pathways that differ from the widely studied mouse mammalian model.

• Methodologies Used :

As the BDR unit had a longstanding experience in reproductive biotechnologies, the team develops different strategies of additive transgenesis and, from more recently, of genome editing in domestic mammals such as goats and rabbits. By these technologies we were able to demonstrate the crucial role of the FOXL2 gene in goat ovarian differentiation; role that has been lost in the mouse model.

Publications

Daniel-Carlier N, Harscoët E, Thépot D, Auguste A, Pailhoux E, Jolivet G (2013). Gonad differentiation in the rabbit: evidence of species-specific features., PLoS One. 8(4), e60451

Boulanger L, Pannetier M, Gall L, Allais-Bonnet A, Elzaiat M, Le Bourhis D, Daniel N, Richard C, Cotinot C, Ghyselinck NB, Pailhoux E. (2014). FOXL2 is a female sex-determining gene in the goat., Current Biology. 24(4), 404-408

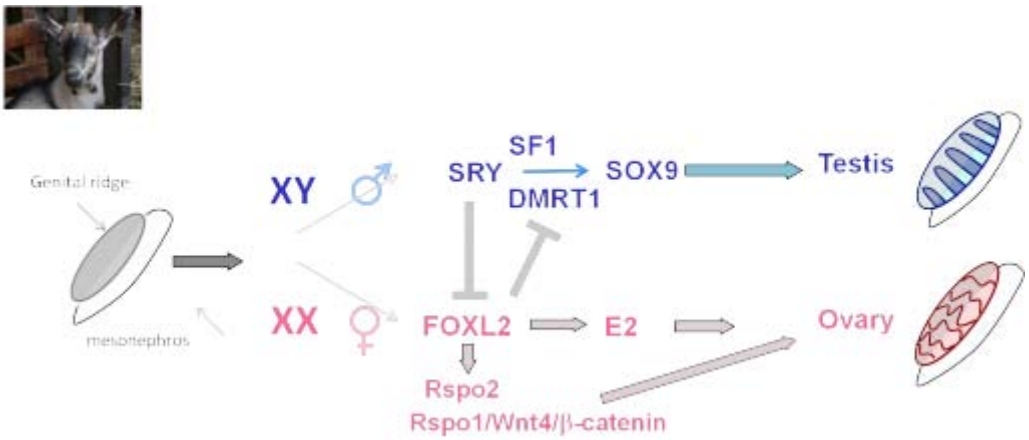
Elzaiat M, Jouneau L, Thépot D, Klopp C, Allais-Bonnet A, Cabau C, André M, Chaffaux S, Cribiu EP, Pailhoux E, Pannetier M. (2014). High-throughput sequencing analyses of XX genital ridges lacking FOXL2 reveal DMRT1 up-regulation before SOX9 expression during the sex-reversal process in goats., Biology of Reproduction. 91(6), 153

Luangpraseuth-Prosper A, Lesueur E, Jouneau L, Pailhoux E, Cotinot C, Mandon-Pépin B. (2015). TOPAZ1, a germ cell specific factor, is essential for male meiotic progression, Developmental Biology. 406(2), 158-171

Pannetier M, Chassot AA, Chaboissier MC, Pailhoux E (2016). Involvement of FOXL2 and RSPO1 in Ovarian Determination, Development, and Maintenance in Mammals., Sexual Development. 10(4), 167-184

Parma P, Veyrunes F, Pailhoux E (2016). Sex Reversal in Non-Human Placental Mammals., Sexual Development. 10(5-6), 326-344

Sex determination process in the goat species: a working model.



In goats, FOXL2 factor appears to repress the male-differentiating pathways, acting directly or not on DMRT1 gene expression. In the goat, DMRT1 may be able to promote SOX9 activation. Moreover, some clues allow the hypothesis that in addition to promoting SOX9 activation, SRY may also be involved in repressing the FOXL2gene.

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http://www6.jouy.inra.fr/bdr/Les-Recherches/Les-equipes/Differenciation-gonadique-et-ses-perturbations-DGP

Hervé Tostivint

Development and evolution of Neurosecrectory Systems

Museum National d'Histoire
Naturelle
CNRS UMR7221
Laurent Sachs
Paris

Our team studies the fonctions of neuropeptides in an evolutionary perspective

Research Brief :

Our work revolves around 3 main axes:

Evolution of multigene families of neuropeptides
Roles of the peptides of the urotensin II families
Origin, development and functions of the caudal neurosecretory system in fish

• **Methodologies Used :**

Genome editing, imaging

Key facts

Team

• Researchers : 4
• Technicians : 2
• Postdoc fellows : 0
• PhD Students : 1

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 0

International research links

• Singapore
• Sweden
• Spain

Keywords

• Neuroendocrinology
• Neuropeptides
• Evolution
• Development
• Physiology
• Zebrafish
• Xenopus
• non-conventional models
• Genome editing
• Imaging

Publications

Lambert F.M., Cardoit L., Courty E., Bougerol M., Thoby-Brissson M., Simmers J., Tostivint H., Le Ray D. (2018). Functional limb muscle innervation prior to cholinergic transmitter specification during early metamorphosis in Xenopus., eLife. 7(), e30693

Gaillard A.L., Tay B.H, Perez Sirkin D.I., Lafont A.G., De Flori C., Vissio P.G., Mazan S., Dufour S., Venkatesh B., Tostivint H. (2018). Characterization of gonadotropin-releasing hormone (GnRH) genes from cartilaginous fish: evolutionary perspectives., Frontiers in Neurosciences. 12(), 607

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Cantaut-Belarif Y, Orts Del'Immagine A, Penru M, Pézeron G, Wyart C, Bardet PL (2020). Adrenergic activation modulates the signal from the Reissner fiber to cerebrospinal fluid-contacting neurons during development., eLife. 13(), e59469

Alejevski F., Leemans M., Gaillard A.L., Leistenschneider D, de Flori C., Bougerol M., Le Mével S., Herrel A., Fini J.B., Pézeron G., Tostivint H. (2021). Conserved role of the urotensin 2 receptor 4 signaling pathway to control spine straightness in a tetrapod., Open Biology. 11(), 210065

Quan F.B., Gaillard A.L., Alejevski F., Pézeron G., Tostivint H. (2021). Urotensin II-related peptide (Urp) is expressed in motoneurons in zebrafish, but is dispensable for locomotion in larva, Peptides. 146(), 170675

Lucile Capuron

Nutrition and neurospychiatric dimensions

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Lucile Capuron
Bordeaux

we pursue animal and clinical studies in the field of nutrition and immunopsychiatry

Key facts

Team

- Researchers : 10
- Technicians : 3
- Postdoc fellows : 4
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 5
- Industry partnerships : 2

Keywords

- Depression
- Inflammation
- immunopsychiatry
- high fat diet
- Glucocorticoids
- behavior
- transcriptomics
- microdialysis
- pharmacogenetics

Research Brief :

The overarching scientific objective of the Nutripsy team is to understand how nutrition can contribute to mental health, and to identify the mechanisms by which nutritional imbalances promote the development of neuropsychiatric symptoms, focusing on inflammatory processes. For this purpose, we propose a translational and integrative research program with the following complementary specific aims:

i) to elucidate the mechanisms by which inflammation, in relation to dietary habits, leads to neuropsychiatric symptom dimensions and antidepressant resistance
ii) to determine the influence of environmental factors and genetic variants related to inflammation on depressive symptoms and antidepressant response in clinical and preclinical models of nutritional imbalances,
iii) to propose innovative personalized treatment strategies through targeted nutritional approaches guided by the clinical, biological/inflammatory, and nutritional profiles of patients.

This research program represents a critical step toward a precision medicine applied to mental health, in a context where the efficacy of standard treatments remains mitigated

- **Methodologies Used :**

behavior in rodents
clinical assesment of depression
endocrinology
genomics

Publications

Rincel M, Aubert P, Chevalier J, Grohard PA, Basso L, Monchaux de Oliveira C, Helbling JC, Lévy É, Chevalier G, Leboyer M, Eberl G, Layé S, Capuron L, Vergnolle N, Neunlist M, Boudin H, Lepage P, Darnaudéry M. (2019). Multi-hit early life adversity affects gut microbiota, brain and behavior in a sex-dependent manner., Brain Behav Immun. 80(), 179

Delgado I, Dexpert S, Sauvant J, Cryan JF, Capuron L. (2021). Influence of pro-obesogenic dietary habits on stress-induced cognitive alterations in healthy adult volunteers., Neurobiol Stress. 15(), 100353

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Moisan MP, Foury A, Dexpert S, Cole SW, Beau C, Forestier D, Ledaguenel P, Magne E, Capuron L. (2021). Transcriptomic signaling pathways involved in a naturalistic model of inflammation-related depression and its remission, Transl Psychiatry. 11(1), 203

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Gastroenterology

Pascal de Santa Barbara
Sandrine Faure

Development of the visceral smooth muscle cells and associated pathologies

Université de Montpellier
Inserm U1046 CNRS UMR9214
Alain Lacampagne
Montpellier

The team combines fundamental and translational research to identify mechanisms regulating the differentiation and plasticity of digestive smooth muscle under pathophysiological conditions in order to develop innovative therapies based on chemical synthesis and nanotechnology.

Key facts

Team

• Researchers : 10
• Technicians : 6
• Postdoc fellows : 0
• PhD Students : 3

Translational approaches

• Patents : 4
• Clinical research grants : 0
• Industry partnerships : 1

International research links

• Canada
• USA
• Hungary

Keywords

• Gastroenterology
• Smooth muscle
• Developmental biology
• Neuromuscular disorders
• Therapeutics
• Primary smooth muscle culture
• Avian in ovo misexpression approaches
• peptide-based nanoparticles
• CAM approach
• high resolution echography

Biological Resources

• Avian model
• Primary smooth muscle culture from human patients
• SPOT approach
• Human Gastrointestinal tissus from patients
• peptide-based nanoparticles
• Retroviral constructs to activate or inhibit different signaling pathways

Research Brief :

The strength of our team is based on multidisciplinary approaches (from development to physiopathology and chemical synthesis) in the gastroenterology field. Digestive motor skill results of the contraction and relaxation of smooth muscle under the control of the enteric nervous system and interstitial cells of Cajal (Faure, 2015; Chevalier, 2020). During development, the digestive mesenchymal progenitors differentiate into smooth muscle cells (SMCs) by entering sequentially into a program of determination, differentiation and maturation (McKey, 2016). SMCs do not terminally differentiate and have the ability to switch between a differentiated contractile state and a highly proliferative phenotype. In humans, the disruption of this balance and the reactivation of developmental processes are a major cause of gastrointestinal disorders (Guerin, 2020; Martire, 2021).
Our team showed that the BMP, FGF, NOTCH and HIPPO pathways control the differentiation of SMCs and their plasticity (Le Guen, 2015). Our objectives are to better characterize the underlying mechanisms, with a particular emphasis on mitochondrial metabolic regulation and to identify the pathways that govern SMC maturation and the establishment of digestive motor skill. We are evaluating the importance of the identified mechanisms in functional pathologies (pediatric and adult) and sarcomas to develop targeted approaches (Boisguerin, 2020) in order to improve SMC differentiation and functionality.

• **Methodologies Used :**

- Cell (smooth muscle cells) and organ (gastrointestinal tract) cultures
- Embryological approaches
- Development of avian retroviral vectors
- Misexpression of gene into the digestive tract in vivo (cDNAs or ShRNAs)
- Gene expression profilin, in situ hybridization and immunohistochemistry
- peptide-based nanoparticles
- SPOT approach
- CAM approach

Publications

Notarnicola C, Rouleau C, Le Guen L, Virsolvy A, Richard S, Faure S, De Santa Barbara P (2012). The RNA-binding protein RBPMS2 regulates development of gastrointestinal smooth muscle., Gastroenterology. 143(3), 687-97.e1-9

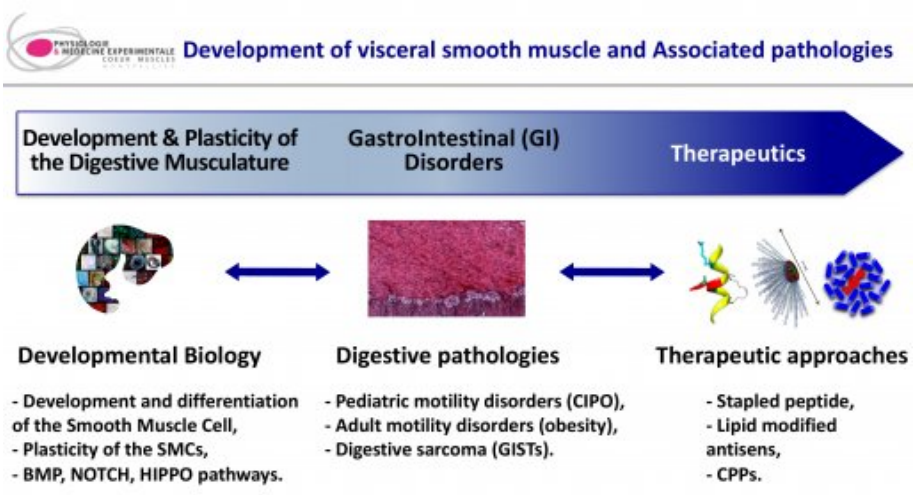
Sagnol S, Yang Y, Bessin Y, Allemand F, Hapkova I, Notarnicola C, Guichou JF, Faure S, Labesse G, de Santa Barbara P (2014). Homodimerization of RBPMS2 through a new RRM-interaction motif is necessary to control smooth muscle plasticity, Nucleic Acids Res. 42(15), 10173-84

Faure S, McKey J, Sagnol S, de Santa Barbara P. (2015). Enteric neural crest cells regulate vertebrate stomach patterning and differentiation, Development. 142(2), 331-42

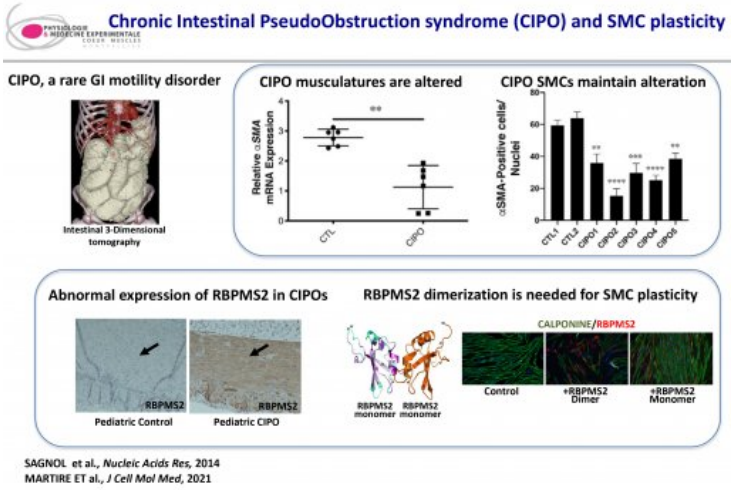
McKey J, Martire D, de Santa Barbara P, Faure S. (2016). LIX1 regulates YAP1 activity and controls the proliferation and differentiation of stomach mesenchymal progenitors, BMC Biol. 14(), 34

Chevalier NR, Ammouche Y, Gomis A, Teyssaire C, de Santa Barbara P, Faure S (2020). Shifting into high gear: how interstitial cells of Cajal change the motility pattern of the developing intestine, Am J Physiol Gastrointest Liver Physiol. 319(4), G519-G528

Martire D, Garnier S, Sagnol S, Bourret A, Marchal S, Chauvet N, Guérin A, Forgues D, Berrebi D, Chardot C, Bellaiche M, Rendu J, Kalfa N, Faure S, de Santa Barbara P. (2021). Phenotypic switch of smooth muscle cells in paediatric chronic intestinal pseudo-obstruction syndrome, J Cell Mol Med. Mar 3.. (),

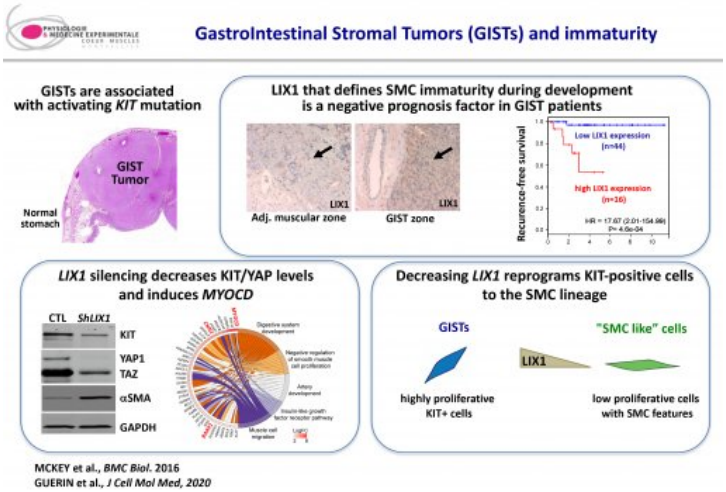


Because tissue plasticity in gastrointestinal disorders involves the reactivation of developmental processes, developmental studies of the process regulating the differentiation of mesenchymal progenitors into SMCs have proven to be useful in identifying the molecular mechanisms involved in the regulation of digestive musculature plasticity in pathological conditions in order to develop innovative therapies to restore smooth muscle differentiation and functionality.



SAGNOL et al., *Nucleic Acids Res*, 2014
MARTIRE ET al., *J Cell Mol Med*, 2021

Chronic constipation constitutes an extremely frequent symptom of consultation in the pediatric discipline. We demonstrated that SMC differentiation is impaired in CIPO patients. We showed that RBPMS2 protein is highly expressed in CIPO smooth muscle and that RBPMS2 homodimerization is a pre-requite to bind its RNA targets and protein partners to achieve its function, highlighting the mechanisms that control the dedifferentiation process as source of therapeutic targeting.



MCKEY et al., *BMC Biol*. 2016
GUERIN et al., *J Cell Mol Med, 2020*

GISTs are the most common mesenchymal tumors of the GI tract that originate from ICCs or their mesenchymal progenitor cells common to the ICCs/SMCs. During development, LIX1 regulates the proliferation of digestive mesenchymal cells. High LIX1 expression is associated with unfavorable prognosis in GIST patients. LIX1 silencing suppresses KIT and YAP/TAZ in GIST cells and promote their differentiation toward a SMC feature. These identify LIX1 as an attractive target for GIST therapeutics.

Laurent Dubuquoy David Launay

INFINITE - Institute for Translational Research in Inflammation

Université de Lille
Inserm U1286 CHU Lille U1286
Laurent Dubuquoy
Lille

Key facts

Team

- Researchers : 51
- Technicians : 39
- Postdoc fellows : 12
- PhD Students : 27

Translational approaches

- Patents : 10
- Clinical research grants : 30
- Industry partnerships : 20

International research links

- Belgium
- USA
- Spain

Keywords

- Pathophysiology
- Inflammatory diseases
- Environmental factors
- Regeneration
- Immunity
- Immunohistochemistry
- Molecular biology
- Microbiology
- Cellular biology
- Animal models

Biological Resources

- Autoimmune diseases (scleroderma, lupus, ...) biobank
- Intestinal organoids
- Inflammatory bowel diseases biobank
- Alcoholic liver disease biobank
- Adherent Invasive Escherichia coli (AIEC) collection

The Institute for Translational Research in Inflammation (INFINITE) seeks to understand the origins, mechanisms and consequences of chronic inflammation and to develop innovative treatments and biomarkers in the field of chronic inflammatory diseases.

Research Brief :

Infinite is a unified institute devoted to the study of inflammation, from its origins to its consequences. We use digestive and systemic inflammatory diseases as models to assess the origin of inflammation, its pathophysiology, and its consequences (fibrosis and impaired regeneration). We are developing new drugs, therapeutic strategies, and biomarkers. Each model and each project will benefit from INFINITE's complementary, cross-disciplinary skills (complementary medical and scientific skills) to characterize the causes and consequences of chronic inflammation. The close relationship between INFINITE and the FHU/clinical departments ensure that scientists have access to biological resource centers and well-defined cohorts of patients with chronic inflammatory diseases. This enables high-level translational research, which is INFINITE's hallmark.
Our program is built on scientific questions organized into four interconnected WPs exploring the origins of inflammation (environment, microbes) (WP1), the mechanisms of chronic inflammation, impaired regeneration (WP2), fibrosis (WP3), and innovative therapeutic and diagnostic approaches (WP4). The WPs are strongly inter-connected with interactions between environmental factors/microbes, epithelial cells, the mucosal barrier and the immune system, leading to the development of innovative treatments and diagnostic tools.

- **Methodologies Used :**

- Animal models of colitis (TNBS, DSS, HLAB27 Tg...), hepatitis (CCl4, ConA, Ischemia/reperfusion...), experimental fibrosis, transgenic/ KO mucin
- Cellular models of intestinal epithelium (Caco2, HT29, organoid...), Liver (hepatocyte, progenitor...), skin (fibroblasts), and immune cells (PMN, macrophages, lymphocytes...)
- ex-vivo models (organoids, embryo explants, precision cut tissus slices)
- Molecular biology (Q-PCR, plasmids, Transfection, ShRNA...)
- Histology, immunohistochemistry and imaging
- Immunology (FACS, phenotyping...)
- Microbiology (culture, metagenomic...)
- Drug discovery (chemisty, molecular modelisation)
- Epimad, the world's largest registry of inflammatory bowel disease
- Translational approaches
- Clinical trials

Publications

Ley D, Desseyn JL, Gouyer V, Plet S, Tims S, Renes I, Mischke M, Gottrand F (2019). Early life nutrition influences susceptibility to chronic inflammatory colitis in later life, Sci Rep. 9(1), 18111

Demaret J, Lefèvre G, Vuotto F, Trauet J, Duhamel A, Labreuche J, Varlet P, Dendooven A, Stabler S, Gachet B, Bauer J, Prevost B, Bocket L, Alidjinou EK, Lambert M, Yelnik C, Meresse B, Dubuquoy L, Launay D, Dubucquoi S, Montaigne D, Woitrai E, Maggiotto F, Bou Saleh M, Top I, Elsermans V, Jeanpierre E, Dupont A, Susen S, Brousseau T, Poissy J, Faure K, Labalette M, Lille Covid Research Network (LICORNE) (2020). Severe SARS-CoV-2 patients develop a higher specific T-cell response, Clin Transl Immunology. 9(12), e1227

Bou Saleh M, Louvet A, Ntandja-Wandji LC, Boleslawski E, Gnemmi V, Lassailly G, Truant S, Maggiotto F, Ningarhari M, Artru F, Anglo E, Sancho-Bru P, Corlu A, Argemi J, Dubois-Chevalier J, Dharancy S, Eeckhoute J, Bataller R, Mathurin P, Dubuquoy L (2021). Loss of hepatocyte identity following aberrant YAP activation: A key mechanism in alcoholic hepatitis, J Hepatol. 75(4), 912-923

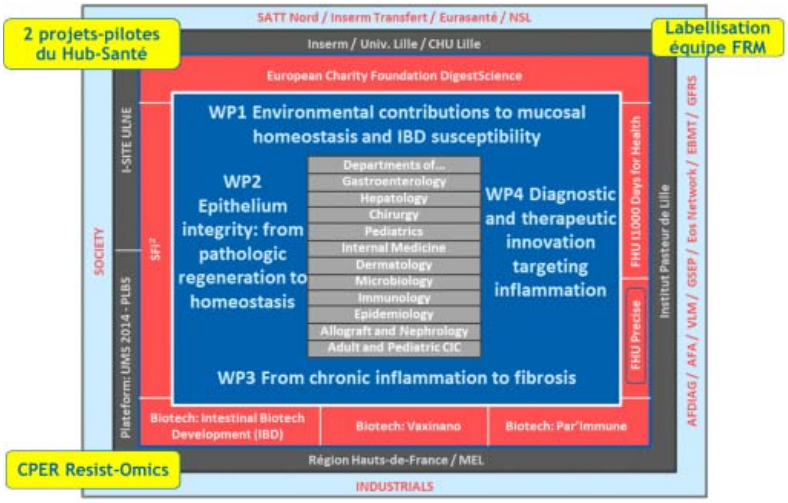
Chepy A, Vivier S, Bray F, Ternynck C, Meneboo JP, Figeac M, Filiot A, Guilbert L, Jendoubi M, Rolando C, Launay D, Dubucquoi S, Marot G, Sobanski V (2022). Effects of Immunoglobulins G From Systemic Sclerosis Patients in Normal Dermal Fibroblasts: A Multi-Omics Study, Front Immunol. 29(13), 904631

Djouina M, Vignal C, Dehaut A, Caboche S, Hirt N, Waxin C, Himber C, Beury D, Hot D, Dubuquoy L, Launay D, Duflos G, Body-Malapel M (2022). Oral exposure to polyethylene microplastics alters gut morphology, immune response, and microbiota composition in mice, Environ Res. 212(Pt B), 113230

Leleu-Chavain N, Regnault R, Ahouari H, Le Biannic R, Kouach M, Klupsch F, Magnez R, Vezin H, Thuru X, Bailly C, Goossens JF, Millet R (2022). Antioxidant Properties and Aldehyde Reactivity of PD-L1 Targeted Aryl-Pyrazolone Anticancer Agents., Molecules. 27(10), 3316

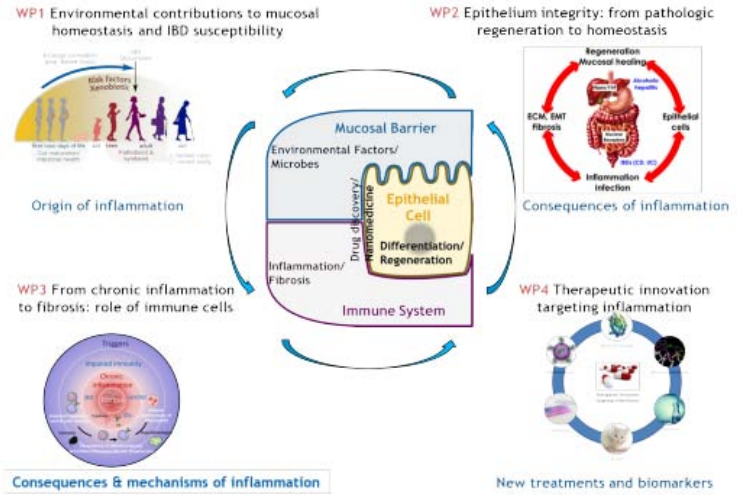
Dubuquoy Laurent - laurent.dubuquoy@inserm.fr - +33(0)320974208 - http://lille-inflammation-research.org/fr/

Infinite environment



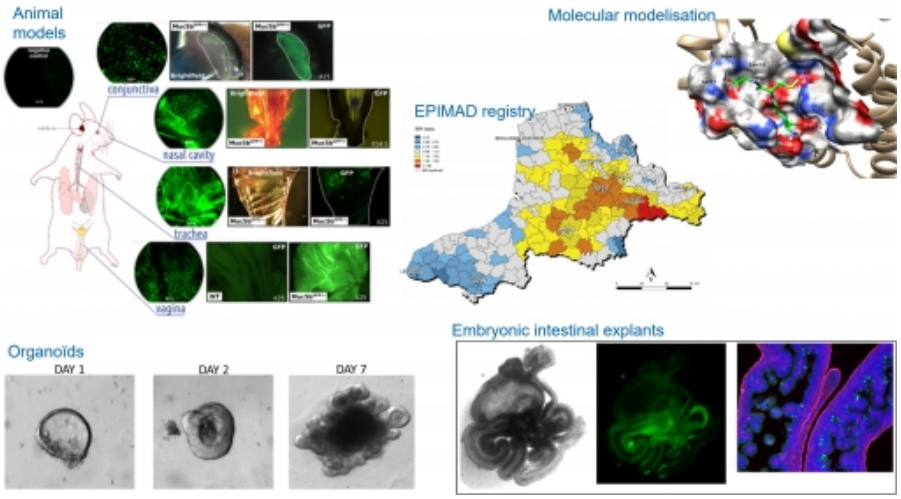
In blue, INFINITE composed of 4 WPs.
A well-structured, integrated, multidisciplinary institute that interacts strongly with its environment

Infinite structuration



INFINITE seeks to understand the origins, mechanisms and consequences of chronic inflammation and to develop innovative treatments and biomarkers in the field of chronic inflammatory diseases

Infinite innovatives tools, models and approaches



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Nathalie Vergnolle

Pathophysiology of the intestinal epithelium

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Inserm U1220 INRA UMR 1416
Nathalie Vergnolle
Toulouse

The team, composed of nine researchers (physiologists, pharmacologists, geneticians) and one clinician gastroenterologist, has a strong expertise on several cellular actors of the intestine: epithelial cells, enteric neurons, immune cells of the lamina propria, intestinal stem cells and fibroblasts.

Key facts

Team

- Researchers : 9
- Technicians : 4
- Postdoc fellows : 3
- PhD Students : 4

Translational approaches

- Patents : 2
- Clinical research grants : 1
- Industry partnerships : 4

International research links

- Canada
- USA
- Italy

Keywords

- Inflammation
- Intestinal stem cells
- Irritable Bowel Syndrome
- Inflammatory Bowel Disease
- Pain
- 3D organoids
- Proteases
- Culture of human and murine intestinal organoids
- Primary cultures of sensory neurons (human and murine)
- In vivo models of acute and chronic colitis (DSS, TNBS, CD45RB high, IL10, etc...)
- In vivo models of somatic and visceral pain and electrography measures of pain
- In vivo and in vitro gene overexpression and silencing

Biological Resources

- Biobanks: Colonic biopsies from controls, IBS, IBD and colon cancer patients
- Human sensory neurons
- Murine neurons
- In vitro models: Colonic organoids
- Colonic epithelial cell cultures
- Measurements of PAR activatiopn in cell models

Research Brief :

We study the mediators released in chronic intestinal diseases with a focus on inflammation, infection, pain-associated pathologies and carcinogenesis. Our ultimate goal is to highlight new therapeutic targets for the treatment of intestinal diseases.
More specifically, we investigate:
- the type of proteases released by inflamed tissues and the pathophysiological effects of these proteases on epithelial barrier function, and in different other cell types involved in the inflammatory response: epithelial cells, leukocytes, monocytic cells, neurons and fibroblasts
- the mechanisms by which pathogens induce host?s protease release upon infection, and the role of proteases as mediators of host immune response
- the effects of proteases on the transmission of pain message and visceral hypersensitivity symptoms, in the context of irritable bowel syndrome and functional disorders
- the involvement of Protease Activated Receptors (PAR) in carcinogenesis pathways, their crosstalk with integrin signaling in intestinal stem cells
- the effects of the microenvironment of the colon crypts in the transition of the crypts to pre-cancerous and cancerous status, this work involves the study of immune cells, fibroblasts, but also of the enteric nervous system
- the effects of nanoparticules on epithelial barrier function and the induction of carcinogenesis
- the therapeutic potential of protease inhibitors in intestinal pathologies

Methodologies Used :

- Culture of human and murine intestinal organoids
- Primary cultures of sensory neurons (human and murine)
- Co-culture systems of host epithelial cells and pathogens
- in vivo models of acute and chronic colitis (DSS, TNBS, CD45RB high, IL10, etc...)
- in vivo models of somatic and visceral pain and electrography measures of pain
- In vivo and in vitro gene overexpression and silencing
- Intestinal stem cell isolation
- Ussing chambers
- Protease identification and characterization
- Protease-Activated receptor pharmacology
- mRNA and protein expression studies
- Immunohistochemistry
- In vitro recombinant protein production

Publications

Motta, J.P., Magne, L., Descamps, D., Rolland, C., Squarzoni-Dale, C., Rousset, P., Martin, L., Cenac N., Balloy, V., Huerre, M., Jenne, D., Wartelle, J., Belaaouaj, A., Mas, E., Vinel J.P., Alric, L., Chignard, M., Vergnolle, N. & Sallenave J.M. (2011). Modifying the protease/anti-protease expression pattern by elafin over-expression protects mice from colitis, Gastroenterology. (),

Motta, JP., Bermudez-Humaran, L Deraison, C Martin, L., Rolland, C., Rousset, P., Chapman, K., Vinel, JP., Alric, L., Mas, E., Sallenave, JM., Langella, P., Vergnolle, N. (2011). Food-Grade Bacteria Expressing Elafin Protect Against Inflammation and Restore Colon Homeostasis, Science translational medicine. (),

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Cenac N, Bautzova T, Le Faouder P, Veldhuis NA, Poole DP, Rolland C, Bertrand J, Liedtke W, Dubourdeau M, Bertrand-Michel J, Zecchi L, Stanghellini V, Bunnett NW, Barbara G, Vergnolle N. (2015). Quantification and potential functions of endogenous agonists of Transient Receptor Potential channels in patients with Irritable Bowel Syndrome., Gastroenterology. (),

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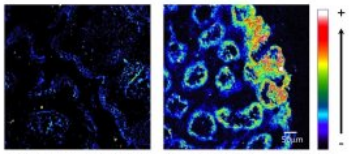
Axis 1 « Understand the role of proteolytic homeostasis in the gut »

1- Identification of proteases and protease inhibitors present in pathologies

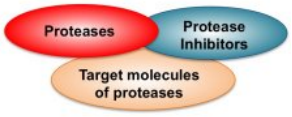
2- Study of the role of proteolytic actors in intestinal pathologies

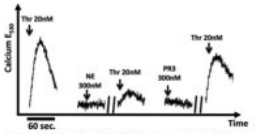
3- Role of proteolytic actors in epithelial cell-neighboured cell interactions

4- Therapeutic intervention



In situ zymography of proteolytic (here, elastolytic) activity in human intestinal tissues from healthy controls (CTR) and Crohn's disease (CD) patients. The intensity of colors is representative of the intensity of proteolytic activity.





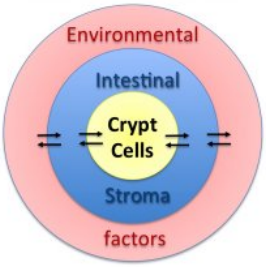
Traces showing cytoplasmic calcium release in response to Protease-Activated Receptor cleavage by active proteases

Axis 2 « Intestinal Stem Cells »

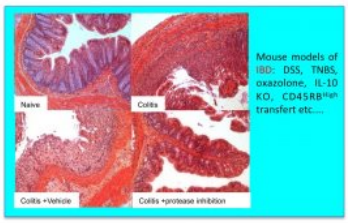
1- Identification of cellular and molecular events involved in colon tumor initiation

2- Understanding the impact of (micro)environmental alterations on the crypt cells

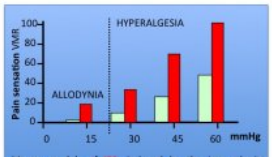
3- Identification of new colorectal cancer biomarkers and therapeutic targets



Axis 3 « Models of intestinal pathologies »

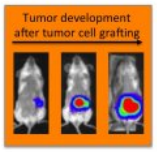


Mouse models of IBD: DSS, TNBS, oxazolone, IL-10 KO, CD45RB^{High} transfert etc....



Mouse models of IBS: induced by the intracolonic administration of supernatants from IBS patient biopsies (red), compared to the effects of supernatants from healthy control biopsies (light green).
Other models include water avoidance stress and post-infectious (*citrobacter rodentium*) hypersensitivity models.

Develop 3D cultures of human colon "organoïds" that mimics molecular and cellular *in vivo* complexity to test therapeutic approaches.



Vergnolle Nathalie - nathalie.vergnolle@inserm.fr - +33562744500 - http://en.irsd.fr/team-1-pathophisiology-of-the-intestinal-epithelium.html

Audrey Ferrand

Intestinal Epithelium and Environment Interactions

Université Paul Sabatier
Toulouse III
Inserm U1220 INRA U1416
Nathalie Vergnolle
Toulouse

We recently patented a human-based colon microphysiological system combining 3D scaffold and microfluidic addressing and allowing to study the tissue (functions, architecture...). It is a great tool to study microbiota and nutrients impacts on the gut epithelium as well as drug screening.

Key facts

Team

- Researchers : 4
- Technicians : 3
- Postdoc fellows : 1
- PhD Students : 2

Translational approaches

- Patents : 1
- Clinical research grants : 1
- Industry partnerships : 3

Keywords

- Intestinal Stem Cells
- Stroma
- Cancer Initiation
- Inflammatory Bowel Disease
- Familial Adenomatous Polyposis
- 3D colon organoids (Human and Murine)
- Microphysiological System (gut-on-chip)
- In vivo models of acute and chronic colitis
- Human colon fibroblasts primary cultures
- High Content Screening

Biological Resources

- Biobank of human colon biopsies, 3D organoids and fibroblast primary cultures
- Crohn disease mice model (NOD2 KO)
- Ulcerative colitis mice model (IL10 KO + NOX KO)

Research Brief :

The team, composed of 3 researchers (physiologist, pharmacologist, cell biologist) and 4 clinician (gastroenterologists), has a strong expertise on cellular actors of the intestine: epithelial cells (especially intestinal stem cells), fibroblasts and immune cells of the lamina propria.
The intestinal epithelium is one of the main barrier between our body and the external world. It allows the absorption of nutrients, salts and water while providing protection against harmful luminal contents. Intestinal epithelium cells are renewed every 5 days, putting the intestinal linen under significant stress in the control of proliferation, differentiation and cellular organization. Intestinal turnover is tightly controlled. It depends on the spatial organization of the signals emanating from the mesenchymal support cells, mainly fibroblasts surrounding the crypt. Homeostasis, and thus the integrity of the intestinal epithelium, is constantly challenged by 'external' environmental factors in the intestinal lumen (food additives, nutritional compounds...) or 'internal' (stromal cells and extracellular matrix). Any alteration of intestinal homeostasis will favor in the establishment of chronic inflammatory bowel disease (IBD) and tumor transformation. By combining morphological, functional, pharmacological & organ-on-chip approaches to 3D cell primocultures of colorectal organoids and fibroblasts, and to IBD murine models, we study environmental impacts on the intestinal pathophysiology.

- **Methodologies Used :**

- Culture of human and murine intestinal organoids
- Primary cultures of sensory neurons (human and murine)
- Co-culture systems of host epithelial cells and stromal and immune cells
- in vivo models of acute and chronic colitis (DSS, TNBS, CD45RB high, IL10, etc...)
- In vivo and in vitro gene overexpression and silencing
- Imaging (Confocal, SPIM, HCS, FLIM...)
- In silico tissue architecture modelling
- Ussing chambers

Publications

Devaud C, Tilkin-Mariamé AF, Vignolle-Vidoni A, Souleres P, Denadai-Souza A, Rolland C, Duthoit C, Blanpied C, Chabot S, Bouillé P, Lluel P, Vergnolle N, Racaud-Sultan C, Ferrand A. (2019). FAK alternative splice mRNA variants expression pattern in colorectal cancer., Int. J. Cancer. (),

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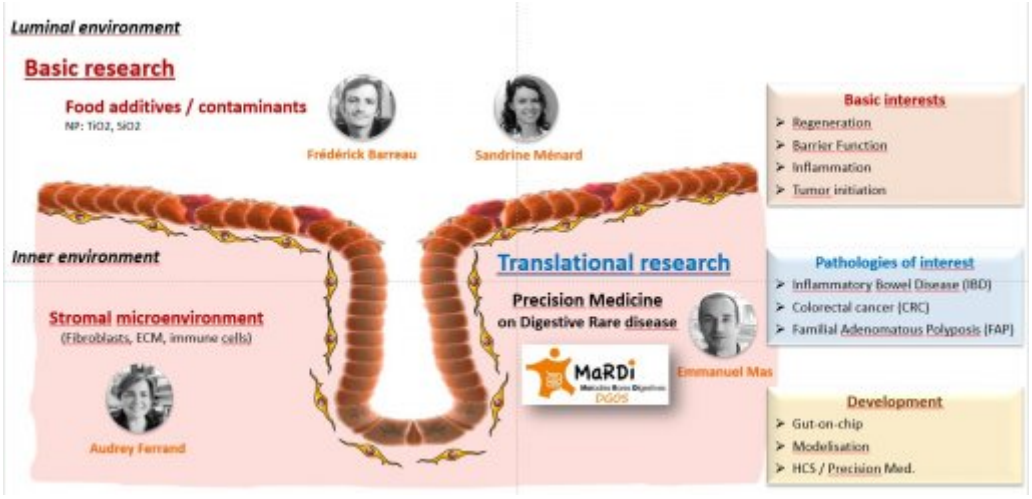
Interactions between the intestinal epithelium and environment - Team overview



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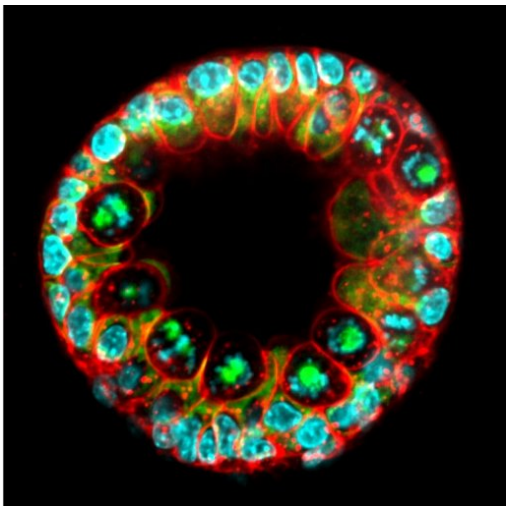
3D human colon columnar organoid



Green: Tubulin, Red: Membranes, Blue: Nuclei

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Key facts

Team

• Researchers : 4
• Technicians : 2
• Postdoc fellows : 1
• PhD Students : 8

Translational approaches

• Patents : 2
• Clinical research grants : 0
• Industry partnerships : 2

International research links

• Canada
• UK
• Belgium

Keywords

• Gut to Brain axis
• Functional gastrointestinal disorders
• Intestinal microbiota
• Diabetes
• Intestinal inflammatory diseases
• Primary cell culture (DRG neurons, lymphocytes, monocytes, dendritic cells, mast cells..)
• Tissue- and microbial-derived lipids
• Real-time measurement of reactive oxygen and nitrogen species
• Intestinal contraction (telemetry, isotonic)
• Pharmacology

Biological Resources

• Animal models of colitis
• Animal models of visceral pain
• Animal models of metabolic disorders

Gilles Dietrich

Physiopathology Of the Gut-Brain Axis (POGBA)

Université Paul Sabatier
Toulouse III
Inserm U1220
Nathalie Vergnolle
Toulouse

The team, composed of 2 researchers and 2 professors of University, has a strong expertise on the enteric nervous system and intestinal mediators (hormones, neuropeptides, cytokines, bioactive lipids ...) originating from both host's cells (epithelial, nervous and immune cells) and microbiota.

Research Brief :

Intestinal inflammation often results in abdominal pain, intestinal hypercontractility and metabolism alterations including chronic hyperglycemia. Our research group in neuro-gastroenterology primarily aims at deciphering the endogenous mechanisms of regulation of visceral pain and digestive functions in the context of intestinal inflammation including endocrine and metabolic disorders such as obesity and diabetes.
Our research aims at:
- Identifying lipid compounds produced by the intestinal flora and involved in the regulation of pain and intestinal inflammation
- Better understanding the mechanisms of endogenous regulation of pain and intestinal inflammation by immune cell-derived opioids
- Better understanding the effects of intestinal mediators including immune cell-derived opioids and microbiota-derived compounds on the gut-brain axis and their consequences on glucose metabolism and insulin resistance

• **Methodologies Used :**

Primary culture (Immune cells, neurons)
Cell imaging
Cytometry (multi-staining analysis, cell sorting)
Cell biology
Molecular biology (Q RT-PCR...)
Pain measurement in vivo (visceromotor response to colorectal distention, von Frey filaments)
Identification and quantification of lipids by mass-spectrometry
Primary human/mouse sensory neurons and mast cells cultures
Lipids and glucose metabolism (in vitro & in vivo)
Pharmacological studies in vitro and in vivo
Real time NO and H2O2 release in tissues in vivo and cell culture

Publications

Fournel, A., Drougard, A., Duparc, T., Marlin, A., Brierley, S.M., Castro, J., Le-Gonidec, S., Masri, B., Colom, A., Lucas, A., Rousset, P., Cenac, N., Vergnolle, N., Valet, Ph., Cani, P.D, Knauf, C. (2017). Apelin targets gut contraction to control glucose metabolism via the brain, Gut. 66(), 258-269

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Anne Abot, Eve Wemelle, Claire Laurens , Adrien Paquot, Nicolas Pomie, Deborah Carper, Arnaud Bessac, Xavier Mas Orea, Christophe Fremez, Maxime Fontanie, Alexandre Lucas, Jean Lesage, Amandine Everard, Etienne Meunier, Gilles Dietrich, Giulio G Muccioli, Cedric Moro, Patrice D Cani, Claude Knauf (2021). Identification of new enterosynes using prebiotics: roles of bioactive lipids and mu-opioid receptor signalling in humans and mice, Gut. 70(), 1078-1087

Julien Pujo, Camille Petitfils, Pauline Le Faouder, Venessa Eeckhaut, Gaelle Payros, Sarah Maurel, Teresa Perez-Berezo, Matthias Van Hul, Frederick Barreau, Catherine Blanpied, Stephane Chavanas, Filip Van Immerseel, Justine Bertrand-Michel, Eric Oswald, Claude Knauf, Gilles Dietrich, Patrice D Cani, Nicolas Cenac (2021). Bacteria-derived long chain fatty acid exhibits anti-inflammatory properties in colitis, Gut. 70(), 1088-1097

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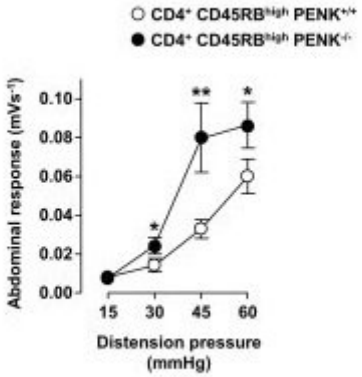
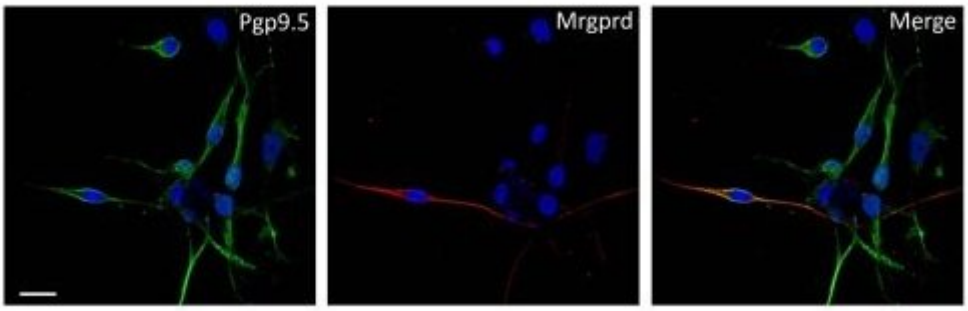
Endogenous regulation of visceral inflammatory pain by T cell-derived opioids



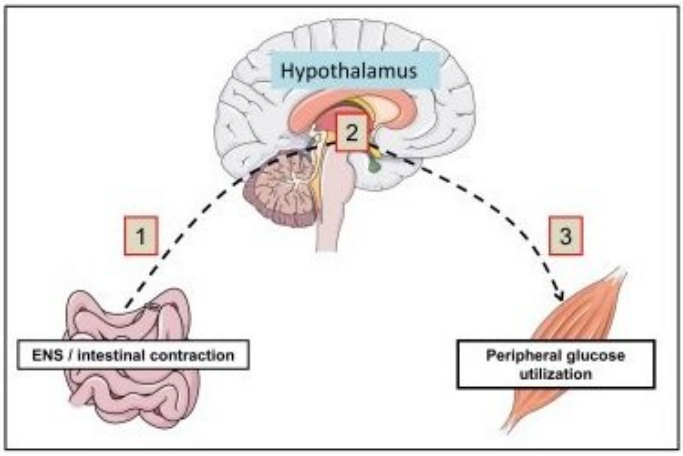
T cell-derived opioids act on mucosal immune cells and enteric nervous system (ENS) including extrinsic afferent sensory neurons (visceral pain). The figure shows colonic sensitivity to colorectal distension of RAG-2-/- mice 5 weeks after adoptive transfer of CD4+CD45RBhigh T lymphocytes from wild-type (white) or proenkephalin (PENK)-knockout mice (black). Abdominal muscle contraction was recorded in response to distension pressure of 15, 30, 45 and 60 mmHg. Data are expressed as mean ± SEM.

Fatty acids produced by the host's intestinal cells and microbiota regulate visceral pain



The long-chain fatty acid, 5-oxoETE found in colon of irritable bowel syndrome patients activates sensory neurons expressing MAS-related G protein coupled receptor D. Expression of Mrgprd (in red) in primary culture of human sensory neurons identified by the pan-neuronal marcker Pgp9.5 (in green; scale bar = 10 µm)

Impact of intestinal cells and microbiota on gut-brain axis



Modulation of ENS/duodenal contractions induces afferent signal (1) which modifies hypothalamic activity (2) and, as a result, glucose utilization in tissues (3). Intestinal motility may be modulated by a number of factors including (neuro)peptides, lipids and lipopeptides released by host's cells and/or microbiota

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Key facts

Team

• Researchers : 18
• Technicians : 18
• Postdoc fellows : 4
• PhD Students : 6

Translational approaches

• Patents : 6
• Clinical research grants : 2
• Industry partnerships : 15

International research links

• Europe (Spain, Belgium, Italy, United Kingdom, Switzerland, Denmark, Ireland)
• Other : Canada, Australia, Thailand, Chile

Keywords

• Gut microbiota (metabolism, dysbiosis)
• Zoonotic enteric pathogens
• Therapeutic innovations
• Probiotics, prebiotics
• In vitro gut simulation
• In vitro digestion models
• Gnotobiotic animal models
• Intestinal cell lines
• Omics technologies
• Galenic formulations

Biological Resources

• Gnotobiotic animal models
• In vitro digestive models (TIM-1, ESIN, ARCOL, SHIME)
• Intestinal cell lines (HT-29, HCT-8, Caco-2, macrophages)
• Galenic formulations
• Genomic, proteomic
• Bioinformatic, gene capture

Mickael Desvaux-Lenôtre Stéphanie Blanquet-Diot

Microbiology Digestive Environment and Health

Université Clermont Auvergne
INRAE UMR 454 MEDIS
Mickael Desvaux-Lenôtre
Clermont-Ferrand

Through complementary in vitro/in vivo approaches, our research aims to study the interrelationships between diet, environmental factors, enteric pathogens, intestinal microbiota and their host, with the aim of preventing digestive and extra-digestive disease and improve health for human and animal

Research Brief :

Four research axes are currently investigated in MEDIS:
1- Food zoonotic pathogens (PAZ): (i) study the ecophysiology of food-borne pathogens such as diarrheic Escherichia coli and Listeria in the food chain, from animal reservoir to food and ultimately human gastrointestinal tract, and (ii) develop preventive strategies based on pre, probiotics or vaccines to reduce colonization and prevent infection
2- Metabolic functions of gut microbiota and dysbiosis (FM2D): (i) investigate the metabolism of beneficial (polyphenols, dietary fibers) and hazardous compounds (food pollutants and microplastics) by human and animal gut microbiota, (ii) better understand the etiology of gut microbial dysbiosis
3- Innovative galenic formulations (GALINN): (i) development of drug delivery systems to improve bioavailability of active compounds or bioaccessibility of probiotics strains, (ii) strategies to ensure gastro-intestinal resistance and drug targeting based on multiparticular vectors
4- Innovation and development of in vitro models (INNOVITRO): (i) development of in vitro gut models and protocols as an alternative to animal assays or clinical studies simulating the gastrointestinal tract of human or monogastric animals under healthy or pathological situations, (ii) better describe gut microbiota by omics techniques including gene capture

• **Methodologies Used :**

Laboratories equipped for the study of strict anaerobic microorganisms (anaerobic chambers, Hungate technique)
Bio-Safety Level 3 laboratory for the culture of pathogenic microorganisms (with in vitro gut models and cell culture)
Animal facility: breeding of axenic rats, experiments on gnotobiotic animals (controlled intestinal microbiota), zone A2 (for experiments on pathogenic human microorganisms) and EOPS zone (transgenic rodents)
Digestive environment simulation platform (Digest-IV): systems simulating the upper digestive tract (TIM-1, ESIN) and the lower gut (M-ARCOL, SHIME)
Galenic platform (Galbiopharm): drug delivery systems development and in vitro (dissolution, permeability) and ex vivo (absorption) biopharmaceutic evaluations

Publications

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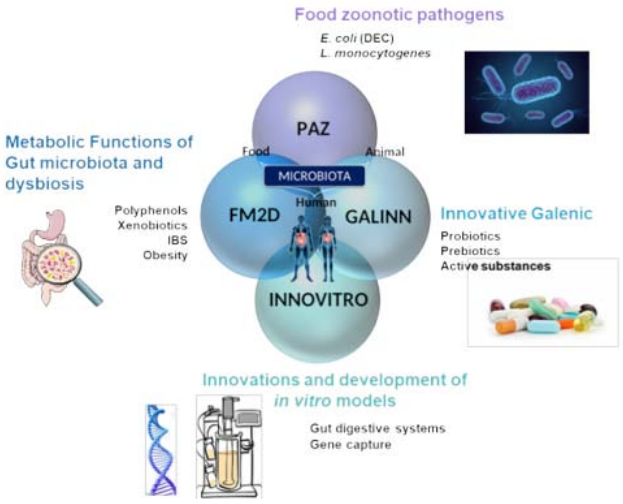
Structure of MEDIS researches



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CRI CENTRE de RECHERCHE sur l'INFLAMMATION

Maude Le Gall André Bado

Plasticity of gastro-intestinal mucosa in nutritional pathologies and after surgery

Université de Paris
Inserm UMRS1149
Renato Monteiro
Paris

Our team gathers physiologists of the gastro-intestinal tract, basic scientists and clinicians (digestive surgeons, gastroenterologists and nutritionists) to develop basic and transitional researches on gastro-intestinal adaptations in response to over- or under-nutrition.

Key facts

Team

• Researchers : 9
• Technicians : 2
• Postdoc fellows : 1
• PhD Students : 3

Translational approaches

• Patents : 0
• Clinical research grants : 3
• Industry partnerships : 1

International research links

• USA
• Canada
• Germany

Keywords

• Gastrointestinal physiology
• Leptin and Insulin
• Obesity
• Exocrine and endocrine secretions
• Nutrient transporters
• bariatric surgery and short bowel syndrome
• murine models of gastro-intestinal surgery
• Ussing chambers and transport in isolated jejunum loops
• multiplex assays (luminex, MSD)
• in vivo metabolic analyses

Biological Resources

• Cohorts of obese subjects before and after bariatric surgery
• Cohorts of Short Bowel Syndrom patients
• Rat models of bariatric surgery
• Rat models of Short Bowel Syndrom

Research Brief :

We focus on gastro-intestinal adaptations in response to over- or under-nutrition and gut surgeries.
We set up unique rat models of bariatric surgeries - vertical sleeve gastrectomy (VSG), Roux-en-Y gastric bypass (RYGB), one-anastomosed gastric bypass (OAGB), Sleeve Gastrectomy with Transit Bipartition ... - and Short Bowel Syndrome (jejuno-colon or -ileum anastomosis).
Combining experimental research in these models with clinical studies, we identified differences in alimentary glucose absorption and intestinal blood glucose handling after RYGB versus VSG bariatric surgeries. We also characterized the protein malabsorption and oesophagus reflux after the controversial OAGB.
In parallel, we characterized factors that impact on structural and functional adaptations of the remnant intestinal mucosa and microbiota in humans and rats suffering from SBS.
In all those studies we highlighted the plasticity of the epithelial cells constitutive of the gastrointestinal tract.
To decipher the mechanisms of cell remodeling, we now extend our studies to either side of the epithelium: the mucosa layers containing immune cells versus the luminal microbiota. We want to determine the functional consequences of intestinal immune cells changes and how they impact on epithelial cell functions. Finally, the metabolome of intestinal mucosa and microbiota in preclinical models and patients will allow the identification of new biomarkers and/or therapeutic targets to supply or replace surgery.

• **Methodologies Used :**

Animal models of gastrointestinal weight-loss surgeries and short bowel syndrome,
In vivo studies, Quantification of gastrointestinal secretions (endocrine, exocrine), Assay of intestinal nutrient transport, Molecular biology and pharmacology, Cell signaling, Clinical studies, Transgenic mouse models

Publications

Gillard L, Billiauws L, Stan-Iuga B, Ribeiro-Parenti L, Jarry AC, Cavin JB, Cluzeaud F, Mayeur C, Thomas M, Freund JN, Lacorte JM, Le Gall M, Bado A, Joly F, Le Beyec J. (2016). Enhanced Ghrelin Levels and Hypothalamic Orexigenic AgRP and NPY Neuropeptide Expression in Models of Jejuno-Colonic Short Bowel Syndrome., Scientific Reports. 6(), 28345

Cavin JB, Couvelard A, Lebtahi R, Ducroc R, Arapis K, Voitellier E, Cluzeaud F, Gillard L, Hourseau M, Mikail N, Ribeiro-Parenti L, Kapel N, Marmuse JP, Bado A, Le Gall M. (2016). Differences in Alimentary Glucose Absorption and Intestinal Disposal of Blood Glucose After Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy., Gastroenterology. 150(2), 454

Jarry AC, Merah N, Cisse F, Cayetanot F, Fiamma MN, Willemetz A, Gueddouri D, Barka B, Valet P, Guilmeau S, Bado A, Le Beyec J, Bodineau L, Le Gall M. (2019). Neuromedin U is a gut peptide that alters oral glucose tolerance by delaying gastric emptying via direct contraction of the pylorus and vagal- dependent mechanisms., Faseb Journal. 33(4), 5388

Duboc H, Nguyen CC, Cavin JB, Ribeiro-Parenti L, Jarry AC, Rainteau D, Humbert L, Coffin B, Le Gall M, Bado A, Sokol H. (2019). Roux-en-Y Gastric-Bypass and sleeve gastrectomy induces specific shifts of the gut microbiota without altering the metabolism of bile acids in the intestinal lumen, Int J Obes (Lond).. 43(2), 428-431

Le Beyec J, Billiauws L, Bado A, Joly F, Le Gall M. (2020). Short Bowel Syndrome: A Paradigm for Intestinal Adaptation to Nutrition?, Annual Reviews of Nutrition. 40(), 299-321

Ribeiro-Parenti L, Jarry AC, Cavin JB, Willemetz A, Le Beyec J, Sannier A, Benadda S, Pelletier AL, Hourseau M, Léger T, Morlet B, Couvelard A, Anini Y, Msika S, Marmuse JP, Ledoux S, Le Gall M, Bado A. (2021). Bariatric surgery induces a new gastric mucosa phenotype with increased functional glucagon-like peptide-1 expressing cells, Nature Communication. 12(1), 110

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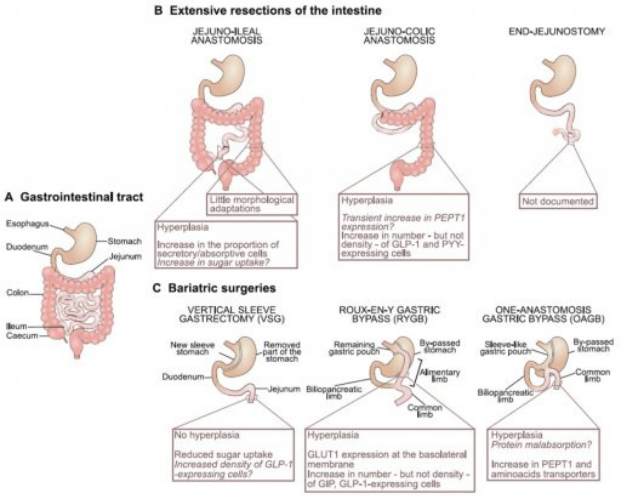
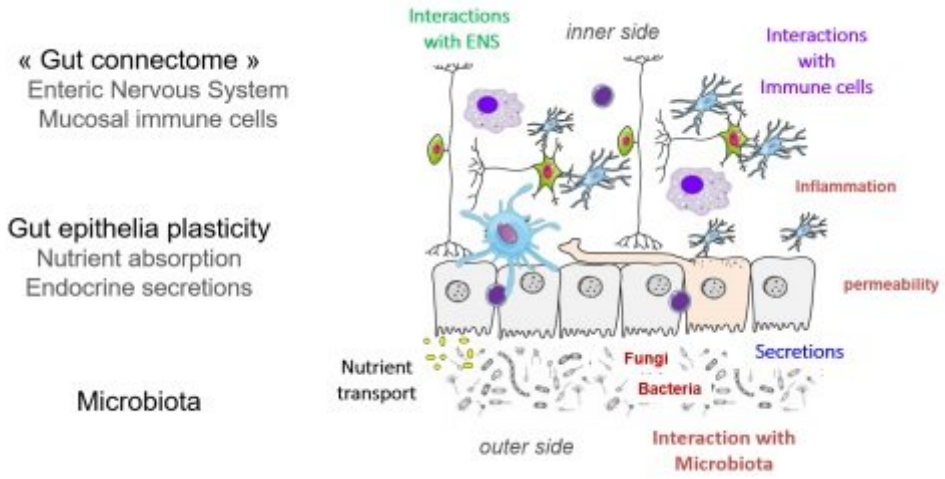
Gastrointestinal tract anatomy in physiology and after remodeling by surgery.



A. Normal gastrointestinal tract anatomy.
B. Gastrointestinal tract anatomy after massive resection of the intestine leading to short bowel syndrome (SBS).
C. Gastrointestinal tract anatomy after vertical sleeve gastrectomy (VSG), Roux-en-Y gastric bypass (RYGB), or one-anastomosis gastric bypass (OAGB) and the principal intestinal adaptation reported in the literature
Adapted from Le Gall et al. Nutrition Reviews 2019 77(3):129-143.

Cellular and molecular mechanisms involved in the cellular plasticity of gastro-intestinal mucosa



Both sides of the gastro-intestinal epithelium could contribute to the adaptations in response to surgery readouts since glial and neurons of the enteric nervous system and immune cells communicate with epithelial cells.

Research strategies

Our team gathers physiologists of the gastro-intestinal tract, basic scientists and clinicians (digestive surgeons, gastroenterologists and nutritionists) to develop bench-to-bedsides researches.

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Michel Neunlist

The Enteric Nervous System in Gut and Brain Disorders (TENS)

Nantes Université
Inserm U1235
Michel Neunlist
Nantes

Key facts

Team

- Researchers : 16
- Technicians : 8
- Postdoc fellows : 5
- PhD Students : 10

Translational approaches

- Patents : 2
- Clinical research grants : 2
- Industry partnerships : 5

Keywords

- Neurogastroenterology
- Enteric nervous system
- enteric glial cell
- Intestinal barrier function
- Animal models (pigs/rats/mice)
- immunohistochemistry
- cellular and molecular biology
- endoscopy (micro/macro)
- Neuromodulation of the gut

Biological Resources

- Animal models (pigs/rats/mice)
- Animal/Human primary cell culture (enteric neurons, glial cells, intestinal epithelial stem cells, immune cells)
- Biobanks (gut biopsies, cell media, RNA/Proteins/metabolites)

Our team developps translational research projects aimed at 1) understanding the role of the enteric nervous system (ENS) in digestive and extra-digestive diseases and 2) identifiying novel therapeutical approaches targetting the ENS in these diseases (neurostimulation, nutritional approaches ...).

Research Brief :

Our Inserm Unit of Neurogastroenterology, created in 2008, belongs to the Institute of Digestive Diseases of the University Hospital of Nantes (IMAD).
Our research is focused on the study of the enteric nervous system (ENS) and its role in health and in key digestive and extra digestive diseases.
Our research is organized along three main objectives :
1) to understand the role of enteric neurons and glial cells in the control of gastrointestinal motility and intestinal barrier functions,
2) to characterise, in humans and animal models, the lesions of the ENS and determine their functional consequences in chronic diseases of interest (digestive and extra-digestive diseases);
3) to develop new therapeutic approaches to target the ENS (nutritional factors, probiotics, neurostimulation ...), to improve patient care with digestive disorders.

We study pathologies with a real public health challenges affecting the gastro-intestinal tract (digestive cancers, inflammatory bowel diseases, irritable bowel syndrome...), but affecting also other organs, and in particular the brain (neurodegenerative disorders such as Parkinson disease).

- **Methodologies Used :**

Immunohistology, biochemistry and molecular biology
Biocollection of gut biopsies, serum, supernatants of biopsies
Microscopy (epifluorescence and confocal, calcium imaging)
Primary culture and co-culture of intestinal cells of animal or human origin (neurons, glial cells, intestinal epithelial stem cells)
In-vivo and ex-vivo assessment of gastrointestinal motility and barrier functions (permeability, proliferation,...)
Diagnostic and interventional endoscopy (confocal endomicroscopy; full thickness biopsy...)

Publications

Lebouvier T, Neunlist M, Bruley des Varannes S, Coron E, Drouard A, N'Guyen JM, Chaumette T, Tasselli M, Paillusson S, Flamand M, Galmiche JP, Damier P, Derkinderen P (2010). Colonic biopsies to assess the neuropathology of Parkinson's disease and its relationship with symptoms., PloS one. 5(9), e12728

Soret R, Chevalier J, De Coppet P, Poupeau G, Derkinderen P, Segain JP, Neunlist M (2010). Short-chain fatty acids regulate the enteric neurons and control gastrointestinal motility in rats., Gastroenterology. 138(5), 1772-82

Flamant M, Aubert P, Rolli-Derkinderen M, Bourreille A, Neunlist MR, Mahé MM, Meurette G, Marteyn B, Savidge T, Galmiche JP, Sansonetti PJ, Neunlist M (2011). Enteric glia protect against Shigella flexneri invasion in intestinal epithelial cells: a role for S-nitrosoglutathione., Gut. 60(4), 473-84

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Neunlist Michel - michel.neunlist@univ-nantes.fr - +33 (0)2 40 41 29 50 - www.inserm-tens.com

Research teams with secondary association to PMN Institute

Key facts

Team

- Researchers : 4
- Technicians : 1
- Postdoc fellows : 0
- PhD Students : 2

Translational approaches

- Patents : 2
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- UK
- Portugal

Keywords

- Pathobiont
- Enterococcus
- Adaptation and virulence
- Colonisation resistance
- Antibiotics and alternatives
- Gastrointestinal tract and liver
- Intestinal microbial ecology
- Host-pathogen interactions
- Cell wall glycopolymers
- Preclinical models

Biological Resources

- Collection of enterococcal isolates
- Cell lines: intestinal, urothelial and kidney cells and hepatocytes
- Ex vivo models (primary mouse hepatocytes, peritoneal macrophages)
- Preclinical models

Pascale Serror

Commensalism and Pathogeny of Enterococci

Paris-Saclay University
INRAE UMR1319
Philippe Noirot
Jouy-en-Josas

Our team aims at understanding the mechanisms of transition from commensal to pathogenic state of intestinal bacteria responsible for opportunistic infections in humans and animals, such as enterococci, to propose preventive and interventional methods to control them and limit the use of antibiotics

Research Brief :

Prevention of infections caused by multi-resistant pathogens from the intestinal microbiota is a major challenge for human and animal health in order to limit the use of antibiotics. Disruption of the gut microbiota by antibiotics, drug treatments, or alcohol lead to the proliferation of pathobionts that are commensal bacteria that become pathogenic in individuals or animals with impaired immune systems. Among these pathobionts, Enterococcus faecalis is one of the top five causes of hospital-acquired infections worldwide. Our research aims to decipher the mechanisms of E. faecalis adaptation and interaction with the host and the intestinal microbiota during the infectious process. Our strategy is based on in vitro and in vivo studies using global or targeted approaches on the determinants we have identified. More specifically, we are studying i) the early events of E. faecalis adaptation to intestinal dysbiosis and the factors of persistence in the intestine, ii) the barrier effect of the microbiota on its intestinal persistence and the underlying mechanisms and iii) its translocation to the liver and its role in liver diseases. These lines of research will provide knowledge for the development of preventive strategies for the transition from commensal to pathogenic state.

- **Methodologies Used :**

Bacterial functional genetics/genomics
Cellular models (cell lines and primary cells)
Conventional and gnotobiotic mouse models (colonisation, translocation, and infectivity)
Flow cytometry
Microbiota ecology

Publications

Crouzet L, Derrien M, Cherbuy C, Plancade S, Foulon M, Chalin B, van Hylckama Vlieg JET, Grompone G, Rigottier-Gois L, Serror P. (2018). Lactobacillus paracasei CNCM I-3689 reduces vancomycin-resistant Enterococcus persistence and promotes Bacteroidetes resilience in the gut following antibiotic challenge, Scientific Reports. 8(1), 5098

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Guerardel Y, Sadovskaya I, Maes E, Furlan S, Chapot-Chartier MP, Mesnage S, Rigottier-Gois L, Serror P. (2020). Complete structure of the Enterococcal Polysaccharide Antigen (EPA) of vancomycin-resistant Enterococcus faecalis V583 reveals that EPA decorations are teichoic acids covalently linked to a rhamnopolysaccharide backbone., mBio. 11(2), e00277-20.

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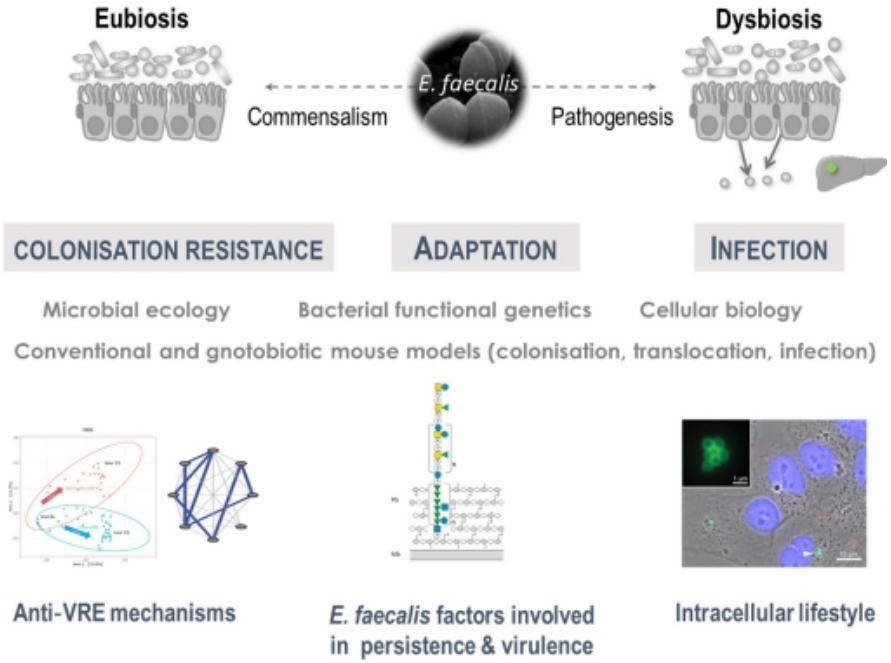
CPE research topics and strategies



Serror Pascale - pascale.serror@inrae.fr - https://www.micalis.fr/Poles-et-Equipes/Pole-Adaptation-Bacterienne-et-Pathogenese/Commensalisme-et-Pathogenie-des-Enterocoques-Pascale-Serror

Hepatology

Key facts

Team

- Researchers : 7
- Technicians : 6
- Postdoc fellows : 1
- PhD Students : 4

Translational approaches

- Patents : 0
- Clinical research grants : 3
- Industry partnerships : 2

Keywords

- Liver regeneration
- Genetic Cholestasis
- Cholangiocytes
- Bile acids
- In vivo mouse experimental models
- Cell culture
- Microscopy - Imaging

Thierry Tordjmann

Biliary Homeostasis and Liver Repair

Université Paris Saclay
Inserm UMRs1193
Didier Samuel
Orsay

> ***International recognition for our studies on : bile acids and liver regeneration; genetic cholestasis.***

Research Brief :

A. Biliary homeostasis and liver repair (resp: Thierry Tordjmann). Our studies focus on the impact of bile acids (BA) (especially their receptor TGR5), and of the purinergic system (in particular extracellular ATP receptors, P2X4), on liver repair processes in mice and human. Experimental models: in vivo (bile duct ligation, partial or extended hepatectomy, BA-enriched or BA sequestering diets...) and in vitro (hepatocyte, cholangiocyte or myofibroblast cultures). B. Pathophysiology and treatment of genetic cholestasis (resp: Emmanuel Jacquemin). PFIC2 and 3 (Progressive Familial Intrahepatic Cholestasis type 2-3) are severe genetic cholestatic diseases due to mutations in the genes ABCB11 encoding BSEP (Bile Salt Export Pump) and ABCB4 encoding MDR3 (MultiDrug Resistance protein type 3), respectively, requiring liver transplantation during childhood in most patients. In cell models, we perform site-directed mutagenesis of these ABC transporters to develop targeted pharmacotherapies that may be an alternative to liver transplantation. C. Ciliopathies and biliary organogenesis (resp: Pascale Dupuis-Williams). We study the impact of the Primary Cilia on biliary tree organogenesis and homeostasis, which are impaired in most ciliopathies. We also develop in vitro models of polarized biliary organoids and tubules, with strong implication in a tissue engineering program developed in the RHU (Réseau Hospitalo-Universitaire) « iLiTe ».

- **Methodologies Used :**

In vivo mouse experimental models
Imaging Microscopy
Cell culture

Publications

Le Guilcher C, Garcin I, Dellis O, Cauchois F, Tebbi A, Doignon I, Guettier C, Julien B, Tordjmann T. (2018). The P2X4 purinergic receptor regulates hepatic myofibroblast activation during liver fibrogenesis., Journal of HEPATOLOGY. 69(), 644-653

Vauthier V, Ben Saad A, Elie J, Oumata N, Durand-Schneider AM, Bruneau A, Delaunay JL, Housset C, Aït-Slimane T, Meijer L, Falguières T. (2019). Structural analogues of roscovitine rescue the intracellular traffic and the function of ER-retained ABCB4 variants in cell models., Sci Rep.. 9(), 6653

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Amzal R, Thébaut A, Lapalus M, Almes M, Grosse B, Mareux E, Collado-Hilly M, Davit-Spraul A, Bidou L, Namy O, Jacquemin E, Gonzales E. (2020). Pharmacological premature termination codon readthrough of ABCB11 in bile salt export pump deficiency: an in vitro study., HEPATOLOGY. Jul 23. doi: 10.1002/hep.31476.(),

Merlen G, Kahale N, Ursic-Bedoya J, Bidault-Jourdainne V, Simerabet H, Doignon I, Tanfin Z, Garcin I, Péan N, Gautherot J, Davit-Spraul A, Guettier C, Humbert L, Rainteau D, Ebnet K, Ullmer C, Cassio D, Tordjmann T. (2020). TGR5-dependent hepatoprotection through the regulation of biliary epithelium barrier function., GUT. 69(), 146-157

Bouzhir L, Gontran E, Loarca L, Collado-Hilly M, Dupuis-Williams P. (2020). Generation and Quantitative Characterization of Functional and Polarized Biliary Epithelial Cysts., J Vis Exp. 64(3), 941-953

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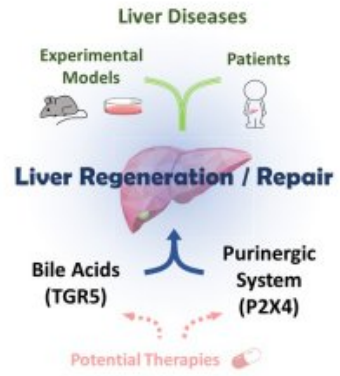
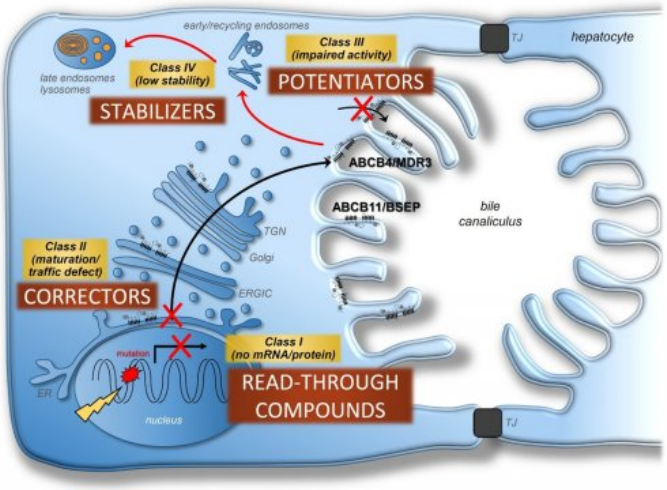
Bile acids and purinergic system in liver regeneration and repair.



We aim to decipher the impact of bile acids and extracellular ATP (purinergic system) on liver regeneration and repair processes. We use mouse experimental models of liver regeneration and fibrogenesis, as well as in vitro cell cultures (primary liver cells and cell lines), to study mechanisms involving in bile acid (focused on their receptor TGR5) and purine (focused on their receptor P2X4) signalling pathways. Potential therapies targeting these receptors are envisionned.

Mutation-specific targeted pharmacotherapy for Progressive Familial Intrahepatic Cholestasis.



The four different classes of molecular defects of the canalicular ABC transporters ABCB4/MDR3 and ABCB11/BSEP are indicated (yellow boxes), as well as the proposed drug therapies for each of these classes (brown boxes). The analysis of the expression, localization, degradation and residual function of the mutated transporters constitute the rationale to guide a mutation-specific drug therapy strategy.

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Philippe Gual

Chronic liver diseases associated with obesity and alcohol

Université de Nice - Sophia
Antipolis Université Côte d'Azur
Inserm U1065
Patrick Auberger
Nice

Key facts

Team

- Researchers : 7
- Technicians : 2
- Postdoc fellows : 1
- PhD Students : 2

Translational approaches

- Patents : 1
- Clinical research grants : 1
- Industry partnerships : 1

International research links

- EASD-NAFLD Study group

Keywords

- NAFLD, ALD, NASH, ASH, HCC
- Mice, Human

Biological Resources

- mouse models of NAFLD (from steatosis to HCC)
- Cohort of obese patients (Liver, adipose tissue and serum banks)
- mouse models of ALD
- Cohorts of alcoholic patients (Liver and serum biobanks)

Study of chronic liver diseases associated with obesity and alcohol: from the diagnosis to the treatment

Research Brief :

The aims of the present team (created in 2008), composed of clinicians and basic scientists, are to better understand the hepatic complications associated with obesity (Non alcoholic fatty liver disease: NAFLD) and with chronic alcohol consumption (alcoholic liver disease, ALD). These chronic liver diseases range from steatosis to steatohepatitis (Non Alcoholic or Alcoholic Steatohepatitis, NASH and ASH), fibrosis, cirrhosis and finally hepatocellular carcinoma. NAFLD and ALD are the main causes of cirrhosis and increase the risk of liver-related death with limited therapeutic options available. It is urgent to better diagnosis and treat these chronic liver diseases. Our translational researches mainly focus on 1) the identification of new markers/actors of the progression of these chronic liver diseases (NAFLD/ALD). We take advantage of our cohorts of obese and alcoholic patients; 2) the study of potential players in the progression of NAFLD and ALD including the cell matrix interaction- (CD44), non-receptor tyrosine kinase- and innate lymphoid cell- dependent pathways as well as metabolic pathways regulating immune functions; 3) the impact of targeting these pathways is investigated by preclinical approaches. Over the past few years, the team have made significant contributions to provide new insights into the understanding of these chronic liver diseases in order to propose a better diagnostic and new therapeutic targets.

- **Methodologies Used :**

animal models
cellular models
human biopsies
histologic analysis
IHC
Gene and protein expression

Publications

BekriS, Gual P*(co-first authors), Anty R, Luciani N, Dahman M, Ramesh B, Iannelli A, Staccini-Myx A, Casanova D, Ben Amor I, Saint-Paul MC, Huet PM, Sadoul JL, Gugenheim J, Srai SK, Tran A, Le Marchand-Brustel Y. (2006). Increased adipose tissue expression of hepcidin in severe obesity is independent from diabetes and NASH., Gastroenterology. 131(3), 788-796*

Anty R, Marjoux S, Iannelli A, Patouraux S, Schneck AS, Bonnafous S, Gire C, Amzolini A, Ben-Amor I, Saint-Paul MC, Mariné-Barjoan E, Pariente A, Gugenheim J, Gual P, Tran A. (2012). Regular coffee but not espresso drinking is protective against fibrosis in a cohort mainly composed of morbidly obese European women with NAFLD undergoing bariatric surgery., J Hepatol.. 57(5), 1090-6

Patouraux S, Rousseau D* (co-first authors), Bonnafous S, Lebeaupin C, Luci C, Canivet CM, Schneck AS, Bertola A, Saint-Paul MC, Iannelli A, Gugenheim J, Anty R, Tran A, Bailly-Maitre B, Gual P. (2017). CD44 is a key player in non-alcoholic steatohepatitis., J Hepatol.. 67(2), 328-338*

Lebeaupin C, Vallée D, Rousseau D, Patouraux S, Bonnafous S, Adam G, Luciano F, Luci C, Anty R, Iannelli A, Marchetti S, Kroemer G, Lacas-Gervais S, Tran A, Gual P, Bailly-Maitre B. (2018). Bax inhibitor-1 protects from nonalcoholic steatohepatitis by limiting inositol-requiring enzyme 1 alpha signaling in mice., Hepatology. 68(2), 515-532

Anty R, Morvan M*, Le Corvec V, Canivet CM, Patouraux S, Gugenheim J, Bonnafous S, Bailly-Maitre B, Sire O, Tariel H, Bernard J, Piche T, Loréal O, Aron-Wisnewsky J, Clément K, Tran A, Iannelli A, Gual P. (2019). The mid-infrared spectroscopy: a novel non-invasive diagnostic tool for NASH diagnosis in severe obesity., JHEP Reports. 1(5), 361-368*

Luci C, Vieira E*, Bourinet M, Rousseau D, Bonnafous S, Patouraux S, Lefevre L, Larbret F, Prod'homme V, Iannelli A, Tran A, Anty R, Bailly-Maitre B, Deckert M$, Gual P$ ($ co-last authors) (2022). SYK-3BP2 Pathway Activity in Parenchymal and Myeloid Cells Is a Key Pathogenic Factor in Metabolic Steatohepatitis., Cell Mol Gastroenterol Hepatol.. 13(1), 173-191*

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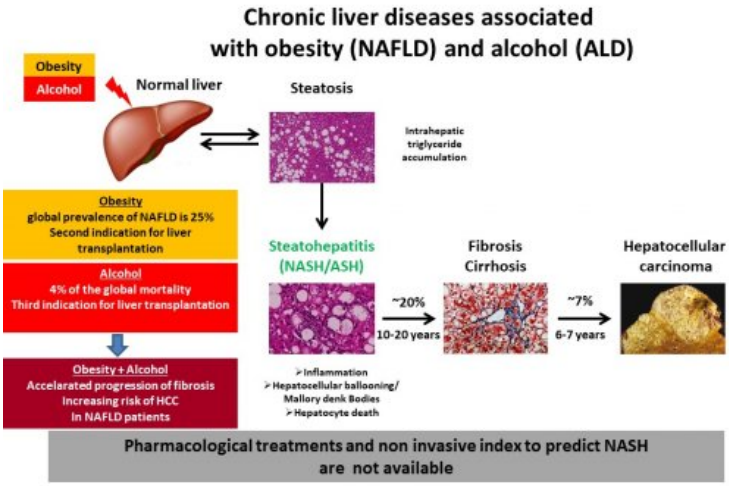
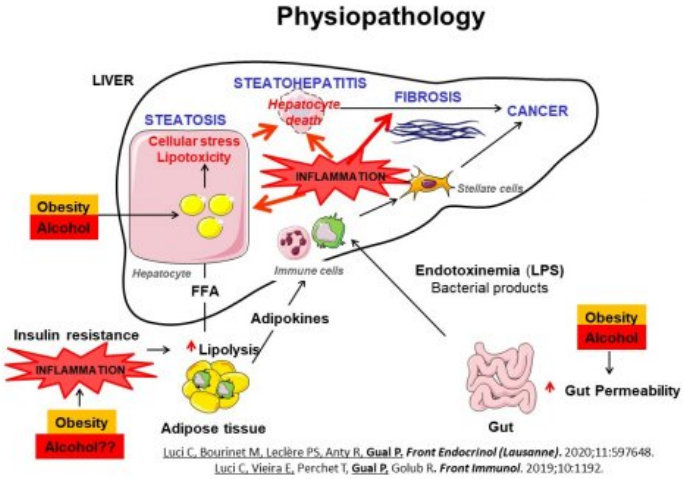
NAFLD and ALD



Obesity and regular alcohol use are associated with the development of liver diseases. The prevalence of NAFLD is 33% and up to 40% of patients with severe acute alcoholic hepatitis die within six months. The spectrum of these hepatic abnormalities extends from isolated steatosis to steatohepatitis and steatofibrosis, sometimes leading to cirrhosis and HCC. NAFLD and ALD are two of the three principal causes of cirrhosis and increase the risk of liver-related death and HCC.

Physiopathology of NAFLD AND ALD



Cross talks between the liver, adipose tissue and gut are involved in the pathogenesis of NAFLD and ALD. In obesity, increased adipose tissue inflammation leads to lipolysis and altered adipokines secretion. Obesity and alcohol consumption are associated with dysbiosis and increased gut permeability leading to elevated bacterial products. These factors enhance hepatic inflammation and hepatocyte death which initiate the fibrogenic process and the progression of liver complications

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Key facts

Team

• Researchers : 8
• Technicians : 1
• Postdoc fellows : 4
• PhD Students : 4

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 0

International research links

• P. Lampertico (University of Milan, Italy)
• C. Ferrari (University of Parma, Italy)
• O. Andrisani (Purdue University, USA)

Keywords

• Liver cancer
• Hepatocellular carcinoma
• NASH
• Viral hepatitis
• Hepatitis B and D virus
• Epigenetics
• Transcriptomics
• miRNAs
• lncRNAs

Biological Resources

• Cohorts of HBV/HDV, HCV and HCC patients
• Plasma/serum and liver samples
from chronic hepatitis and HCC patients

Massimo Levrero

Epigenetics, microenvironment and liver cancer

UCBL1
Inserm U1052 CNRS 5286
Patrick Mehlen
Lyon

The team brings together researchers and clinicians with complementary expertise in epigenetic modifications, microbiome, viral hepatitis, HCC and liver transplantation.

Research Brief :

Hepatocellular carcinoma (HCC), the most common type of liver cancer, is a major cause of liver transplantation and cancer death worldwide. The majority of HCCs can be associated with chronic infection with hepatitis B, D and C viruses (HBV, HDV, HCV), ethanol consumption and non-alcoholic fatty liver disease.

Driving forces in HCC development and progression include chronic inflammation, DNA damage and epigenetic modifications. Our research efforts have enabled to gain new knowledge on i) the epigenetic changes that precede and accompany HCC development and progression; ii) the interaction of HBV, HDV and HCV with the host epigenome; iii) the virological and immunological basis of viral pathogenicity and persistence in the setting of HBV and HDV chronic liver diseases.

Basic research axes aiming at the characterization of the epigenetic changes in virus- and non-virus-related HCCs focus on:

- histone methyl-transferases as HCC epi-drivers and therapeutic targets
- deciphering the intrahepatic inflammatory microenvironment in HCCs of different etiologies
- HBV and HDV proteins as epigenetic modulators in viral pathogenicity and HCC development

Translational research axes:
- a new diagnostic test to assess curative treatments for hepatitis B based on circulating HBV RNAs
- novel immunomodulatory strategies for HBV cure
- circulating miRNA signatures associated with HCC development to improve HCC risk scores
- new technologies to improve liver grafts prior transplantation

• **Methodologies Used :**

Cell models (hepatoma cell lines, primary human hepatocytes)
HBV/HDV infection of target cells
ChIP/ChIP-seq, RNA-seq, mRNA/miRNA profiling
Single cell secretome
Precision-cut liver slices

Publications

Fisicaro P, Barili V, Montanini B, Acerbi G, Ferracin M, Guerrieri F, Salerno D, Boni C, Massari M, Cavallo MC, Grossi G, Giuberti T, Lampertico P, Missale G, Levrero M, Ottonello S, Ferrari C (2017). Targeting mitochondrial dysfunction can restore antiviral activity of exhausted HBV-specific CD8 T cells in chronic hepatitis B, Nature Medicine. 23(3), 327-336

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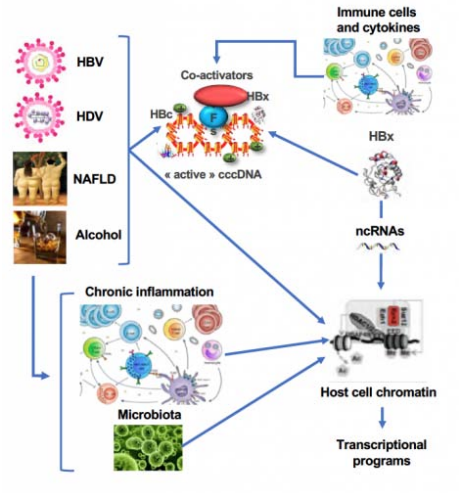
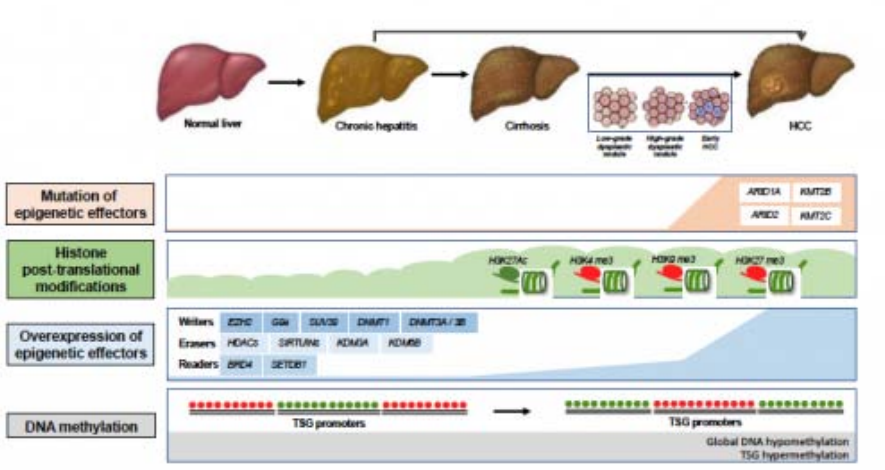
Graphical abstract of the team's research axes



Alterations of epigenetic modifiers, chromatin modifications and DNA methylation



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Léon Kautz

Erythroferrone and iron homeostasis

Université Paul Sabatier
Toulouse III
Inserm U1220
Nathalie Vergnolle
Toulouse

Key facts

Team

- Researchers : 1
- Technicians : 2
- Postdoc fellows : 1
- PhD Students : 1

Translational approaches

- Patents : 3
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- USA
- Italy
- Netherlands

Keywords

- Iron
- Liver
- Anemia
- Erythropoiesis
- Signaling
- Transcriptomic analysis
- Production of recombinant protein
- Animal models
- Molecular Biology
- Protein interaction

The team has a strong expertise in studying the inter-organ communication governing the proper supply of iron for red blood cells synthesis. We have contributed to the discovery of the hormone erythroferrone and developed multiple tools to investigate its biology.

Research Brief :

Iron is essential for most living organisms as functional component of iron-requiring proteins involved in oxygen transport and storage, cellular respiration, mitochondrial metabolism and DNA replication and reparation. However, excess iron promotes the formation of reactive oxygen species leading to tissue damage and organ dysfunction. Iron homeostasis therefore needs to be tightly regulated to prevent insufficient or excessive iron availability and severe clinical complications.
The bone marrow is the main consumer of iron for the synthesis red blood cells (RBC) hemoglobin. Most of the plasma iron is provided by the recycling of iron from senescent RBCs by macrophages and by the absorption of dietary iron by duodenal enterocytes. Iron is exported from these cells by the transporter ferroportin. The liver-produced hormone hepcidin regulates iron efflux into the bloodstream by degrading Fpn. During anemia, the erythroid hormone erythroferrone (ERFE) is secreted by erythroid precursors to repress hepcidin, increase iron availability for erythropoiesis and rapidly restore normal oxygen saturation.
Our main objective is to decipher the mechanisms by which ERFE and erythropoiesis control iron metabolism. Delineating these mechanisms is of high biomedical importance to develop novel therapeutic strategies for various forms of anemia. In parallel, we are investigating the potential alternative functions of ERFE in vertebrate biology.

Methodologies Used :

Production of recombinant proteins
Molecular Biology (Western blot, cloning..)
Imaging (IHC, IF)
Isolation of mouse primary hepatocytes
Transcriptomic analysis (qPCR and microarrays)

Publications

Kautz, L., G. Jung, E. V. Valore, S. Rivella, E. Nemeth and T. Ganz (2014). Identification of erythroferrone as an erythroid regulator of iron metabolism, Nature Genetics. 46(7), 684

Kautz, L., G. Jung, X. Du, V. Gabayan, J. Chapman, M. Nasoff, E. Nemeth and T. Ganz (2015). Erythroferrone contributes to hepcidin suppression and iron overload in a mouse model of beta-thalassemia, Blood. 124(16), 2569-2574

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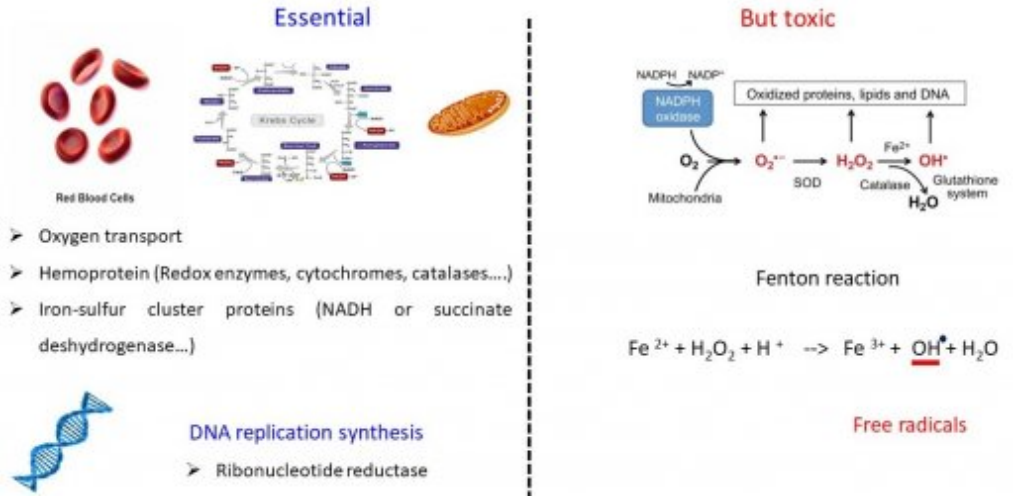
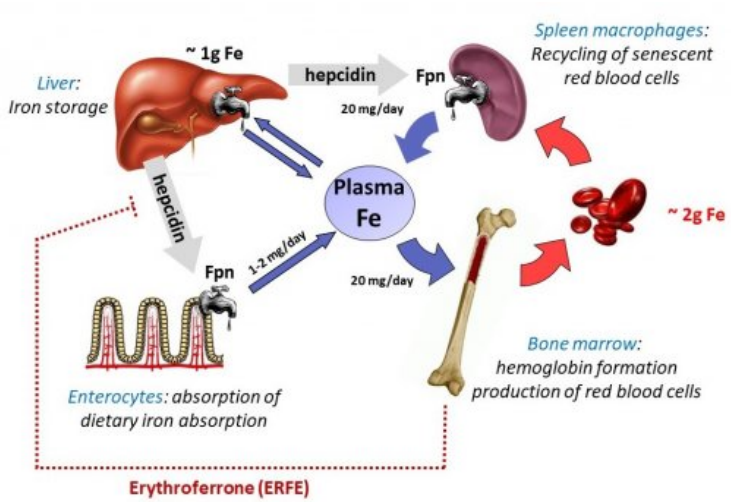
The iron paradox



Iron is essential for most living organisms as functional component of iron-requiring proteins involved in oxygen transport and storage, cellular respiration, mitochondrial metabolism and DNA replication and reparation. However, excess iron promotes the formation of reactive oxygen species leading to iron toxicity, tissue damage and organ dysfunctional.

The regulation of iron homeotasis



The bone marrow is the main consumer of iron. Iron is provided by the recycling of iron from senescent RBCs by macrophages and by the absorption of dietary iron by enterocytes. Iron is exported from these cell by the transporter ferroportin (Fpn). The liver-produced hormone hepcidin induces the degradation of Fpn to prevent iron efflux into the bloodstream. During anemia, ERFE is secreted by erythroid precursors to repress hepcidin and increase iron availability for erythropoiesis.

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Anne Corlu Bernard Fromenty

EXPRES

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Key facts

Team

- Researchers : 23
- Technicians : 4
- Postdoc fellows : 1
- PhD Students : 7

Translational approaches

- Patents : 3
- Clinical research grants : 4
- Industry partnerships : 5

International research links

- Pr. E. Barreto (Federal University of Alagoas, Maceio, Brazil)
- Dr N. Nieto (University of Illinois, Chicago, US)
- Dr J Legler (Utrecht university, Netherlands - Coordinator of EU project Goliath)

Keywords

- Stress
- Liver
- Gut
- Reparation
- Metabolisms
- Cell culture
- in vivo models (mice and rats)
- Mitochondrial function

Biological Resources

- - Bioclinical studies: cohorts of patients suffering from liver cancer,Inflammatory bowel disease, spina bifida and septic shock.

Our team gathers researchers and clinicians with high-level expertise in toxicology, cell defense and plasticity, metabolism and microenvironment to study the emergence and progression of metabolic and neoplastic hepatogastrointestinal diseases arising in an inflammatory context.

Research Brief :

The liver can be exposed to toxic xenobiotics including drugs and environmental contaminants, excess of nutrients (fatty acids, carbohydrates) and inflammatory mediators released by the gastrointestinal tract. Although these tissues are able to set up mechanisms of defence and repair, the adaptive responses can be impaired in some individuals, thus favouring the occurrence of diseases such as inflammatory bowel diseases, colorectal cancer, steatohepatitis, fibrosis, cirrhosis and liver cancer. Our team aims to improve the understanding of the mechanisms involved in: i) cell and tissue damage induced by different stressors including infections and sepsis, lipid overload, surgery, hypoxia and xenobiotics, ii) cell defence and tissue repair aiming at limiting stress-induced liver and gastrointestinal tract injury, iii) the occurrence of different pathological responses that can be secondary to a failure of cell defences and tissue repair. When appropriate, we also study the impact of obesity and/or NAFLD on the response to stress and on disease progression. These objectives are included in two major research themes that are intertwined, in particular regarding cell defence, tissue repair, inflammation and mitochondrial dysfunction: 1) Biological and toxicological effects of xenobiotics and lipids; 2) Tissue remodeling and metabolic reprogramming.

• Methodologies Used :

Animal models: rodent models of liver regeneration, ischemia/reperfusion, hepatocellular carcinoma and obesity (genetic and non-genetic)
Cell models: primary culture of hepatocytes (human, rat, mouse). Cell lines (HepaRG, HepG2, Caco2...), cocultures and organoids from liver and gut, cellular models of steatosis and cholestasis
Exploratory Investigations on mitochondrial function (Seahorse), oxidative stress and endoplasmic reticulum stress
Clinical studies with cohorts of patients suffering from hepatocellular carcinoma, inflammatory bowel disease and septic shock.
Access to transcriptomics, histopathology, microscopy, high-content screening, mass-spectrometry analyses, A1 & A2 animal facilities, biological resource center (CRB Santé).

Publications

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Nesseler N, Launey Y, Aninat C, White J, Corlu A, Pieper K, Mallédant Y, Seguin P (2016). Liver Dysfunction Is Associated with Long-Term Mortality in Septic Shock, Am J Respir Crit Care Med. 193(335), 337

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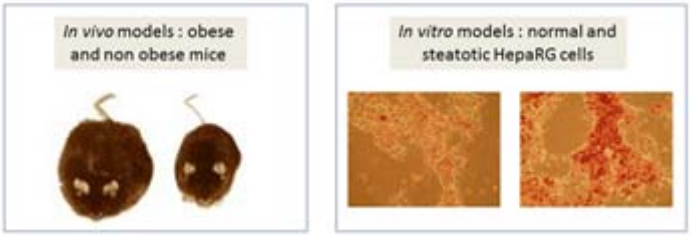
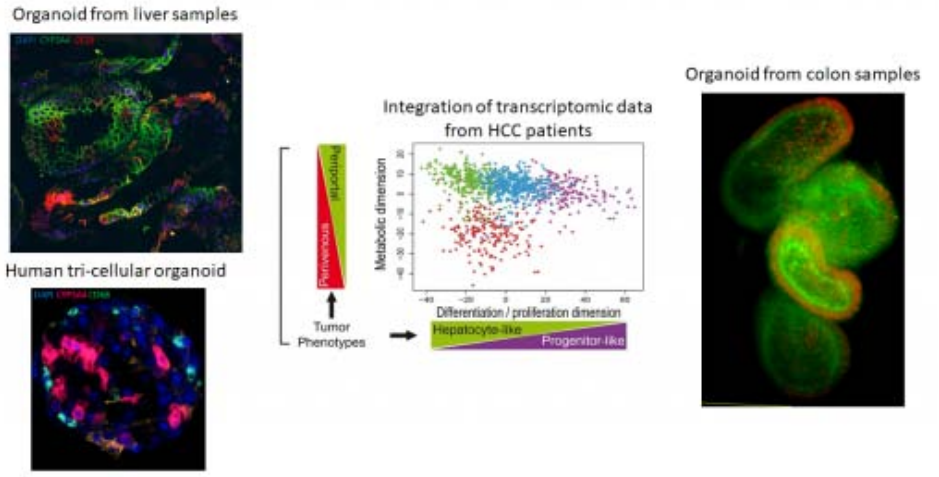
Biological and toxicological effects of xenobiotics and lipids



Numerous xenobiotics including drugs and environmental toxicants can induce liver injury, whose risk can be significantly enhanced in obese patients with NAFLD and insulin resistance. Hence, our main objectives are to further characterize the mechanisms of hepatotoxicity and to better understand why some compounds are more deleterious in NAFLD, with a particular focus on cytochromes P450. We also investigate the deleterious and beneficial effects of some alimentary and endogenous fatty acids.

Tissue remodeling and metabolic reprogramming



Inflammation is pivotal to maintain tissue homeostasis but its deregulation can promote hepatic and gastrointestinal diseases. Our main objectives are first to improve the knowledge of the complex crosstalks between inflammation, hypoxia and tissue defence system to design new strategies to treat these diseases and second to study the contribution of liver inflammation to the emergence of pro-tumorigenic microenvironment and to the induction of metabolic reprogramming and hepatocyte plasticity.

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Pascal Loyer Pascal Guggenbuhl

Metals, Diseases and Vectorised Therapies (METHER)

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Olivier Loréal
Rennes

Key facts

Team

- Researchers : 23
- Technicians : 7
- Postdoc fellows : 1
- PhD Students : 7

Translational approaches

- Patents : 3
- Clinical research grants : 3
- Industry partnerships : 2

International research links

- R. Salem (Northwestern University, USA) for clinical trials of radioembolization in liver cancers
- Instituto Nacional de Enfermedades Neoplásicas (INEM, Lima, Peru), IST/IRD Ile-de-France (S. Bertani) and Pasteur Institute (P. Pineau) to study liver cancers
- European network for Research Initiative in Haemochromatosis Arthropathy

Keywords

- Iron metabolism and related diseases
- metals
- microbiota
- Metabolic radiotherapy
- liver cancers
- Genetic and Genomic profiling
- Metalome analysis
- microbiota profiling
- petide-chelate conjugate synthesis
- Radioembolization

Biological Resources

- Team members contributing to the national BIOBANQUES infrastructure, guidelines and recommendations for biobanking
- Access to well-annotated human resources and involvement in the management of the collections and CRB of Rennes
- Initiators of biobanks of liver cancers and Giant Cell tumors of bones

The team METHER brings together researchers and hospital practitioners towards a common interest in metal's metabolisms, the clinical impacts of iron overload in liver diseases, bone, oral and intestinal microbiota, and innovative radioactive/stable metal-based therapies to target liver cancers.

Research Brief :

Disruption of metal homeostasis for instance in genetic and secondary iron overload diseases, induces liver, heart and pancreas damages and contributes to bone lesions. The maintenance of metal homeostasis implies a tightly controlled regulation of their systemic and cell metabolisms resulting from equilibrium between amounts absorbed by the gastrointestinal tract, losses, storage, and proper addressing in the different cells and organs.
Other metals, including rare-earth and transition metals are increasingly used as stable isotopes to create cytotoxic drugs or as radionuclides for applications in theranostics and therapy in oncology. Metal-based therapies are undoubtedly promising approaches for clinical applications in cancer vectorized therapy when combined to synthetic molecules, nanoparticles or microspheres that allow site specific addressing.
Our objectives are to follow up with previous studies on iron-related diseases, including characterization of interactions with microbiota and other metals, and to develop metal-based therapies using innovative peptide-metal-chelator conjugated macromolecules and radioactive metals conjugated microspheres/lipiodol for therapies of primary liver cancers.

- **Methodologies Used :**

In vitro models of hepatic and pancreatic cells, establishment of recombinant cell lines, in vivo experiments in rodents, clinical trials, genomic profiling, RNA interference, RT-qPCR, protein expression and catalytic activity analysis, HPLC, phage display, formulation and cell uptake of polymeric nanoparticles, nanotoxicological evaluation, radiolabeling of microspheres.

Publications

Kenawi M., Rouger E., Island M.L., Leroyer P., Robin F., Remy S., Tesson L., Anegon I., Nay K., Derbre F., Brissot P., Ropert M., Cavey T., Loreal O (2019). Ceruloplasmin deficiency does not induce macrophagic iron overload: lessons from a new rat model of hereditary aceruloplasminemia, FASEB J. 33(13492), 13502

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Landemaine A, Hamdi-Roze H, Cunat S, Loustaud-Ratti V, Causse X, Si Ahmed SN, Drénou B, Bureau C, Pelletier G, De Kerguenec C, Ganne-Carrie N, Durupt S, Laine F, Loréal O, Ropert M, Detivaud L, Morcet J, Aguilar-Martinez P, Deugnier YM, Bardou-Jacquet E (2022). A simple clinical score to promote and enhance ferroportin disease screening., J Hepatol. 76(568), 576

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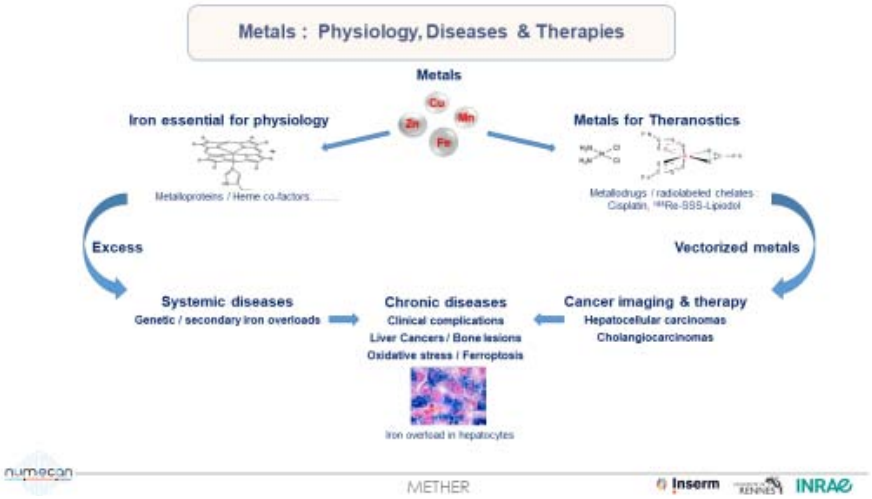
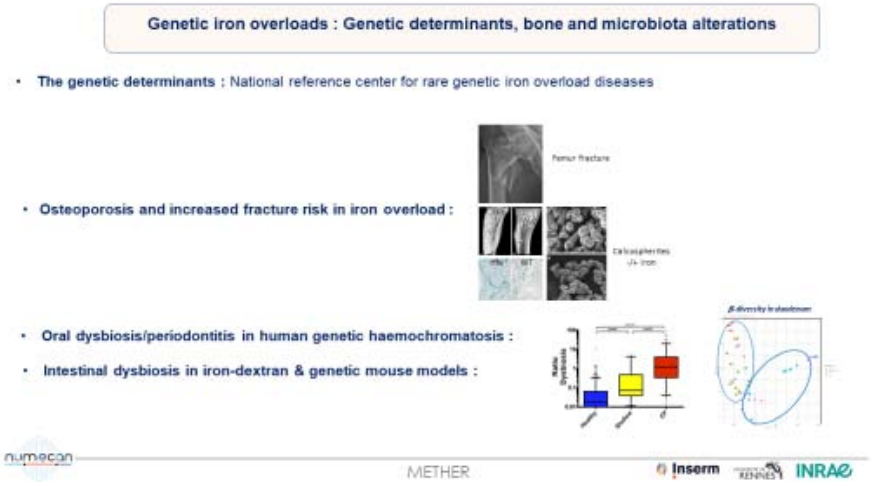
METHER themes



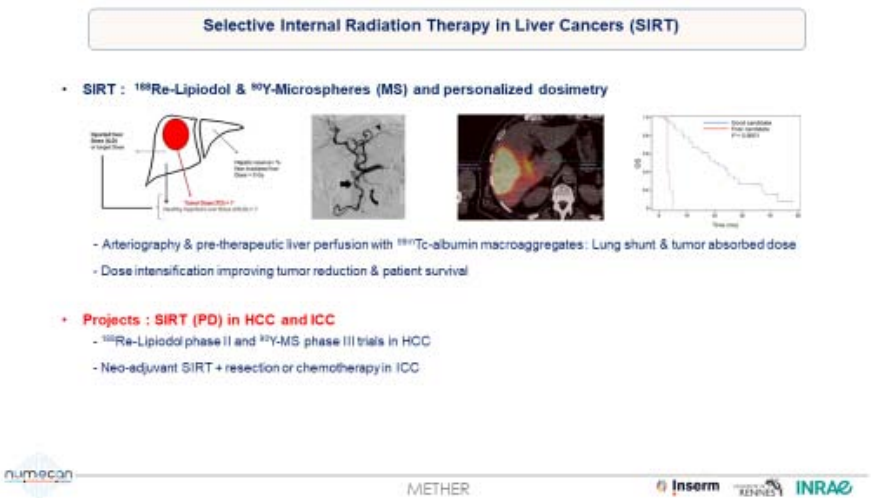
Essential metals, including iron, are crucial for cell fate through their roles as co-factors of multiple metalloproteins. When present in excess, iron generate systemic and chronic diseases characterized by multiple clinical complications including cirrhosis, hepatocellular carcinomas, but also bone lesions and dysbiosis. On the other hand, metallodrugs and radioactive metals incorporated in different organic molecules are used as therapeutic for the treatment of liver cancers.

Genetic iron overlaods and relaetd diseases



Team members are involved in the national center for the genetic iron overload diseases to identify new genetic determinants. We are also investigating whether hepcidin levels and alterations in other metal contents play a role in bone alterations observed during iron overload. Our team reported oral and intestinal dysbiosis in hemochromatosis patients and in mouse models of iron overloads. The project is to study the effects of microbiota alterations on systemic iron metabolism.

Internal Radiotherapy in liver cancers



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Our team is pioneer in the development of metabolic radiotherapy in hepatocellular and cholangio-carcinomas. The pre-therapeutic evaluation of 99Tc albumin aggregates accumulation led to the concept of personalized dosimetry significantly improving patient survival. We conducted clinical trials for 188Re lipiodol (phase I), 90Y microspheres (multicentric randomized phase II) and neo-adjuvant radioembolization for large tumor down-sizing.

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Key facts

Team

- Researchers : 12
- Technicians : 2
- Postdoc fellows : 1
- PhD Students : 5

Translational approaches

- Patents : 3
- Clinical research grants : 3
- Industry partnerships : 2

Keywords

- Innate and adaptive immunity
- liver diseases
- cirrhosis
- animal models
- clinical studies and trials

Biological Resources

- In vitro models
- In vivo models
- cohort

Sophie Lotersztajn

Inflammatory responses in chronic liver diseases

Université de Paris 07
(Université Denis Diderot)
Inserm UMR1149
Renato Monteiro
Paris

Translational research in the field of advanced chronic liver diseases

Research Brief :

The team of S Lotersztajn studies the mechanisms underlying chronic liver disease progression to cirrhosis and its complications, with an emphasis on the identification of prognosis markers and therapeutic targets for fatty liver diseases. Our research program focuses on the identification of immunometabolic targets and biomarkers of liver and systemic inflammation.

Non-alcoholic and alcoholic fatty liver diseases (NAFLD, ALD) are leading causes of liver diseases worldwide. They share common pathogenic features including steatosis and steatohepatitis (alcoholic-ASH and non-alcoholic-NASH) that lead to fibrosis and cirrhosis. Persistent inflammation is a driving force of liver fibrosis progression during NAFLD and ALD. Among patients with cirrhosis, excessive inflammation results in the development of multiorgan failure (defining acute-on-chronic liver failure, ACLF), which often leads to death. The lack of treatment highlights the urgent need for new prognosis markers and specific therapeutic targets that could limit liver injury, fibrosis, progression of cirrhosis to ACLF, and favour liver regeneration.

Methodologies Used :

Animal models
Metabolomics/transcriptomics/RNA Seq
Confocal Microscopy

Publications

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Lotersztajn Sophie - sophie.lotersztajn@inserm.fr - 0157277429 - http://www.cri1149.fr/

Key facts

Team

- Researchers : 2
- Technicians : 3
- Postdoc fellows : 2
- PhD Students : 3

Translational approaches

- Patents : 3
- Clinical research grants : 2
- Industry partnerships : 3

International research links

- Spain
- Italy
- Germany

Keywords

- liver
- endothelial cells
- extracellular vesicles
- cirrhosis
- NASH
- Isolation of liver sinusoidal cells
- animal model
- qNano

Biological Resources

- Animal models
- Cohorts of plasma from human

Pierre-Emmanuel Rautou

Roles of vessels in liver diseases

Université Paris Cité
Inserm U1149
Renato Monteiro
Paris

Our team can isolate liver sinusoidal endothelial cells from mouse to understand their roles in liver diseases. We can also isolate and analyze extracellular vesicles from blood or tissue (mouse and human) and characterize them.

Research Brief :

Our team is working on the role of vessels in liver disease. Specifically, our current research directions focus on:
(1) liver endothelial cells and their role in non-alcoholic steatohepatitis, cirrhosis and aging.
(2) extracellular vesicles, that are membrane-bound vesicles released by cells into the extracellular space, with 2 aims: (a) analyze their interest as biomarkers in liver diseases; (b) determine their role in liver disease progression.
(3) porto-sinusoidal vascular disorder

- **Methodologies Used :**

- Isolation, culture and characterization of liver sinusoidal cells (WB, qPCR, microscopy)
- Animal model of cirrhosis and NASH; transgenic animals
- Generation and isolation of extracellular vesicles from plasma and tissue (mouse and human)
- Immunofluorescence, western blot, quantification and proteomics of extracellular vesicles

Publications

Vion AC, Kheloufi M*, Hammoutene A, Poisson J, Lasselin J, Devue C, Pic I, Dupont N, Busse J, Starke K, Lafaurie-Janvore J, Barakatf AI, Loyer X, Souyri M, Viollet B, Julia P, Tedgui A, Codogno P, Boulanger CM*, Rautou PE* (2017). Autophagy is required for endothelial cell alignment and atheroprotection under physiological blood flow., Proc Natl Acad Sci U S A.. (),*

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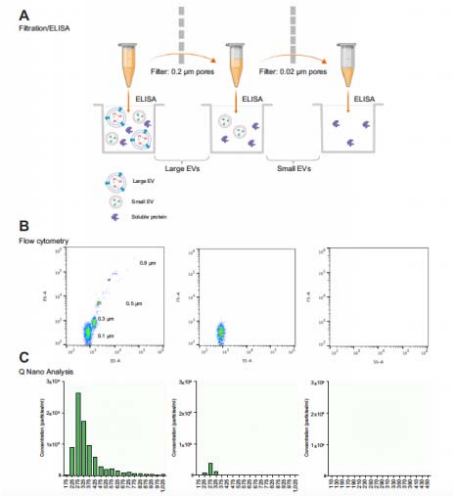
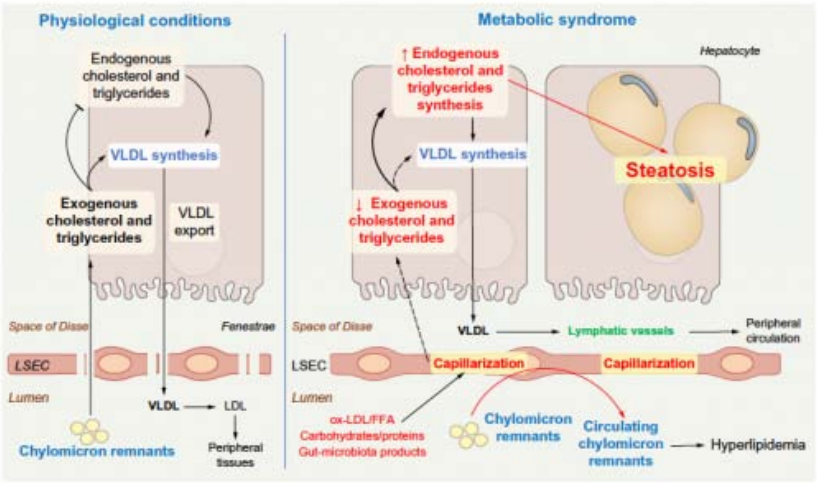
Extracellular vesicle subpopulation detection method by filtration/ELISA



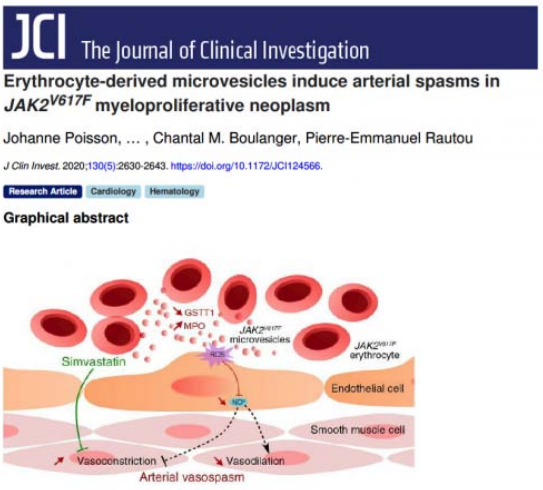
Graphical representation of the filtration/ELISA method (Thietart & Rautou, J Hepatol 2020).
ELISA is performed on platelet-free plasma before filtration, after double filtration through 0.2 um pores, and after filtration through 0.02 um pores.

LSEC capillarization promotes steatosis



FFA, free fatty acids; LDL, low-density lipoprotein; LSECs, liver sinusoidal endothelial cells; NAFLD, non-alcoholic fatty liver disease; ox-LDL, oxidized low-density lipoprotein; VLDL; very low-density lipoprotein. (Hammoutène & Rautou, J Hepatol 2019)

Erythrocyte-derived microvesicles induce arterial spasms in JAK2V617F myeloproliferative neoplasm



Genetically modified mice developing JAK2V617F myeloproliferative neoplasms have a strong arterial contraction in response to vasoconstrictors that could account for arterial cardiovascular events observed in patients.Microvesicles, derived from red blood cells, and circulating in the blood of patients with JAK2V617F myeloproliferative neoplasms transfer a protein (myeloperoxidase) to endothelial cells thus increasing arterial response. (Poisson et al, J Clin Invest 2020)

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Uro-Nephrology

Key facts

Team

• Researchers : 11
• Technicians : 9
• Postdoc fellows : 0
• PhD Students : 3

Translational approaches

• Patents : 2
• Clinical research grants : 1
• Industry partnerships : 2

International research links

• Germany, Greece, UK, Italy, Spain, Poland, Belgium, The Netherlands.

Keywords

• kidney disease
• cardiovascular complications
• personalised medicine
• biomarkers
• inflammation, fibrosis, calcification
• animal models
• Translational research
• omics (transcript- (single cell) proteo- metabol-)
• semi quantitative immunohistochemistry
• Cohorts

Biological Resources

• In vivo models
• Cohorts of diabetic type 1 diabetic individuals, individuals with developmental nephropathies, with CKD, with AKI after cardiac surgery or chemotherapy
• Biobank (urine, plasma) of individuals with kidney disease.

Joost Schanstra

Biomarkers, mechanisms and complications of kidney disease

Université de Toulouse 3
(Université Paul Sabatier)
Inserm U 1297
Dominique Langin
Toulouse

Development of new concepts of nephroprotection using translational research and state of the art technologies

Research Brief :

Chronic kidney disease (CKD) patient numbers are dramatically rising, reaching nowadays 15% of the general adult population. This is due to the increased incidence of diabetes, aging and recently also acute kidney injury (AKI). Individuals, even with early-stage CKD, have a significantly increased risk of cardiovascular disease (CVD) complications.
Early detection of AKI and CKD or prediction of CVD complications and early treatment is key in the clinical management of kidney disease. We focus our research on the early detection of these entities in both the pediatric and adult population using innovative mostly non-invasive, omics-based, approaches. In parallel we analyze this omics data for the identification of novel targets using systems medicine and drug repurposing techniques. We believe that such novel approaches will significantly improve the clinical management of individuals, both children and adults, with kidney disease.

• **Methodologies Used :**

Animals models of CKD (Unilateral ureteral obstruction, Remnant kidney, Glomerulonephritis, Diabetic nephropathy) and AKI (LPS, Hemorrhagic Shock, rhabdomyolysis).
Molecular biology (qPCR, ChipSeq).
Immunohistochemistry (animal and human renal tissue).
Omics: -transcriptomics (single cell), proteomics and metabolomics.
Bioinformatics

Publications

Casemayou A, Fournel A, Bagattin A, Schanstra J, Belliere J, Decramer S, Marsal D, Gillet M, Chassaing N, Huart A, Pontoglio M, Knauf C, Bascands JL, Chauveau D, Faguer S. (2017). Hepatocyte Nuclear Factor-1 ? Controls Mitochondrial Respiration in Renal Tubular Cells, J Am Soc Nephrol. 28(11), 3205

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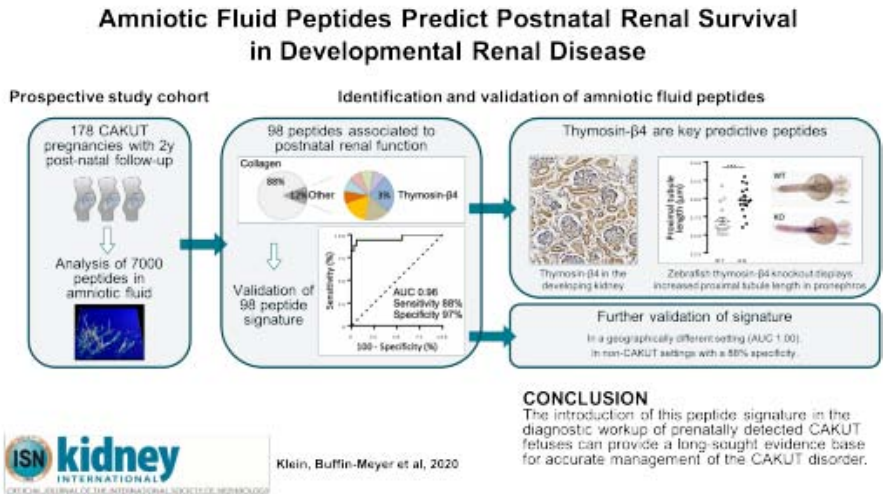
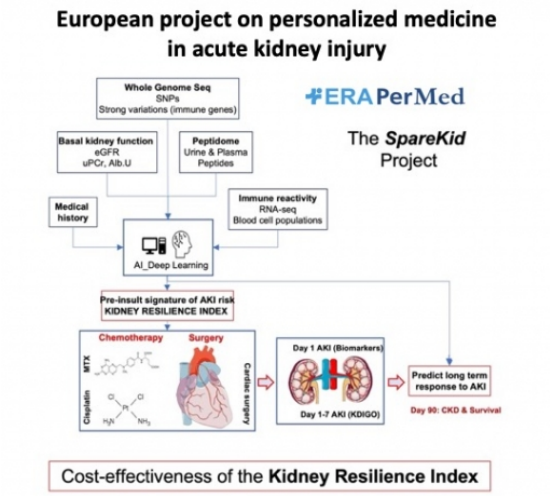
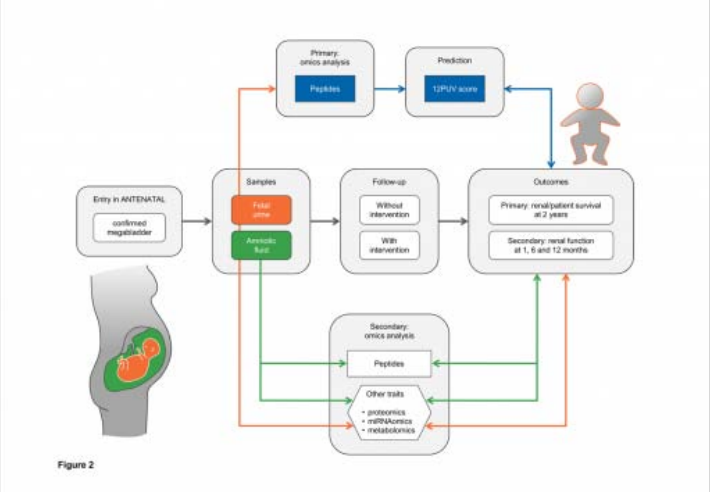
Amniotic Fluid Peptides Predict Postnatal Renal Survival in Developmental Renal Disease



Personalized medicine in acute kidney injury



Pan European clinical trial for implementation of omics analysis in clinical routine



Schanstra Joost - joost-peter.schanstra@inserm.f r - 0531224078 - http://www.renalfibrosis.fr/ and http://www.i2mc.inserm.fr/index.php/en/research-teams/team-12

Christos Chatziantoniou

Common and Rare Kidney Diseases: from Molecular Events to Precision Medicine (CoRaKiD)

Faculty of Medicine Sorbonne Université
Inserm UMR S 1155
Christos Chatziantoniou
PARIS

These studies significantly contribute to a better understanding of the mechanisms involved in the development of renal disease and to provide important clues of how this incurable today pathology can be stopped or even better reversed.

Key facts

Team

- Researchers : 29
- Technicians : 14
- Postdoc fellows : 5
- PhD Students : 12

Translational approaches

- Patents : 6
- Clinical research grants : 5
- Industry partnerships : 4

International research links

- USA, China, Germany, Greece, Italy, Norway, Canada, Japan

Keywords

- Renal Inflammation
- Genetics of Renal Disease
- Renal Transplantation
- Acute Kidney Injury
- Chronic Kidney Disease
- Genetic Analysis
- Genetically modified rodents
- Experimental models of renal disease
- Transcriptomics, Real time Q-PCR, siRNA
- Morphometry, Structural Analysis

Biological Resources

- Experimental models of nephropathies that correspond to acute (ischemia-reperfusion), vascular (Ang II), glomerular (anti-GMB) and tubular (unilateral ureteral obstruction) injuries
- European cohort Membranous Nephropathy/EUREnOmics network
- Cohorts: Nephrotest, Corirla, Renal Transplant Biopsies, Idiopathic Nephrotic Syndrome
- Renal cell cultures (mesangial, podocytes, vascular smooth muscle, tubular epithelial, collecting duct)
- Cohorts: Drepanocytose homozygotes, Lithiasis, Marhea

Research Brief :

Our research activities are devoted to pathophysiology of kidney diseases, being bi-directionally oriented from the bench to the bedside (translational research) and from the bedside to the bench (clinical research). Characteristic examples of our research are the identification of antigens and predisposing genes in membranous nephropathy and the description of a new systemic disease related to COL4A1 mutations. Another main objective is the identification of novel biomarkers and druggable molecular targets. Representative examples are DDR1, periostin, calpain, or Cx43. Our findings triggered the interest of the valorisation department of our institutions and of industrial partners as evidenced by the number of patents submitted, signed contracts and awards related to drug development.
Recently we have added 2 new directions corresponding to emerging issues of nephrology: the mechanisms and complications of the AKI and repair, and the mechanisms involved in nephrolithiasis, two important risk factors for developing CKD. The arrival of young dynamic fellows with established expertise in these fields strengthened our capacity to deal with these objectives.
An additional strength results from the fact that we are closely connected with the clinical departments of Nephrology, Physiology and Pathology in Tenon and St Antoine Hospitals, and we have contributed to the establishment of 15 patients? cohorts at the local (Corirla), national (Nephrotest) or international level.

- **Methodologies Used :**

Renal Hemodynamics, BP, RBF, GFR, electrolytes
Transcriptomics, Real Time Q-PCR, siRNA,
Laser microdissection, Renal Morphology, Histology, Immunocytochemistry,
Transgenic animals, Experimental nephropathies,
Intra-vital microscopy, Confocal microscopy, Electron microscopy
Cell cultures, stable-transient transfections

Publications

Gaudry S, Hajage D, Benichou N, Chaïbi K, Barbar S, Zarbock A, Lumlertgul N, Wald R, Bagshaw SM, Srisawat N, Combes A, Geri G, Jamale T, Dechartres A, Quenot JP, Dreyfuss D. (2020). Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials, Lancet. 395(May 9), 1506-1515

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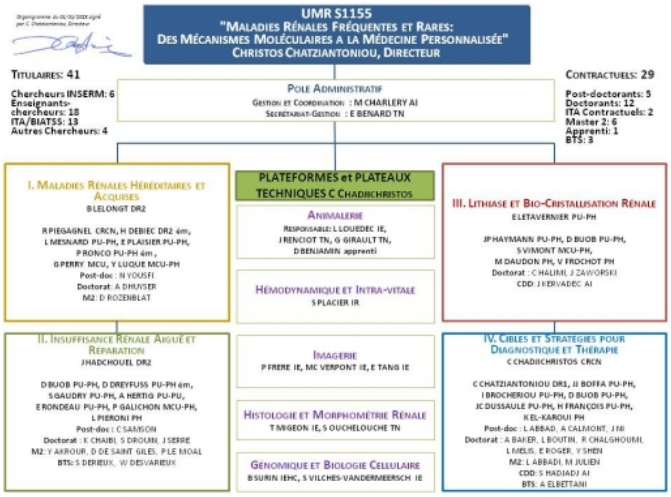
Project for the 2019-2023 period

A schematic overview of the 4 themes with their specific sub-projects

Organizational Chart of Inserm UMR S 1155



Personnel, Themes, Plateforms and Management of Inserm UMR S 1155 at the beginning of 2023.

2022 Annual Retreat

Nogent sur Marne 2022

The 2022 Annual Retreat of UMR S 1155 took place at Nogent sur Marne on September 28-29.

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Pierre-Louis Tharaux Eric Camerer

Kidney and Vascular Signalling: from Development to Disease

Université de Paris
Inserm UMR970
Chantal Boulanger
Paris

Using cultured cells, mouse models and human tissue samples and data, we study the physiological and pathological roles of signalling pathways relevant to disease therapy in embryonic development, adult physiology and pathology with focus on kidney, retina, heart and brain.

Key facts

Team

- Researchers : 3
- Technicians : 1
- Postdoc fellows : 3
- PhD Students : 6

Translational approaches

- Patents : 3
- Clinical research grants : 2
- Industry partnerships : 1

International research links

- United Kingdom
- Germany
- United States

Keywords

- Kidney Diseases
- sphingosine-1-phosphate
- Protease-activated receptors
- Translational research
- endothelial barrier function
- autophagy
- mouse models of human disease
- cell signaling assays
- mouse genetics and embryology
- Multi-Omics

Biological Resources

- Partnership with the department of Nephrology and Pathology at the Georges Pompidou European Hospital.
- Cohort of sickle cell patients.
- Mouse knockout and transgenic models.
- Bio-banked human kidney biopsies.
- Cohort of patients with kidney diseases

Research Brief :

Our team aims to unravel fundamental mechanisms that govern the formation and function of blood vessels and the contribution of vascular dysfunction to disease, with a special emphasis on the kidney. Our team consists of three groups: the Camerer group studies functions of G protein- coupled receptors (GPCRs) in vascular development and disease, and the Tharaux group studies the role of GPCRs and receptor tyrosine kinases (RTKs) in pathologies that arise secondary to kidney capillary dysfunctions or cause them. We have a common interest in how these receptor families regulate vascular integrity and how loss of vascular integrity exacerbates inflammatory disease, and we both use genetic and pharmacological tools to address these questions in mouse models. We closely work with the Department of Nephrology at the Hôpital Européen Georges-Pompidou as well as with the Dpt of Interbal Medicine, Cochin hospital on translational aspects. Our main scientific goals are to: 1. Identify roles for and mechanisms of GPCR signaling in development and 2. Improve our understanding of the pathogenesis of vascular and glomerular diseases (primarily focal segmental glomerulosclerosis (FSGS), sickle cell nephropathy, crescentic glomerulonephritis (RPGN), diabetic nephropathy) with endothelial and podocyte damage 3. Identify critical switches in the pathogenesis of glomerular diseases with mouse-human cross-species multiscale studies for mechanistic insights and drug target validations.

• Methodologies Used :

To address mechanisms of receptor activation, signaling consequences on cellular programming and behavior, and ultimately function, we couple biochemical and cell culture experiments to mouse genetic models of deficiency, gain of function and time- and tissue- specific expression. Our embryonic studies focus on vascular development, while studies in adults focus on microvascular and kidney diseases. We study multiple animal models of human kidney diseases and conduct systematic cross validation procedures using biobanked human tissues using multi-omic and digital pathology technologies.

Publications

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Bensaada I, Robin B, Perez J, Salemkour Y, Chipont A, Camus M, Lemoine M, Guyonnet L, Lazareth H, Letavernier E, Hénique C, Tharaux PL, Lenoir O (2021). Calpastatin prevents Angiotensin II-mediated podocyte injury through maintenance of autophagy, Kidney Int. 100(1), 90-106

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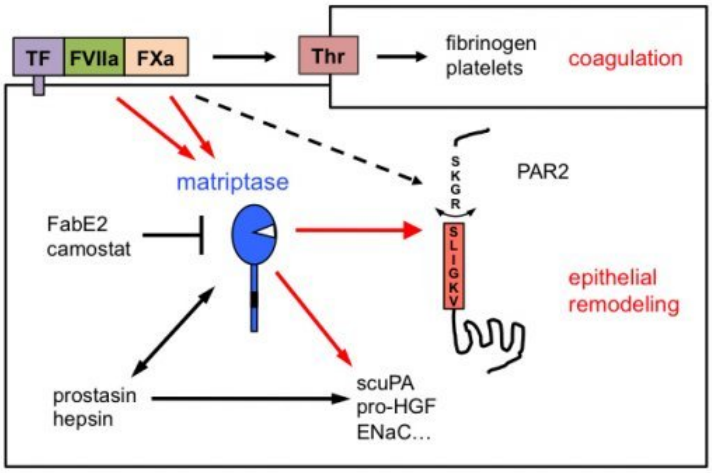
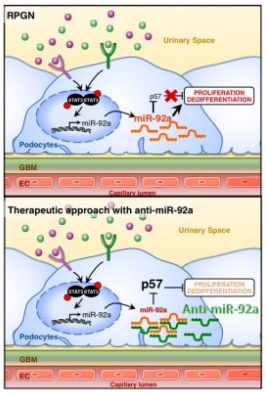
Matriptase connects the coagulation cascade to epithelial signaling and proteolysis.



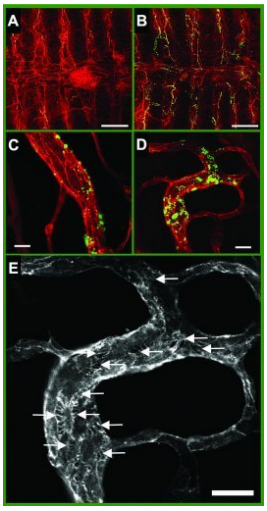
Schematic representation of how matriptase amplifies coagulation factor signaling in epithelia. Our results suggest that FVIIa and FXa both directly activate matriptase, which in turn activates PAR2 and processes other epithelial substrates. This may connect coagulation activation to epithelial remodeling. Matriptase also mediates PAR2 signaling by the epithelial membrane anchored proteases hepsin and prostasin. Le Gall et al, Blood, 2016



Supplementary Figure 9: ***Working model for the involvement of miR-92a in the pathogeny of crescent formation during RPGN and potential therapeutic strategy.***
Various ligands (green dots and purple dots) for podocyte surface receptors are synthesized by autocrine and paracrine mechanisms. These ligands stimulate the STAT3-mediated upregulation of miR-92a and resulting downregulation of $p57^{Kip1}$ (p57).
Upper panel: MiR-92a is pivotal in maintaining podocyte tolerance to inflammatory insults. Among potential other actions, miR-92a eliciting repression of the CDK inhibitor $p57^{Kip2}$ unlocks cell cycle check points. This event, together with mitogenic stimuli elicited by these upstream pathways promotes podocyte proliferation resulting in proteinuria, destruction of the glomerular filtration barrier and declining renal function.
Lower panel: Anti-miR-92a strategy favors podocyte quiescence and tolerance to mediators of immune and mitogenic stress.

Working model for the involvement of miR-92a in the pathogeny of crescent formation during RPGN and potential therapeutic strategy Genetic and pharmacological inhibition of microRNA-92a maintains podocyte cell cycle quiescence and limits crescentic glomerulonephritis. Nat Commun 2017

Mice that lack S1P in plasma display enhanced vascular leak.



Control (A,C) and plasma S1Pless (B,D,E) mice were injected i.v. with fluorescent beads and PAF, then perfused with saline 3 minutes later. (A,B) Merged z-stacks at low power with microspheres in green and an endothelial marker in red. (C, D) Representative single plane images at high power. (E) Enlarged image of (D) showing only the red channel. Arrows point to intercellular gaps bridged by filopodia-like extensions. Note increased leak in plasma S1Pless mice. Camerer et al, JCI, 2009

Key facts

Team

- Researchers : 11
- Technicians : 8
- Postdoc fellows : 3
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- Kidney Physiology
- Ion transport
- Blood pressure
- Lithiasis
- Hyperkalemia hypokalemia
- Metabolic cages
- Renal phenotype
- renal tubule isolation
- microperfusion of isolated tubules
- urine and plasma electrolyte measurements

Gilles Crambert

Renal Physiology and Tubulopathies

Sorbonne Université Université de Paris
Inserm U1138 CNRS ERL8228
Gilles Crambert
Paris

We have a rare combination of expertise, ranging from molecular biology to cellular biology and physiology, in order to study renal tubular structures and to analyze animal models of human diseases.

Research Brief :

The kidney matches urinary excretion to the daily intake of water and nutrients. Homeostatic perturbations may occur due to kidney dysfunctions (tubulopathies) or be secondary to systemic disorders (metabolic syndrome, diabetes ...) or to the side effects of drugs. They are responsible for a number of renal and extrarenal sequelæ (stone disease and/or nephrocalcinosis, hypertension and cardio-vascular events, life-threatening plasma ionic disorders). Our project focuses:
- 1/ on the renal mechanisms that maintain ion (Na+,Cl-, K+, Ca2+ and Mg2+) and water homeostasis. Thus, we develop research projects that concern trans- and paracellular pathways that aim at identifying and characterizing novel transporters and regulatory pathways all along the renal tubule
- 2/ on related human disorders associated to these processes. Mainly tubulopathies of genetic origin like Bartter, Gitelman and Dent syndromes but also of exogenous origin like pharmacological treatments (lithium etc...).
- 3/ on the development of technologies needed to investigate these processes. We have developed a technical platform (available for internal or external collaborations upon request) that allows us to completely establish the renal phenotype of mice and rats, including dissection of tubular segments for qPCR, WB or IF and microperfusion.
For more information regarding our lab, you can visit our Facebook page: https://www.facebook.com/Transport.Ionique.Renal/ and follow us on Twitter @et_rein

- **Methodologies Used :**

Metabolic cages - urine collection and analyse - Plasma and urine ionogramme - renal tubule isolation - microperfusion of isolated renal tubules

Publications

Laghmani K, Beck BB, Yang S-S, Seaayfan E, Wenzel A, Reusch B, Vitzthum H, Priem D, Demaretz S, Bergmann K, Duin LK, Gobel H, Mache C, Thiele H, Bartram MP, Dombret C, Altmuller J, Nurnberg P, Benzing T, Levtchenko E, Seyberth HW, Klaus G, Yigit G, Lin S-H, Timmer A, de Koning TJ, Scherjon SA, Schlingmann KP, Bertrand MJM, Rinschen MM, de Backer O, Konrad M, and Komhoff M. (2016). Polyhydramnios, Transient Antenatal Bartter's Syndrome, and MAGED2 Mutations, The New England Journal of Medicine. 374(), 1853-1863

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Research teams with secondary association to PMN Institute

Key facts

Team

- Researchers : 3
- Technicians : 1
- Postdoc fellows : 1
- PhD Students : 2

Translational approaches

- Patents : 1
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- United States
- Australia
- United Kingdom

Keywords

- endosome
- dendritic cells
- T cells
- inflammation
- dendritic cells culture
- antigen presentation assays
- microscopy
- cellular biology
- mouse models

Biological Resources

- animal models with constitutive and tissues-specific protein deletion

Loredana Saveanu

Antigen presentation to T cells

Université de PAris
Faculté de Médecine Bichat
Inserm U1149
Renato Monteiro
Paris

Our hallmark is the identification of cell specific slow recycling endosomes which are involved in the regulation of both innate and adaptive immune response. We are intending to characterize the endocytic signaling platforms formed at this level by ITAM-coupled immune receptors.

Research Brief :

Antigen presentation to T cells is a key event in the immune defense against pathogens and cancers. Our team investigates the cell biology and molecular mechanisms that allow T cell activation by antigen presenting cells, with an important focus on the role of endocytic system in this process.
An important function of endocytic system is internalization of activated cell surface receptors, which might lead to either extinction or amplification of receptor signaling, depending on the strength of receptor activation and endocytosis pathway. Thus, it has been established that endocytosis tightly regulates the signaling via growth factor receptors. Interestingly, key immune receptors, such as T cell receptor (TCR), B cell receptor (BCR) and the activating FcRs are internalized after ligand binding, but it is not clear if their endocytosis terminates or sustains the signaling. We demonstrated that slow recycling cell specific endosomes are intracellular signaling platforms for the TCR. By a combination of cellular biology methods and immunization of model animals, we aim to: 1) identify TCR and FcgR interactions in the native local milieu of receptor signaling; 2) establish the impact of endosomal signaling on antigen presentation ability of antigen presenting cells.

- **Methodologies Used :**

dendritic cells culture
t cell activation assays
constitutive and ko mouse models
lentiviral expression and knock-down
cell biology
confocal microscopy
TIRF microscopy
molecular biology (cloning, qRT-PCRs)
recombinant protein expression

Publications

Saveanu L, Lotersztajn S (2016). Focus on \\\\\\\"Active vacuolar H+ ATPase and functional cycle of Rab5 are required for the vacuolation defect triggered by PtdIns(3,5)P2 loss under PIKfyve or Vps34 deficiency\\\\\\\", Am J Physiol Cell Physiol. 311(3), 363

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Weimershaus M, Mauvais FX*, SAVEANU L*, Adiko C, Babdor J, Abramova A, Montealegre S, Lawand M, Evnouchidou I, Huber KJ, Chadt A, Zwick M, Vargas P, Dussiot M, Lennon-Dumenil AM, Brocker T, Al-Hasani H, van Endert P. (2018). Innate Immune Signals Induce Anterograde Endosome Transport Promoting MHC Class I Cross-Presentation., Cell Reports. 24(13), 3568*

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Drajac C, Laubreton D, Marquant Q, Chottin C, Ferret C, Bouguyon E, Schwartz-Cornil I, SAVEANU L, Riffault S, Descamps D (2021). Control of IFN-I responses by the aminopeptidase IRAP in neonatal C57BL/6 alveolar macrophages during RSV infection., Mucosal Immunology. 14(4), 949

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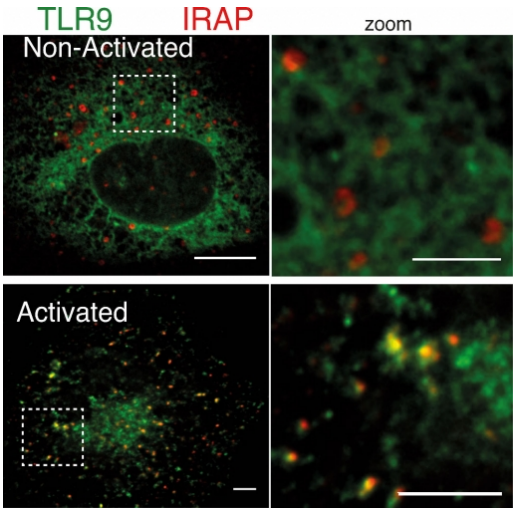
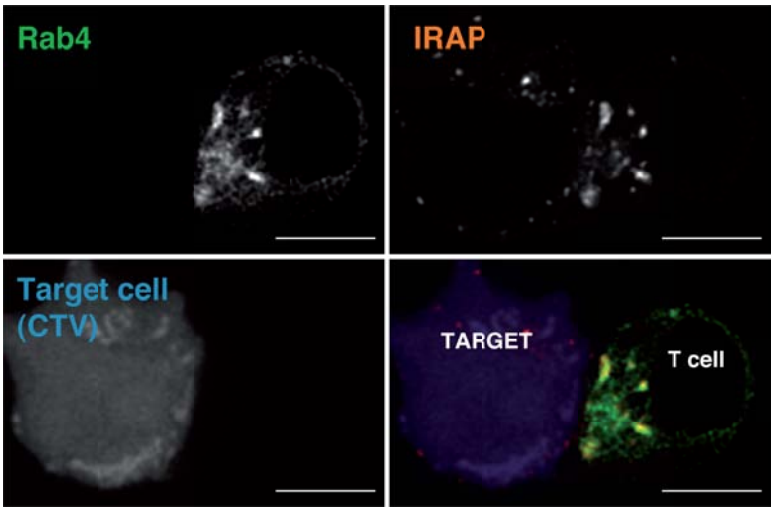
Endosomal TLRs are a cargo of cell specific storage endosomes



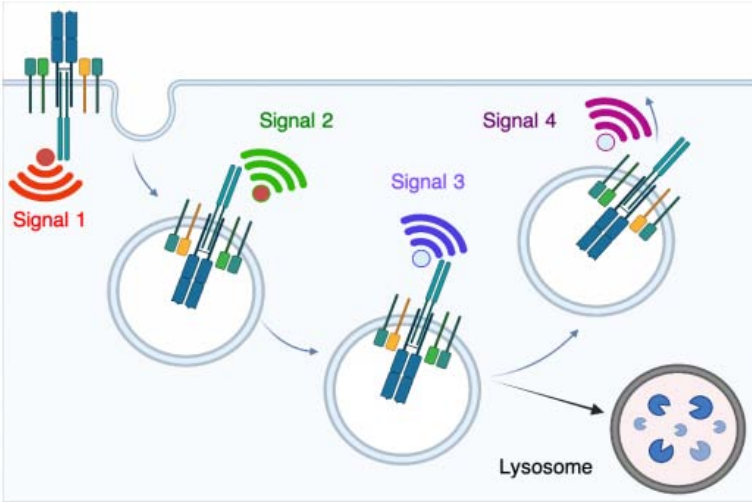
The aminopeptidase IRAP is a marker of cell-specific storage endosomes. These vesicles have a constitutive slow recycling and can be rapidly translocated to the cell surface under cell specific stimulation. In dendritic cells (DC), IRAP and its endosomal compartment are involved in regulation of both, innate and adaptive immunity. In DC, TLR9 (green) is trapped in IRAP endosomes (red), avoiding excessive inflammatory response triggered by TLR9 (Babdor et al. Nature Immunol. 2017)

Cell specific slow recycling endosomes in T cells



Cell specific slow recycling endosomes described by IRAP (red) and Rab4 (green) contains the CD247 chain of the TCR (Evnouchidou et al., Nature Communications 2020)

Antigen T cell Receptor signals from endosomes



Antigen T cell receptor signals along the slow recycling endocytic pathway, leading to signal amplification and diversification.

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Key facts

Team

- Researchers : 5
- Technicians : 3
- Postdoc fellows : 2
- PhD Students : 5

Translational approaches

- Patents : 5
- Clinical research grants : 3
- Industry partnerships : 3

Keywords

- proteinase 3
- remodelling
- apoptosis
- systemic sclerosis
- vasculitis
- neutrophil
- inflammation
- proteomic
- myeloid transfection
- cell biology

Biological Resources

- In vitro and in vivo models of neutrophil activation and apoptosis to test pro-apoptotic anti-inflammatory molecules
- Serum, plasma, cell collections of vasculitis and systemic sclerosis patients
- DNA bank for vasculitis patients
- Collections of vascular smooth muscle cells from patients with vasculitis and collections of fibroblasts from systemic sclerosis patients
- Cohorts and data bases for systemic sclerosis and vasculitis patients

Véronique Witko-Sarsat

Neutrophils and vasculitis

Université de Paris 05
(Université Rene Descartes)
Inserm U1016
Pierre-Olivier Couraud
Paris

The strength of the team is the synergy between basic and clinical research with an access to a large data base and unique biological material and to possess the required know-how to achieve its goals.

Research Brief :

The pathogenesis of anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides is characterized by the involvement of neutrophils as cardinal cells that are activated and responsible for the vessel wall injury resulting in lung and renal lesions. Neutrophil activation increases expression of granule proteins such as proteinase 3 (PR3) in Wegener's granulomatosis, that are targeted by specific autoantibodies exerting pathogenic effects. Immune perturbations extend to other target cells such as endothelial cells with potential deleterious effects.
The team co-directed by Luc Mouthon is focused on the cellular and immunological aspects of vasculitis pathophysiology and takes the opportunity of the very specific recruitment of patients with systemic vasculitis of the "National reference center for systemic vasculitidis and systemic sclerosis" at Cochin Hospital.
The team has a multidisciplinary and integrative project with three aims:
1) study of the mechanisms regulating neutrophil apoptosis and their phagocytosis by macrophages, which is pivotal for the inflammation resolution and for avoiding autoimmunity
2) elucidation of the mechanisms of neutrophil activation and the role of PR3 in triggering a specific vasculitis, Wegener's granulomatosis
3) identification of target antigens and potential pathogenic role of autoantibodies against endothelial cells and vascular smooth muscle cells in vascular diseases.

Methodologies Used :

Molecular biology, cell biology and immunochemistry techniques
Neutrophil isolation, activation and apoptosis measurement by flow cytometry
Stably transfection of myeloid cell lines, which can differentiate into mature granulocytes allow to perform loss- or gain- of function for functional studies.
Animal models of inflammation (peritonitis, vasculitis)
Proteomic analysis two dimension differential in gel electrophoresis (2D-DIGE)
Identification of target autoantigens by proteomic combined to immunoblot analysis

Publications

Witko-Sarsat V, Mocek J, Bouayad D, Tamassia N, Ribeil JA, Candalh C, Davezac N, Reuter N, Mouthon L, Hermine O, Pederzoli-Ribeil M, Cassatella MA. (2010). Proliferating cell nuclear antigen acts as a cytoplasmic platform controlling human neutrophil survival., Journal of Experimental Medicine. 207(12), 2631-45

Bussone G, Tamby MC, Calzas C, Kherbeck N, Sahbatou Y, Sanson C, Ghazal K, Dib H, Weksler BB, Broussard C, Verrecchia F, Yaici A, Witko-Sarsat V, Simonneau G, Guillevin L, Humbert M, Mouthon L. (2012). IgG from patients with pulmonary arterial hypertension and/or systemic sclerosis binds to vascular smooth muscle cells and induces cell contraction., Annals Rheumatic Disease. 71(4), 596-605

Proteinase 3 on apoptotic cells disrupts immune silencing in autoimmune vasculitis. Millet A, Martin KR, Bonnefoy F, Saas P, Mocek J, Alkan M, Terrier B, Kerstein A, Tamassia N, Satyanarayanan SK, Ariel A, Ribeil JA, Guillevin L, Cassatella MA, Mueller A, Thieblemont N, Lamprecht P, Mouthon L, Perruche S, Witko-Sarsat V. (2015). Proteinase 3 on apoptotic cells disrupts immune silencing in autoimmune vasculitis., Journal of Clinical Investigation. 125(11), 4107-21

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Ohayon D, De Chiara A, Chapuis N, Candalh C, Mocek J, Ribeil JA, Haddaoui L, Ifrah N, Hermine O, Bouillaud F, Frachet P, Bouscary D, Witko-Sarsat V. (2016). Cytoplasmic proliferating cell nuclear antigen connects glycolysis and cell survival in acute myeloid leukemia., Scientific Reports. 6(), 35561

Martin KR, Kantari-Mimoun C, Yin M, Pederzoli-Ribeil M, Angelot-Delettre F, Ceroi A, Grauffel C, Benhamou M, Reuter N, Saas P, Frachet P, Boulanger CM, Witko-Sarsat V. (2016). Proteinase 3 Is a Phosphatidylserine-binding Protein That Affects the Production and Function of Microvesicles., Journal of Biological Chemistry. 291(20), 10476-89

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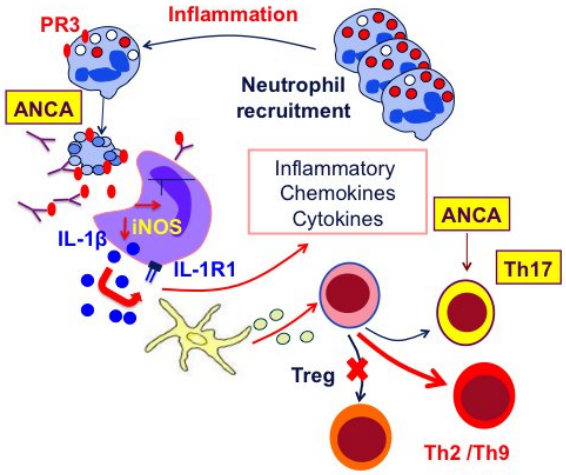
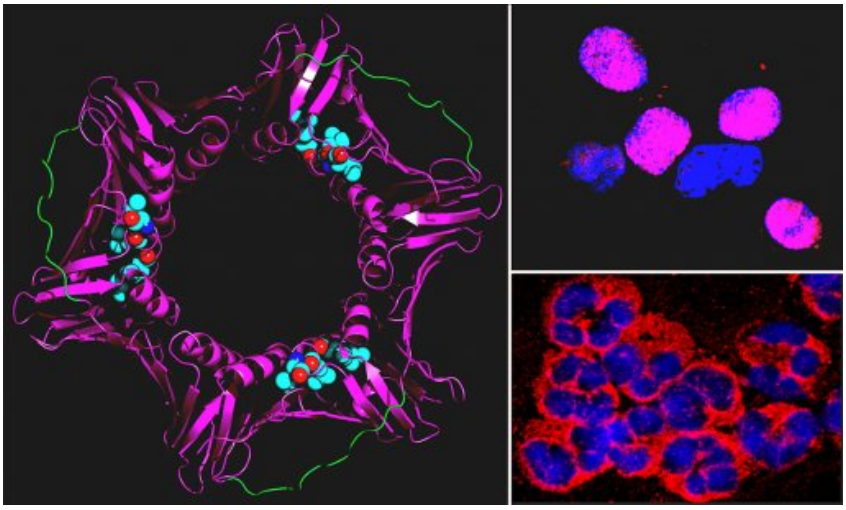
Proteinase 3, the autoantigen in vasculitis is a danger signal for the immune system.



During vascular inflammation, neutrophils can express proteinase 3 at the plasma membrane, which activates macrophages inducing the production of inflammatory cytokines. The inflammatory microenvironment favours activation of plasmacytoid dendritic cells which results in an inhibition of the generation of regulatory T cells favoring autoimmunity.

Key role of cytoplasmic PCNA in neutrophil survival



Trimeric structure of PCNA with the nuclear export sequence (NES) in blue at the inner face of the trimer. Immunofluorescence of PCNA (red) and nuclei (blue) in CD34 progenitors (upper panel). At the end of differentiation, PCNA is exported from nucleus to cytosol via its NES. In mature neutrophils, PCNA is exclusively cytosolic and is associated with different protein partners including procaspases to inhibit apoptosis (adapted from Witko-Sarsat et al J Exp Med 2010 and Immunol Reviews 2016).

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institutmondor
de recherche biomédicale

Djillali Sahali

Pathophysiology of Glomerular Diseases

Université de Paris 12
(Université Paris-Val de
Marne)
Inserm UMR 955
Jorge Boczkowski
Créteil

Key facts

Team

- Researchers : 9
- Technicians : 1
- Postdoc fellows : 1
- PhD Students : 3

Translational approaches

- Patents : 3
- Clinical research grants : 3
- Industry partnerships : 0

International research links

- Netherlands
- Spain
- USA

Keywords

- Pathophysiology
- immune regulation
- Podocyte
- Signaling
- Lymphocyte
- Gene therapy
- mouse models
- proteomics
- lipidomics

Biological Resources

- mouse models
- cohorts/biobanks
- serum library
- Protein library
- RNA library
- DNA library

Molecular pathophysiology of acquired idiopathic nephrotic syndrome

Research Brief :

Our work is mainly based on a bedside-to-bench project aimed to improve understanding the pathophysiology of glomerular diseases and to translate basic scientific findings into diagnostic and therapeutic perspectives for patients.
The team addresses the molecular pathophysiology of acquired glomerular diseases by studying the interplay among glomerular cells (podocytes, parietal epithelial cells and endothelial cells) and with the immune system (lymphocytes). Two research fields are currently developed. The first one relies on clinical and translational approaches to the understanding of idiopathic nephrotic syndrome (INS), including the study of both immunological and podocyte disorders. In this setting, several mouse models have been generated. The second concerns nephro-oncology, a new growing area of research aiming to understand the molecular mechanisms of glomerular alterations induced by targeted therapies in cancer. These projects are driven by different leaders of the team, who have established close collaboration with other teams specialized in the research field. Financial support for these projects is provided by the reference center grant and by current and future contracts.

- **Methodologies Used :**

Subtractive and differential screening
Cloning and construction of target vectors, sequencing
SiRNA in vivo
Immunohistochemistry and confocal microscopy
Immunochemistry
Cell cultures and generation of primary cell lines
Transgenesis and conditional knock out
Proteomics (global, membrane microdomain-related and phosphoproteomics)
Lipidomics

Publications

Anissa Moktefi, Shao-yu Zhang, Pauline Vachin, Virginie Ory, Carole Henique, Vincent Audard, Catherine Rucker-Martin, Elodie Gouadon, Michael Eccles, Andreas Schedl, Laurence Heidet, Mario Ollero, Djillali Sahali and Andre Pawlak (2016). Repression of CMIP transcription by WT1 is relevant to podocyte health, Kidney International. 584(3), 500-6

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4. P Rémy, V Audard, P.A. Natella, G Pelle, B Dussol, H. Leray-Moragues, C.Vigneau, K. Bouachi, J. Dantal, L. Vrigneaud, A. Karras, F. Pourcine, P. Gatault, P. Grimbert, N. Ait Sahlia, E. Daugas, C. Combe, S. Bastuji-Garin and D. Sahali (2018). Low dose steroid plus enteric-coated mycophenolate sodium versus high dose of steroid therapy for the treatment of Minimal Change Nephrotic Syndrome in adults (MSN Study): a French multicenter randomized controlled clinical trial (on behalf of the MSN trial investigators.), Kidney International. 94(), 1217-1226

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1. Zhang SY, Fan Q, Moktefi A, Ory V, Audard V, Pawlak A, Ollero M, Sahali D (2021). CMIP interacts with WT1 and targets it on the proteasome degradation pathway, Clinical and Translational Medicine. 11(7), e460

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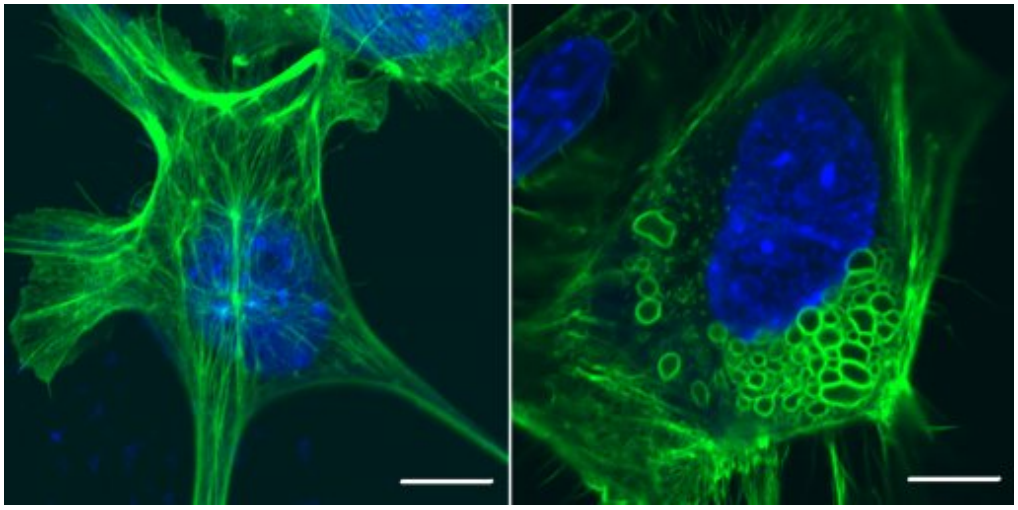
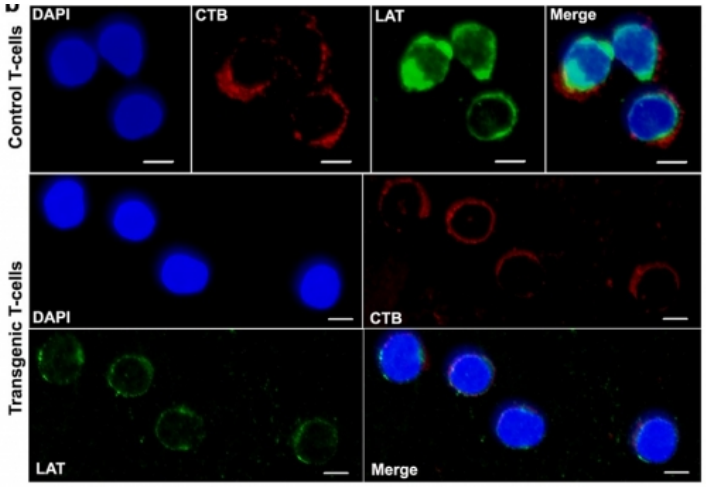
CMIP inhibits lipid raft clustering in T cells



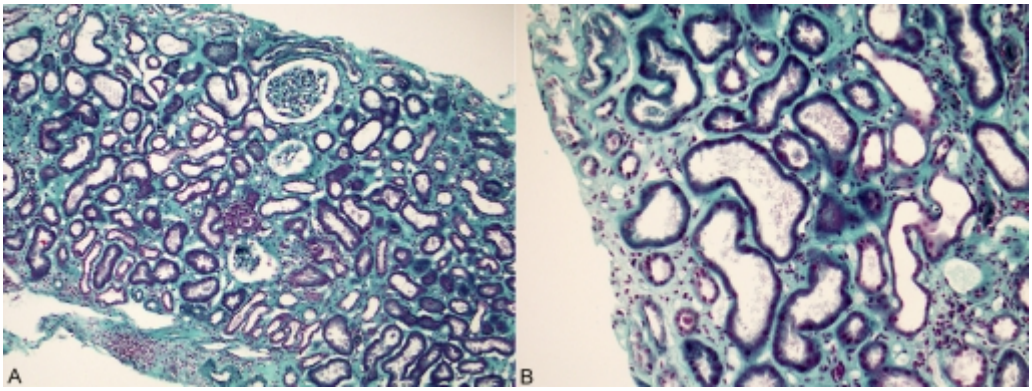
CMIP inhibits clustering into lipid rafts of LAT (linker for activation of T-cells) and CTB (cholera toxin B, lipid raft marker), after CD3/CD28 stimulation (Cell Mol Immunol. 2020. 17: 1026-1041)

Overproduction of CMIP in Reed-Sternberg (HRS) cells of patients with idiopathic nephrotic syndrome



(A) Localization of CMIP in HRS cells from patients with idiopathic nephrotic syndrome (INS) revealing Hodgkin lymphoma (HL-INS). (B) no CMIP induction was detected in the HRS cells of patients with isolated HL. Original magnification, X100. (Blood. 115: 3756-3762; 2010).

Acute tubular necrosis with diffused flattened tubular epithelium in a cancer patient treated with a



(A) Acute tubular necrosis with diffused flattened tubular epithelium (Masson's trichrome staining; original magnification ×100). Interstitial areas showed moderate fibrosis with scarce inflammatory infiltrate and glomeruli were normal. (B) Tubular injury predominated in proximal tubules (arrow)(Eur J Cancer. 2020 Nov;139:177-180)

Sahali Djillali - dil.sahali@inserm.fr - 33149812537

Osteoarticular system

Key facts

Team

• Researchers : 18
• Technicians : 7
• Postdoc fellows : 2
• PhD Students : 13

Translational approaches

• Patents : 5
• Clinical research grants : 5
• Industry partnerships : 3

International research links

• Chile
• Germany
• Ireland

Keywords

• Mesenchymal stem cell
• Osteo-articular diseases
• Regeneration
• Aging
• Energetic metabolism
• Embryology and molecular genetic of the zebrafish
• Purification of extracellular vesicles
• isolation and culture of mesenchymal stem cell
• Imaging
• Immunomodulation

Christian Jorgensen

Adult stem cells and regenerative medicine.

Université de Montpellier
Inserm U1183
Christian Jorgensen
Montpellier

> ***We are proposing original biotechnology to restore cartilage tissue with clinical applications***

Research Brief :

The IRMB team is dedicated to explore new pathways in tissue regeneration as well as immunomodulation and pave the way to translational medicine and medicine of the future
Our team aims at the following objectives:
- Understanding the molecular mechanisms involved in regeneration: application to osteo-articular diseases
- Understanding molecular mechanisms for cartilage formation and development of scaffolds for cartilage engineering
- Understanding the immunosuppressive properties of MSC
- Understanding the molecular and cellular basis of epimorphic regeneration
- Studing the effect of MSCs of the microenvironment on the energetic metabolism of target cells through direct mitochondria transfer
- Studing the paracrine effects of aged/senescent MSCs on tissue homeostasis.
- Investigating several aspects of hepatic physiopathology: liver detoxication functions, hepatitis C virus infection, and stem cell differentiation to hepatocytes, using on an original model of primary cultures of human adult hepatocytes (PHH) and other liver cell types, including mesenchymal cells.
- Using stem cells for the treatment of neurodegenerative diseases.

• **Methodologies Used :**

- Cell biology: mesenchymal stem cell and primary chondrocytes, mitochondria transfer, primary human hepatocytes , embryonic stem cells, spheroids, CD4+ T cells, macrophages and B cells, foetal and adult neural stem cells, iPS cell
- Purification of extracellular vesicles
- In vivo murine models: collagenase-induiced osteoarthritis, collagen-induiced arthritis, systemic sclerosis, biodistribution studies, major hepatectomy in mice, Prion disease modelisation
- Mouse embryo culture
- Embryology and molecular genetic of the zebrafish
- Biochemistry: ELISA, immunofluorescence
- Seahorse
- Molecular biology: RT-qPCR, transcriptomic analysis, qPCR on mitochondrial DNA
- Imaging: confocal, bi-photon and time-lapse microscopy, in vivo µCT

Publications

Relaño-Ginès A, Gabelle A, Hamela C, Belondrade M, Casanova D, Mourton-Gilles C, Lehmann S, Crozet C (2013). Prion replication occurs in endogenous adult neural stem cells and alters their neuronal fate: involvement of endogenous neural stem cells in prion diseases., PLoS Pathog. 2013(9(8)), e1003485

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Jorgensen Christian - christian.jorgensen@inserm.fr

Key facts

Team

- Researchers : 7
- Technicians : 7
- Postdoc fellows : 1
- PhD Students : 7

Translational approaches

- Patents : 7
- Clinical research grants : 3
- Industry partnerships : 2

International research links

- Italy
- UK
- Spain

Keywords

- (Auto)inflammation
- Immunotherapies
- Genetics
- Neutrophils
- Macrophages
- Cytometry
- RNA interference
- animal models
- cell-based therapies
- Monoclonal antibodies

Florence Apparailly

Pathophysiology and immunotherapy of inflammatory disorders

Université Montpellier
Inserm U1183
Christian Jorgensen
Montpellier

Combination of clinicians, geneticists and biologists around translational research in chronic inflammation: from basic research in genetics and immunology to the development of targeted immunotherapies.

Research Brief :

Combining fundamental studies of immune cells in mouse models of immune-merdiated inflammatory disorders with translational studies of immunological and genetic status in patients, our ultimate objectives are to improve disease diagnosis and classification and to provide insight into biological mechanisms to design new immuno-intervention strategies. Gathering skills for genetics, functional genomics, molecular and cellular immunology, gene and cell therapy, experimental animal models of arthritis, biobanking and cutting-edge technologies, we follow 2 main axes:
1) Study the pathophysiological mechanisms of chronic inflammation.
Here, we aim at identifying molecular and cellular mechanisms involved in the triggering, chronicity and resolution of the inflammatory response by focusing on genetic factors and immune cell subsets displaying homeostatic functions (Treg and myeloid cells) in autoimmune and autoinflammatory disorders characterized by chronic joint inflammation.
2) Understand the development of physiological immunomodulation to develop targeted immunotherapies. Here, we aim at addressing fundamental issues related to mechanisms of antibody-mediated immunomodulation in different pathogenic situations and to develop Ab-based innovative targeted therapeutic strategies. We also develop immunotherapies based on monoclonal antibodies and derived molecules (CAR-T cells, immunocytokines...).

• Methodologies Used :

Next generation sequencing - Exome sequencing - miRNome - (sc)RNAseq - Functional genomics - Multi-parametric flow cytometry - Cell sorting - Human and mouse immuno-monitoring - Image Mass Cytometry - Experimental models of inflammation (monitoring of clinical, immunological, histopathological and bone architecture parameters) - Isolation, differentiation and in vitro functional characterization of neutrophils, T cells, B cells, monocytes, dendritic cells, macrophages and osteoclasts - In vitro and in vivo RNAi - Gain and loss of function studies - Reporter systems for validation of miRNA targets - SeaHorse - Fate mapping mouse lines - Parabiosis - Adoptive transfer

Publications

Duroux-Richard I, Roubert C, Ammari M, Présumey J, Grün JR, Häupl T, Grützkau A, Lecellier CH, Boitez V, Codogno P, Escoubet J, Pers YM, Jorgensen C, Apparailly F. (2016). miR-125b controls monocyte adaptation to inflammation through mitochondrial metabolism and dynamics, Blood. 128(26), 3125-36

Naranjo-Gomez M, Lambour J, Piechaczyk M, Pelegrin M (2018). Neutrophils are key players in the induction of vaccine-like effects by monoclonal antibody-based antiviral immunotherapies, JCI insight. 3(9), e97339

Ammari M, Presumey J, Ponsolles C, Roussignol G, Roubert C, Escriou V, Toupet K, Mausset-Bonnefont A-L, Cren M, Robin M, Georgel P, Nehmar R, Taams L, Grün J, Grützkau A, Häupl T, Pers Y-M, Jorgensen C, Duroux-Richard I, Courties G, Apparailly F* (2018). Delivery of miR-146a to Ly6Chigh Monocytes Inhibits Pathogenic Bone Erosion in Inflammatory Arthritis, Theranostics. 8(21), 5972-85*

Cren M, Nziza N, Carbasse A, Mahe P, Delpont M, Chevassus H, Khalil M, Mura T, Duroux-Richard I, Apparailly F, Jeziorski, Louis-Plence* P (2020). Differential Accumulation and Activation of Monocyte and Dendritic Cell Subsets in Inflamed Synovial Fluid Discriminates Between Juvenile Idiopathic Arthritis and Septic Arthritis, Frontiers Immunol. 11(), 1716*

Rittore C, Méchin D*, Sanchez E, Marinèche L, Ea V, Soler S, Vereecke M, Mallavialle A, Richard E, Duroux-Richard I, Apparailly F, Touitou I, Grandemange S (2021). TNFR1-d2 carrying the p.(Thr79Met) pathogenic variant is a potential novel actor of TNF/TNFR1 signalling regulation in the pathophysiology of TRAPS, Scientific Reports. 11(), 4172*

Lambour J, Naranjo-Gomez M, Boyer-Clavel M, Pelegrin M (2021). Differential and sequential immunomodulatory role of neutrophils and Ly6Chi inflammatory monocytes during antiviral antibody therapy., Emerg Microbes and Infections. 10(1), 964-981

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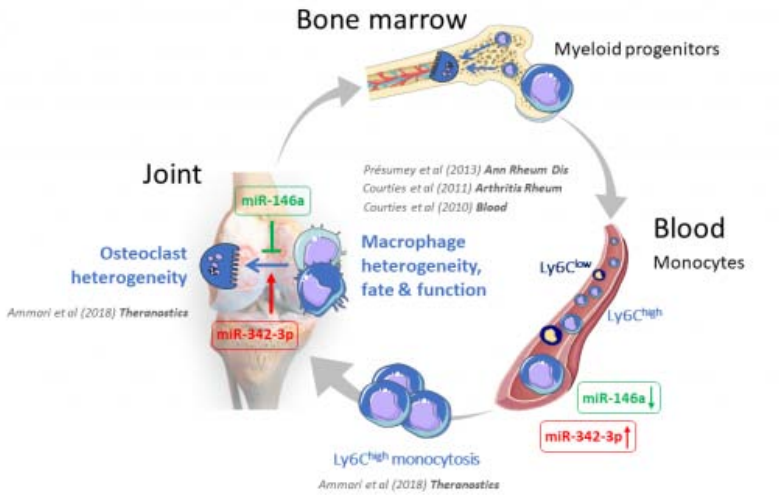
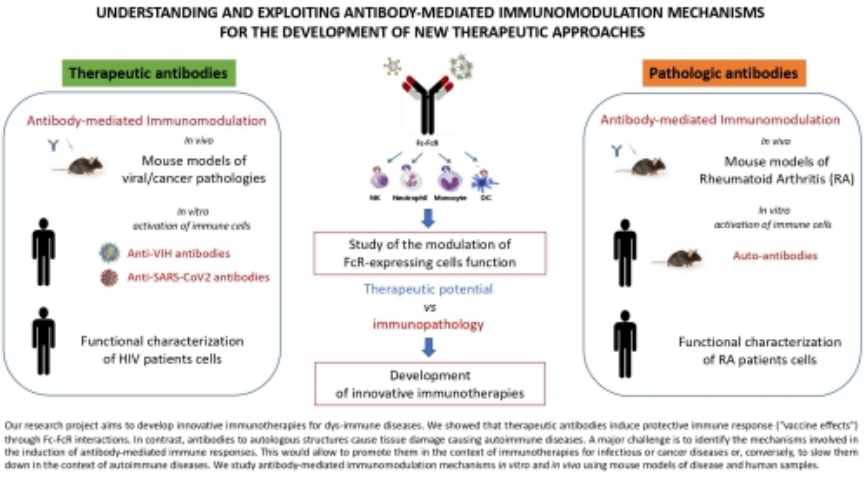
Role of macrophages in joint pathophysiology



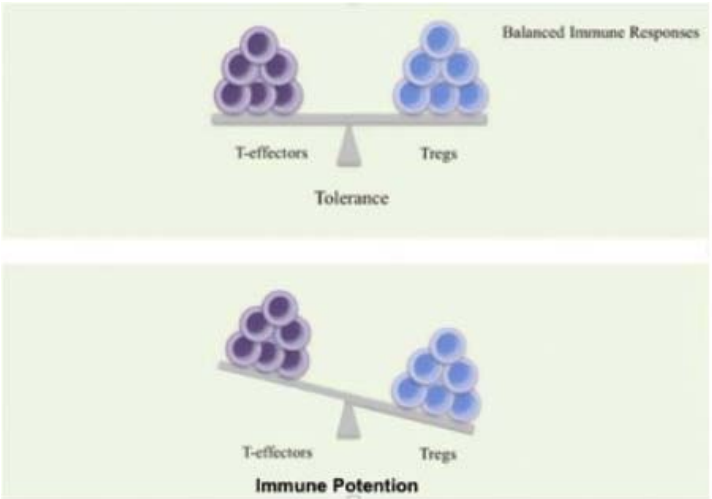
Macrophages are established before birth (light blue cell) or originate from bone marrow myeloid precursors (royal blue cell). In healthy bone marrow, myeloid progenitors support physiological immune responses and bone remodeling. They also exit into the circulation and traffic as LyC6high and LyC6low monocytes. In arthritis, blood LyC6high are increased and infiltrate joints to differentiate into inflammatory macrophages and osteoclasts. This fate is controlled by microRNAs.

Antibody-mediated immunomodulatory mechanisms to develop new therapeutic approaches



We showed that therapeutic antibodies induce protective immune response ("vaccine effects") through Fc-FcR interactions. In contrast, antibodies against self-cause tissue damage and autoimmune diseases. We study antibody-mediated immunomodulatory mechanisms using mouse models of disease and human samples to develop innovative immunotherapies, either by promoting or inhibiting those mechanisms in the context of infection and cancer or autoimmunity, respectively.

Immunotherapy in Rheumatoid Arthritis to restore self-tolerance to achieve long-term remission



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We develop innovative therapeutic strategies to cure RA by targeting autoreactive B cells, or by restoring immune tolerance harnessing the tolerogenic potential of subsets of dendritic cells or regulatory T cells. We develop also humanized mice model to assess the cell-based therapeutic approaches in pre-clinical testing.

Apparailly Florence - florence.apparailly@inserm.fr - https://irmb-montpellier.fr/about/#equipe3

Key facts

Team

• Researchers : 4
• Technicians : 1
• Postdoc fellows : 0
• PhD Students : 1

Translational approaches

• Patents : 2
• Clinical research grants : 1
• Industry partnerships : 2

International research links

• USA

Keywords

• Rheumatoid arthritis
• Peptidyl arginyl deiminase
• anti citrullinated protein antibodies
• Vaccination
• Microchimerism
• HLA-DR/peptide binding
• Protein chips
• PCR quantification of microchimeric DNA
• Mathematical models

Biological Resources

• Thousands of well characterized patients with RA and other joint diseases and serum and DNA from these patients
• Original mouse model for the development of RA characteristic anti citrullinated protein antibodies

Jean Roudier

Autoimmune Arthritis

Aix-Marseille Université
Inserm UMRs1097
Jean Roudier
Marseille

After thirty years of research focused on the development of rheumatoid arthritis (RA), we discovered that RA is triggered by immunisation against peptidyl arginyl deiminases (PADs). Thus, PAD tolerization should allow preventing/treating RA.

Research Brief :

1/ The triggering of Rheumatoid arthritis: from HLA-DR4 to ACPAs. Prospects for PAD tolerising vaccine to prevent RA (J Roudier, I Auger, N Balandraud).
To understand the mechanism triggering rheumatoid arthritis (RA), we analysed how HLA-DRB1 alleles associated with RA help the development of RA specific autoantibodies to citrullinated proteins (ACPAs).
We calculated the risks to develop RA for 106 of the 136 most common HLA-DRB1 genotypes in France and found they range from 30 to 0.2.
Using protein chips, we found that PAD4 (Peptidyl Arginyl Deiminase 4) is a target for IgG autoantibodies in RA patients.
This led us propose the Hapten Carrier model of RA: IgG autoantibodies to citrullin residues on multiple proteins develop because T cells specific for peptides from PADs deliver help to B cells specific for citrullinated substrates of PADs.
We demonstrated this model in normal mice and confirmed this finding in humans.
Finally, we observed that the risk to develop RA for a given HLA-DRB1 genotype correlates with the capability for its two encoded HLA-DR molecules to bind a random peptide from PAD4.
We now want to prevent/treat RA by suppressing ACPA production by PAD tolerization.

2/ Female predominance in autoimmunity (NC Lambert)
We study the factors which explain why autoimmune diseases are more frequent in women.
Among these factors: microchimerism, the presence of small number of cells from a mother in a child or from a child in a mother.

• **Methodologies Used :**

1/ We follow our well characterized cohort of 2000 patients with RA
2/ We have developed an original mouse model of RA by PAD immunization.

Publications

Balandraud N, Picard C, Reviron D, Landais C, Toussirot E, Lambert N, Telle E, Charpin C, Wendling D, Pardoux E, Auger I, Roudier J. (2013). HLA-DRB1 genotypes and the risk of developing anti citrullinated protein antibody (ACPA) positive rheumatoid arthritis., Plos One. 8(5), 64108

Arnoux F, Mariot C, Peen E, Lambert NC, Balandraud N, Roudier J, Auger I. (2017). Peptidyl arginine deiminase immunization induces anticitrullinated protein antibodies in mice with particular MHC types., Proceedings of the National Academy of Sciences USA.. 114(47), 10169-10177

Roudier J, Balandraud N, Auger I. (2018). HLA-DRB1 polymorphism, anti-citrullinated protein antibodies, and rheumatoid arthritis., Journal of Biological Chemistry. 293(18), 7038

Lambert NC. (2019). Nonendocrine mechanisms of sex bias in rheumatic diseases., Nature Reviews Rheumatology. 15(11), 673-686

Martin GV, Kanaan SB, Hemon MF, Azzouz DF, El Haddad M, Balandraud N, Mignon-Ravix C, Picard C, Arnoux F, Martin M, Roudier J, Auger I, Lambert NC. (2019). Mosaicism of XX and XXY cells accounts for high copy number of Toll like Receptor 7 and 8 genes in peripheral blood of men with Rheumatoid Arthritis., Scientific Reports. 9(1), 12880

Auger I, Balandraud N, Massy E, Hemon M, Peen E, Arnoux F, Mariot C, Martin M, Lafforgue P, Busnel JM, Roudier J. (2020). Peptidyl arginine deiminase autoimmunity and the development of ACPA in rheumatoid arthritis. The "hapten carrier" model., Arthritis and Rheumatology. 72(?), ?

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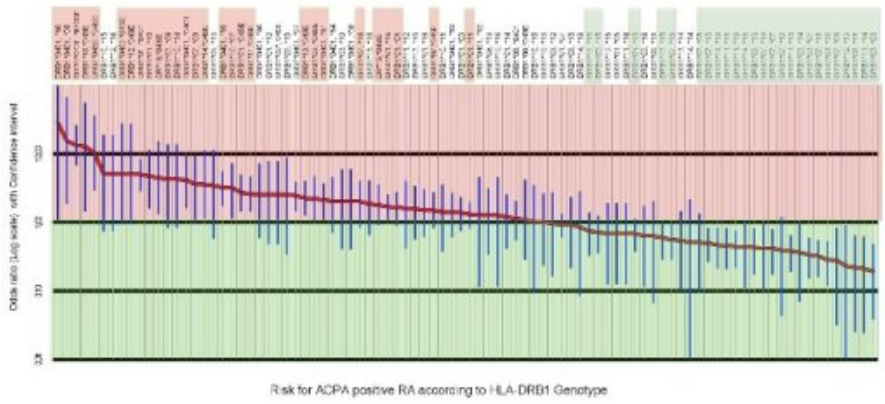
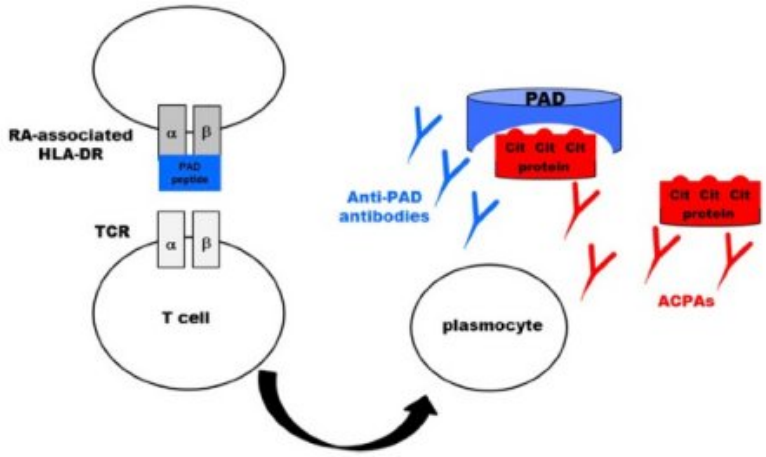
Odds ratios to develop RA according to one's HLA-DRB1 genotype



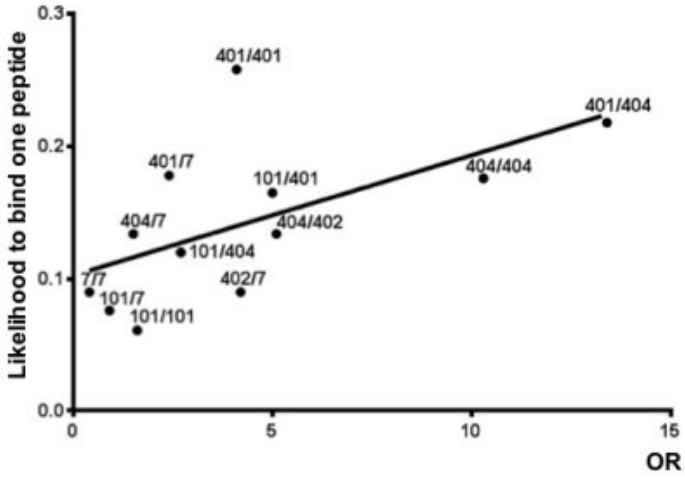
This graph indicates the Odds Ratios to develop RA for 106 of 136 common HLA-DRB1 genotypes. They range from 28 (HLA-DRB1*10/*0401) to 0.2 (HLA-DRB1*03/*03)

The Hapten Carrier model of RA



TfH cells specific for PADs may provide help to B cells specific for PAD associated substrates because citrullinated substrate specific B cells may present PAD peptides to TfHelper cells.

OR to develop RA for HLA-DRB1 genotypes correlates with likelihood of binding PAD4 peptide



The Odds Ratios to develop ACPA positive RA for 12 HLA-DRB1 genotypes were plotted against the likelihood for the 2 HLA-DRB1 molecules encoded by the same genotype to bind at least one random peptide from PAD4.
ORs for RA match PAD4 peptide binding likelihood.

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Lyos
Osteoporosis - Bone Metastasis - Lyon

Olivier Peyruchaud

Bioactive Lipids, Mineral Metabolism and Bone Pathophysiology

Université Claude Bernard
Lyon I
Inserm U1033
Roland Chapurlat
Lyon

Our team has a unique expertise in developing and analyzing animal models mimicking human bone diseases such as breast cancer bone metastasis (immunodeficient, syngenic, systemic and spontaneous models), osteoporosis (ovariectomy), hypocalcemia (low Ca2+ diet), inflammation (hTNF-Tg mice, LPS, CAIA)

Key facts

Team

• Researchers : 6
• Technicians : 2
• Postdoc fellows : 0
• PhD Students : 2

Translational approaches

• Patents : 2
• Clinical research grants : 0
• Industry partnerships : 1

International research links

• USA, Netherlands, Italy, Germany, Hungary, UK, Mexico

Keywords

• Lysophospholipids
• Autotaxin
• Bone
• Inflammation
• Rare Diseases
• Histology
• Cell biology
• Osteoimmunology
• Imaging
• Animal models

Research Brief :

We have shown in the past that the natural bioactive lipid, lysophosphatidic acid (LPA), derived from platelets or arising from the lysophospholipase activity D autotaxin (ATX) produced by tumor cells, stimulates the growth of breast cancer bone metastasis. Targeting of type 1 receptor of LPA (LPA1) is a therapeutic target for patients with bone metastases. Our recent study of Lpar1-KO mice showed that LPA controls differentiation and osteoclast resorption activity via the LPA1. In addition, we have demonstrated that ATX is a new platelet mediator stimulating metastasis dissemination of tumor cells and that tumor LPA1 exerts a key role in metastasis of breast cells in triple negative cancers through activation of a PI3K/Zeb1/miR-21-dependent pathway. The research project is largely based on comprehensive analyses of global and bone tissue-specific knockout mice to develop a new field of study on the role of lysophospholipids in bone pathophysiology. The project is organized into two themes. In Theme 1 « Role of ATX / LPA in bone physiology » we will study the role of ATX on osteoclastic and osteoblastic functions and cross talks between TGF? and LPA-induced signaling pathways in the control of bone resorption. In the Theme 2 « Role of ATX / LPA in bone pathology » we will exploit relevant animal models for the study of ATX and LPA in osteoporosis, rheumatoid arthritis and bone metastasis.

• **Methodologies Used :**

- Global knock out animals
- Bone cell-specific knock out animals
- Animal experimentation (age-related challenges)
- Microcomputed tomography
- Histology and Immunohistology
- Human and mouse, primary and cell line cultures (osteoclasts, osteoblasts, cancer cells)
- Bioluminescence imaging
- Photonique microscopy
- Confocal microscopy
- qPCR, TLDA
- Protein purification (LPLC)

Publications

Coury F, Annels N, Rivollier A, Olsson S, Santoro A, Speziani C, Azocar O, Flacher M, Djebali S, Tebib J, Brytting M, Egeler RM, Rabourdin-Combe C, Henter JI, Arico M, Delprat C. (2008). Langerhans cell histiocytosis reveals a new IL-17A-dependent pathway of dendritic cell fusion., Nature Medicine. 14(1), 81-7

Coury F, Zenger S, Stewart AK, Stephens S, Neff L, Tsang K, Shull GE, Alper SL, Baron R, Aliprantis AO (2013). SLC4A2-mediated Cl-/HCO3- exchange activity is essential for calpain-dependent regulation of the actin cytoskeleton in osteoclasts., Proc Natl Acad Sci U S A. 110(6), 2163-8

David M, Machuca-Gayet I, Kikuta J,Ottewell P,Mima F, Leblanc R, Bonnelye E, Ribeiro J, Holen I, Lopez Vales R, Jurdic P, Chun J, Clézardin P, Ishii M, Peyruchaud O. (2014). Lysophosphatidic acid receptor type 1 (LPA1) plays a functional role in osteoclast differentiation and bone resorption activity., Journal of Biological Chemistry. 289(10), 6551-64

Leblanc R, Lee SC, David M, Bordet JC, Norman DD, Patil R, Miller D, Sahay D, Ribeiro J, Clézardin P, Tigyi GJ, Peyruchaud O. (2014). Interaction of platelet-derived autotaxin with tumor integrin ?V?3 controls metastasis of breast cancer cells to bone., Blood. 124(20), 3141-50

Schwarzer M, Makki K, Storelli G, Machuca-Gayet I, Srutkova D, Hermanova P, Martino ME, Balmand S, Hudcovic T, Heddi A, Rieusset J, Kozakova H, Vidal H, Leulier F. (2016). Lactobacillus plantarum strain maintains growth of infant mice during chronic undernutrition, Science. 351(6275), 854-7

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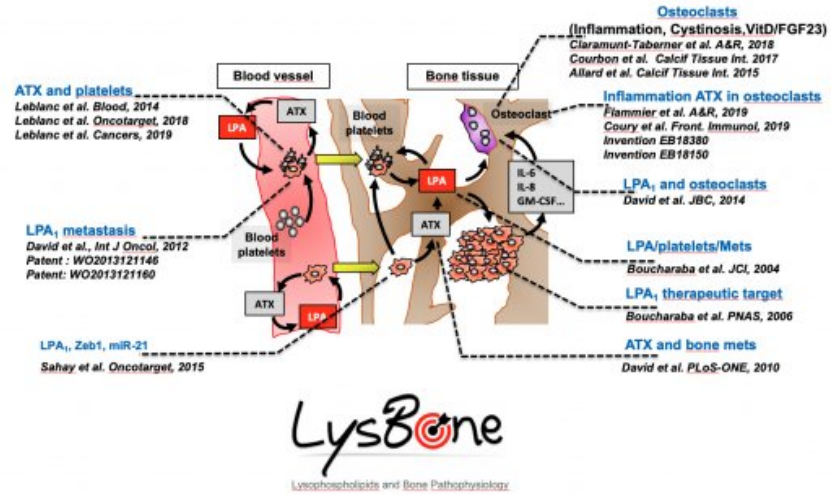
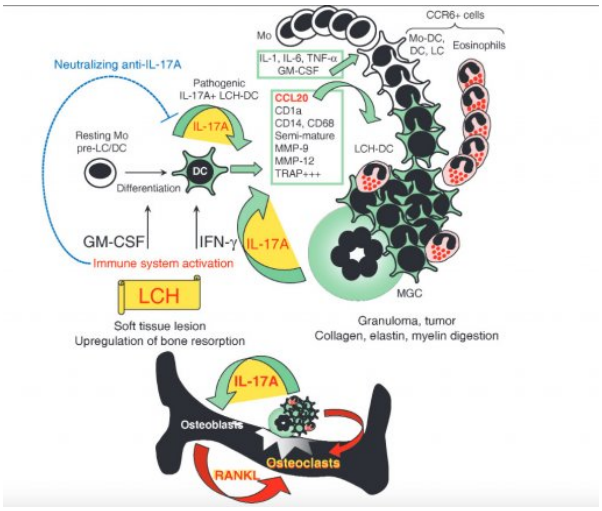
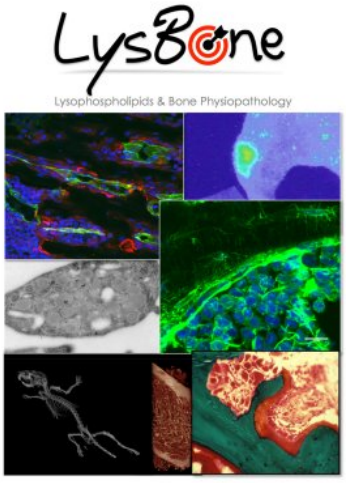
LPA/ATX track in bone : involvement in bone metastasis and bone physiology



Coury et al, Nat Med 2008



Multiple Imaging plateforms available in team LYSBONE (Team 3, INSERM U1033)



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institut Valrose Biologie

Jean-Claude Scimeca

BIPOA, BioIngénierie et Physiopathologie Ostéo-Articulaire

UCA, Université Côte d'Azur
CNRS UMR7277 Inserm U1091
Stéphane Noselli
Nice

Key facts

Team

- Researchers : 4
- Technicians : 2
- Postdoc fellows : 0
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 2

Keywords

- Bone Physiopathology
- Bone Reconstruction
- Bone Cancer
- Bone Tissue Models
- Bone Defect Models

Gathering researchers, clinicians and industrial partners, we aim at developing and transferring into clinic innovative therapeutic solutions for the treatment of musculoskeletal conditions.

Research Brief :

Our project is focused on bone tissue physiopathology and reconstruction in traumatic, tumoral, and aging situations. Within this context, we aim at developing and transferring into clinic innovative therapeutic solutions for the treatment of musculoskeletal conditions.
The main objectives of our experimental work are: (i) to develop calcium phosphate-based new bone substitutes for bone reinforcement and reconstruction; (ii) to design biomaterials incorporating therapeutic compounds targeting bone tumours; (iii) to decipher the molecular mechanisms underlying new bone formation in traumatic and tumoral environments; (iv) to engineer innovative in vitro 3D models of bone-like constructs, as well as in vivo bone cancer models, based on the use of bone substitutes we develop; (v) to use our models to address basic questions about bone cells and cancer cells interactions with each other and with their microenvironment.
In the future, we will continue to use bone substitutes as drug delivery systems to improve bone strengthening and bone reconstruction. We will also investigate strategies involving the combination of these therapeutic agents to enhance their action. Lastly, to identify new therapeutic targets, these bioactive biomaterials will be used to set up in vitro 3D scaffolds allowing us to document the underlying molecular mechanisms governing bone cells and cancer cells interactions within a bone-like microenvironment.

• Methodologies Used :

With a view towards building normal or metastatic bone tissue niches, we designed several 2D-3D cell culture models combining calcium phosphate-based biomaterials and either bone or cancer cells. Moreover, we take advantage of both in vitro and in vivo models for the screening of therapeutic compounds that could improve the treatment of bone defects after traumatic or cancer lesions. We are also interested in triggering the host immune response against tumour cells. In this attempt, in vivo cancer models are used to identify therapeutic targets among chemokines and chemokine receptors, which are key partners regulating the interactions among bone, immune system, and cancer cells.

Publications

P. Richard-Fiardo, B. Cambien, E. Pradelli, F. Beilvert, B. Pitard, H. Schmid-Antomarchi, A. Schmid-Alliana (2011). Effect of fractalkine-Fc delivery in experimental lung metastasis using DNA/704 nanospheres, Cancer Gene Ther. 18(11), 761-72

E. Guillemot, B. Karimdjee-Soilihi, E. Pradelli, M. Benchetrit, E. Goguet-Surmenian, M.A. Millet, F. Larbret, J.F. Michiels, D. Birnbaum, P. Alemanno, H. Schmid-Antomarchi, A. Schmid-Alliana (2012). CXCR7 receptors facilitate the progression of colon carcinoma within lung not within liver, Br J Cancer. 107(12), 1944-9

E. Goguet-Surmenian, P. Richard-Fiardo, E. Guillemot, M. Benchetrit, A. Gomez-Brouchet, P. Buzzo, B. Karimdjee-Soilihi, P. Alemanno, J.F. Michiels, A. Schmid-Alliana, H. Schmid-Antomarchi (2013). CXCR7-mediated progression of osteosarcoma in the lungs, Br J Cancer. 109(6), 1579-85

E. Verron, H. Schmid-Antomarchi, H. Pascal-Mousselard, A. Schmid-Alliana, J.C. Scimeca, J.M. Bouler (2014). Therapeutic strategies for treating osteolytic bone metastases, Drug Discov Today. 19(9), 1419-26

I. Strazic-Geljic, I. Guberovic, B. Didak, H. Schmid-Antomarchi, A. Schmid-Alliana, F. Boukhechba, J.M. Bouler, J.C. Scimeca, E. Verron (2016). Gallium, a promising candidate to disrupt the vicious cycle driving osteolytic metastases, Biochem Pharmacol. 116(), 11-21

I. Strazic Geljic, N. Melis, F. Boukhechba, S. Schaub, C. Mellier, P. Janvier, J.P. Laugier, J.M. Bouler, E. Verron, J.C. Scimeca (2017). Gallium enhances reconstructive properties of a calcium phosphate bone biomaterial, J Tissue Eng Regen Med. doi: 10.1002/term.2396(),

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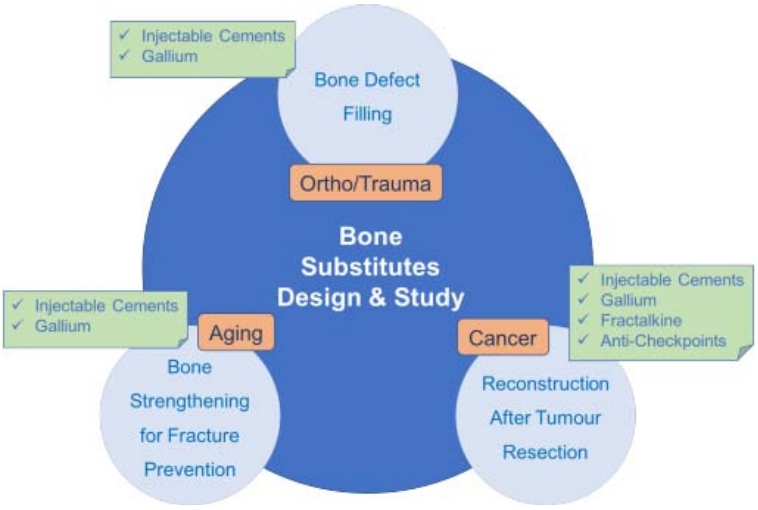
Research Themes



Bone defect filling in the course of ortho/trauma surgery - Bone reconstruction after tumour resection - Osteoporotic bone strengthening for fracture prevention.

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Martine Cohen-Solal

Bone - Cartilage and environment

Université de Paris 7
(Université de Paris)
Inserm U1132
Martine Cohen-Solal
Paris

Key facts

Team

- Researchers : 13
- Technicians : 7
- Postdoc fellows : 5
- PhD Students : 10

Translational approaches

- Patents : 1
- Clinical research grants : 3
- Industry partnerships : 4

International research links

- Europe (ECTS)
- Vietnam

Keywords

- osteoarthritis
- osteoporosis
- cartilage
- Bone
- biobank and patients
- molecular signature
- histology
- bone imaging
- clinical trials

Biological Resources

- Transgenic mice for bone and cartilage
- Tisue and serum biobank
- Cartilage and bone collection

Physiopathology and Identification of target molecules that regulate bone and cartilage remodeling: from mice to patients

Research Brief :

The research unit has been dedicated to the pathophysiology of bone and cartilage diseases and the expertise have positioned the unit as a leader in the field. Our aim is to characterize the mechanisms that regulate bone and cartilage matrix and to identify the molecular targets that result in the development of osteoporosis and osteoarthritis. The different approaches conducted by the scientists and the clinicians actively involved prompted to the development of tools used from basic to translational research. We have therefore validated biochemical and molecular techniques, cellular and animal models that are then translated in humans through a collection of bone and cartilage tissues as well as mouse and human serum and synovial samples.
To identify molecules involved in joint diseases, different projects are under investigation:
- Role of the proteoglycan in cell-cell interactions with bone and cartilage microenvironment.
- Mechanisms of interaction between bone and cartilage to characterize the role of bone cells such as osteoclasts in mechanical-induced osteoarthritis. We focus on the role of Wnt molecules involved in the bone-cartilage crosstalk.
- Characterization of microcrystalline stress on the cartilage and the role of microcrystals in chondrocyte metabolism and apoptosis. This work is translated to humans samples and to a cohort.
- The regulation of chondrocyte function by autocrine and paracrine factors.

Methodologies Used :

- Primary culture of mouse and human bone cells (osteoclasts, osteoblasts, osteocytes), bone resorption and formation assays, pit assays, bone explants.
- Cultures of primary mouse and human chondrocytes and cartilage explants.
- Cell phenotyping (qRT-PCR, Western-blot, proteolytic activity, ELISA, ARN interference, immunocytology, apoptosis assay, cell imaging)
- Histology analysis (histology, immunohistochemistry, analysis of non decalcified bone)
- Characterisation of systemic bone and subchondral bone (microarchitecture, µCT, bone density)
- In vivo model for murine osteoporosis and osteoarthritis.

Publications

Latourte A, Cherifi C, Maillet J, Ea HK, Bouaziz W, Funck-Brentano T, Cohen-Solal M, Hay E, Richette P (2016). Systemic inhibition of IL-6/Stat3 signalling protects against experimental osteoarthritis., Ann Rheum Dis. (),

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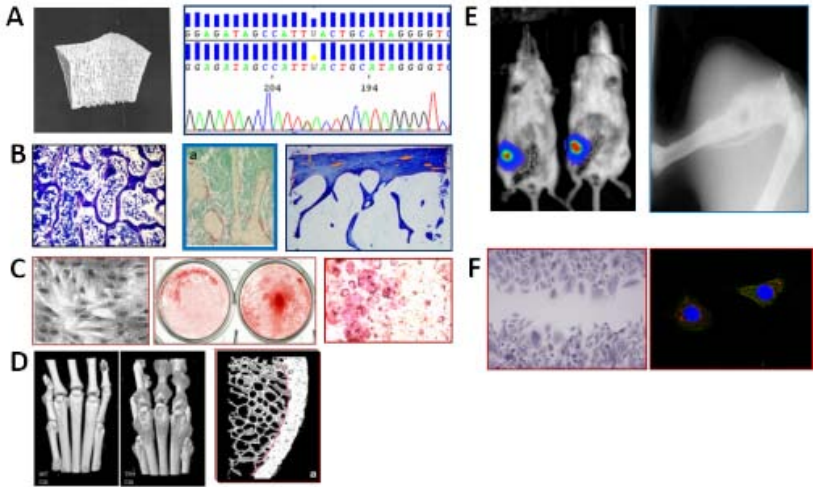
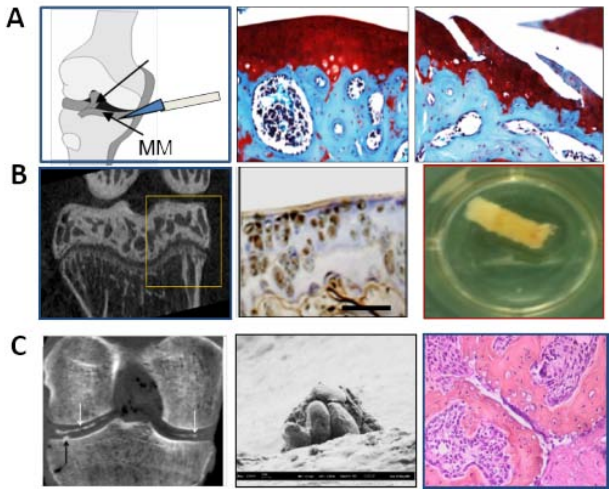
Illustrations of studies on bone



A: Characterisation of microarchitectural changes of bone in young patients with idiopathic osteoporosis. Structural analysis of cortical and trabecular bone is performed by high resolution peripheral quantitative computated tomography and correlated to the genotype (NGS panel)
B: Histomorphometric analysis of cortical and trabecular bone of human and murine undecalcified bone samples
C: Cultures of bone cells (osteoblasts and osteoclasts) and functional tests of bone formation and resorption
D: Evaluation of bone resorption related to inflammation in murine arthritis model (microcomputated tomography).
E: Quantification of bone metastasis by bioluminescence technique and syngenic model of osteosarcoma.
F: Migration test and protein localisation

Illustrations of some studies on cartilage pathology



A: Murin model of joint instability (DMM) that induces a progressive loss of cartilage and osteoarthritis.
B: Analysis of subchondral bone by computed tomography; immunohistochemistry of cartilage; culture of bone and cartilage explants.
C: Microcrystal related joint diseases: characterization of calcifications of meniscus, joint crystals and histology of joints

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U1173 INFECTION ET INFLAMMATION

Maxime Breban

IRIS: Inflammatory Reaction and Immune System / Chronic inflammation and immune system

Université de Versailles
Saint-Quentin en Yvelines Université Paris Saclay
Inserm UMR 1173
Jean-Louis Herrmann
Saint-Quentin en Yvelines

Key facts

Team

- Researchers : 8
- Technicians : 4
- Postdoc fellows : 2
- PhD Students : 4

Translational approaches

- Patents : 0
- Clinical research grants : 2
- Industry partnerships : 2

International research links

- Belgique
- Allemagne
- Australie

Keywords

- autoimmunity
- Chronic inflammatory diseases
- dendritic cell
- genetical genomics
- genetics
- transcriptomics
- cell biology
- imaging

Our research offers a unique opportunity in arthritic diseases to link inflammation and immune system based on a multidisciplinary approach which involves a two-way process going back and forth between genetic data, immunological mechanisms and the transfer of the findings to the clinic

Research Brief :

Three main pillars constitute the organisation of our research program:
- Genomic analysis with diagnostic and therapeutic applications,
- Functional validation of targets,
- Animal models.

Chronic inflammatory diseases result from perturbations of effector cells and soluble mediators of the immune system, and local target tissue abnormalities. The precise mechanisms leading to inflammation in these diseases are incompletely understood and treatments inadequate. The aim of our team is to increase understanding of mechanisms of chronic inflammation. Our goals are: the identification of new genes of susceptibility, and their functional characterization.
These diseases show a strong involvement of the major histocompatibility complex. Because much remains to be learnt on the role of this region in autoimmunity, we are developing specific researches on this topic by focusing on spondylarthritis, autoimmune myasthenia gravis that show a strong association with the MHC and soon on rheumatoid arthritis.
Starting from clinical investigations, and based on genetic and genomic approaches, we use in vitro cellular assays or suitable animal models, as needed. The functional role of dendritic cells and myeloid suppressor cells are analysed. Several targets are already studied. The interactions between scientists and physicians in the team and our large collaborative network contribute importantly to the translation of fundamental research into clinical application.

- **Methodologies Used :**

Transcriptomics
Genetics
Molecular biology
Cell Biology
Biochemistry

Publications

Araujo LM, Fert I, Jouhault Q, Labroquère K, Andrieu M, Chiocchia G, Breban M. (2014). Increased production of interleukin-17 over interleukin-10 by treg cells implicates inducible costimulator molecule in experimental spondyloarthritis., Arthritis Rheumatol.. 66(9), 2412-2422

Fert I, Cagnard N, Glatigny S, Letourneur F, Jacques S, Smith JA, Colbert RA, Taurog JD, Chiocchia G, Araujo LM, Breban M. (2014). Reverse interferon signature is characteristic of antigen-presenting cells in human and rat spondyloarthritis., Arthritis Rheumatol. 66(4), 841-851

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Costantino F, Talpin A, Evnouchidou I, Kadi A, Leboime A, Said-Nahal R, Bonilla N, Letourneur F, Leturcq T, Ka Z, van Endert P, Garchon HJ, Chiocchia G, Breban M. (2015). ERAP1 Gene Expression Is Influenced by Nonsynonymous Polymorphisms Associated With Predisposition to Spondyloarthritis., Arthritis Rheumatol.. 67(6), 1525-1534

Costantino F, Chaplais E, Leturcq T, Said-Nahal R, Leboime A, Zinovieva E, Zelenika D, Gut I, Charon C, Chiocchia G, Breban M, Garchon HJ. (2016). Whole-genome single nucleotide polymorphism-based linkage analysis in spondyloarthritis multiplex families reveals a new susceptibility locus in 13q13., Ann Rheum Dis. 75(7), 1380-1385

Costantino F, Talpin A, Said-Nahal R, Leboime A, Zinovieva E, Zelenika D, Gut I, Charon C, Izac B, Weissman M, Chiocchia G, Reveille J, Breban M, Garchon HJ. (2017). A family-based genome-wide association study reveals an association of spondyloarthritis with MAPK14., Ann Rheum Dis. 76(1), 310-314

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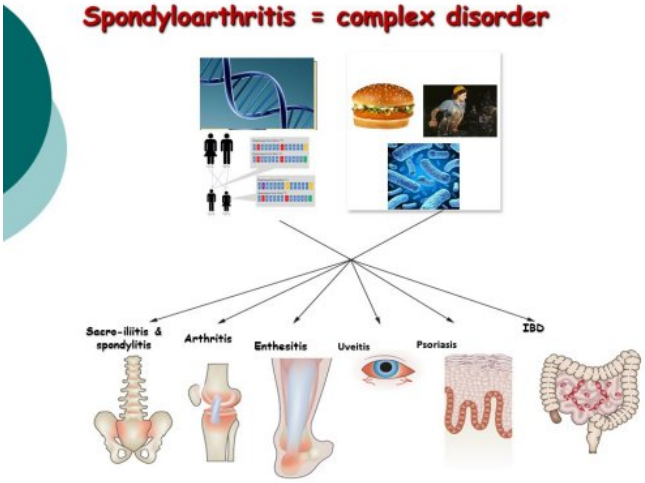
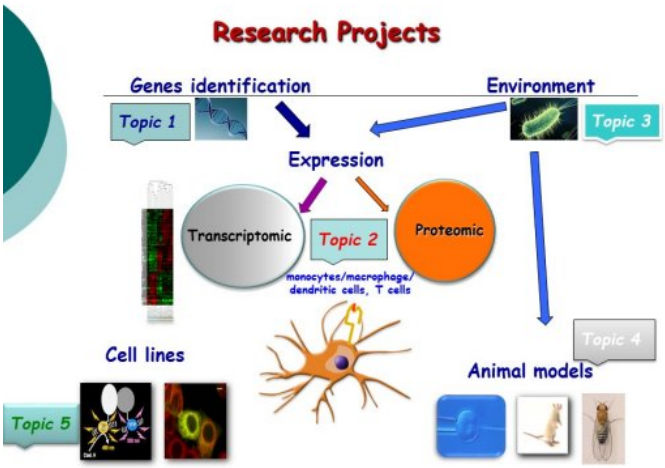
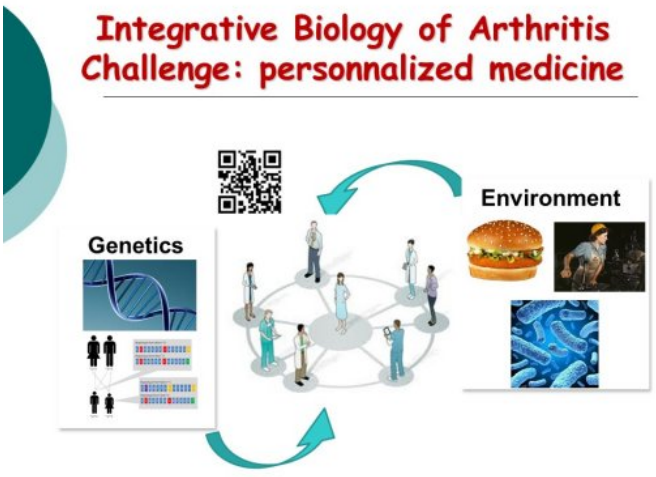
Spondyloarthritis = complex disorder



Research projects



Integrative Biology of Arthritis



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Francis Berenbaum

Metabolic diseases and age-related joint diseases

Sorbonne Université
Inserm U938
Bruno Fève
Paris

Our team associates physiologists, cell biologists and clinicians devoted to find new targets and new biomarkers in osteoarthritis, particularly by exploring the role of metabolic diseases and bone/cartilage/synovial tissue interactions

Key facts

Team

- Researchers : 4
- Technicians : 3
- Postdoc fellows : 2
- PhD Students : 3

Translational approaches

- Patents : 4
- Clinical research grants : 2
- Industry partnerships : 3

International research links

- Hong Kong (Polytechnic University)
- San Diego (Scripps Institute)
- San Francisco (USDF Bakar Institute)

Keywords

- osteoarthritis
- inflammation
- adipose tissue
- cholinergic system
- cartilage
- synovial tissue
- subchondral bone
- murine models of osteoarthritis
- in vitro/ex vivo culture of joint cells
- chondrocyte differentiation models

Biological Resources

- osteoarthritis murine models
- BioJoint (a biobank of human joint tissues and fluids)
- Human and murine chondrocytes, synoviocytes, osteoblasts, macrophages, mesenchymal stem cells, endothelial cells
- DIGICOD (a cohort of patients with hand OA)
- TRANSIMMUNOM (a database with deep phenotyping of 50 osteoarthritic knees)

Research Brief :

Our team has been interested for several years in the physiopathology of osteoarthritis (OA) in the final objective to discover innovative treatments and novel diagnostic and prognostic biomarkers. For these objectives, we have developed several tools, from cell cultures to human cohorts, from preclinical murine models to joint tissue analysis. We focus our projects on the relationship between osteoarthritis and metabolic diseases. Six projects are currently under investigation:
1 Role of chondrocyte differentiation on the angiogenesis of the subchondral bone
2 Role of the cholinergic system in joint protection
3 Role of adipose tissues in OA pathophysiology
4 Identification of the molecular signature of pain in knee osteoarthritis using omics and machine learning
5 Drug development of intraarticular liraglutide as a disease-modifying OA treatment
6 Investigating extracellular matrix changes at the osteochondral junction

- **Methodologies Used :**

- At the cellular level: culture of human and murine chondrocytes, synoviocytes, osteoblasts, macrophages, mesenchymal stem cells, endothelial cells, control of chondrocyte phenotypes and angiogenesis models
- At the tissue level: culture of cartilage explants, histological, biochemical and molecular analysis of joint tissues
- In vivo models: mouse and rat models of osteoarthritis (post-trauma, monoiodoacetate, collagenase)
- Human data: BIOJOINT, a biobank of joint tissues (cartilage, bone, synovial tissue and fluid, adipose tissue), DIGICOD, a cohort of 426 patients with hand OA (extensive clinical phenotyping,DNA, serum, X-rays, MRI, ultrasound), TRANSIMMUNOM, a cohort of inflammatory disease patients including 50 knee osteoarthritis

Publications

Gosset M, Berenbaum F, Thirion S, Jacques C (2008). Primary culture and phenotyping of murine chondrocytes., Nature protocols. 3(8), 1253-60

Eymard F, Pigenet A, Rose C, Bories A, Flouzat-Lachaniette CH, Berenbaum F, Chevalier X, Houard X, Nourissat G (2019). Contribution of adipocyte precursors in the phenotypic specificity of intra-articular adipose tissues in knee osteoarthritis patients., Arthritis Research and Therapy. 21(1), 252

van Eegher S, Perez-Lozano ML, Toillon I, Valour D, Pigenet A, Citadelle D, Bourier C, Courtade-Gaiani S, Gregoire L, Cleret D, Malbos S, Nourissat G, Sautet A, Marie-Helene Lafage-Proust, Philippe Pastoureau, Gaelle Rolland-Valognes, de Ceuninck F, Berenbaum F, Houard X. (2020). The differentiation of prehypertrophic into hypertrophic chondrocytes drives an OA-remodeling program and IL-34 expression, Osteoarthritis and Cartilage. 29(2), 257-268

Courties A, Do A, Leite S, Legris M, Sudre L, Pigenet A, Nourissat G, Cambon-Binder A, Maskos U, Berenbaum F, Sellam J. (2020). Critical role of the non-neuronal cholinergic system in inflammation and degradation processes in osteoarthritis., Arthritis & Rheumatology. 72(12), 2072-2082

Courties A, Belle M, Senay S, Cambon-Binder A, Sautet A, Che?dotal A, Berenbaum F, Sellam J. (2020). Clearing method for 3-dimensional immunofluorescence of osteoarthritic subchondral human bone reveals peripheral cholinergic nerves., Scientific Reports. 10(1), 8852

Meurot C, Martin C, Sudre L, Breton J, Bougault C, Rattenbach R,.Bismuth K, Jacques C, Berenbaum F (2022). Liraglutide, a glucagon-like peptide 1 receptor agonist, exerts analgesic, anti-inflammatory and anti-degradative actions in osteoarthritis, Scientific Reports. sous presse(),

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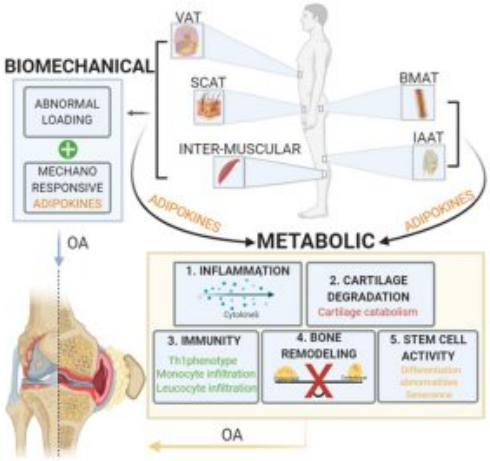
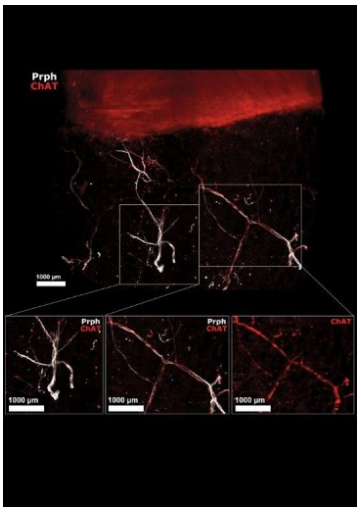
Role of adipose tissues in OA

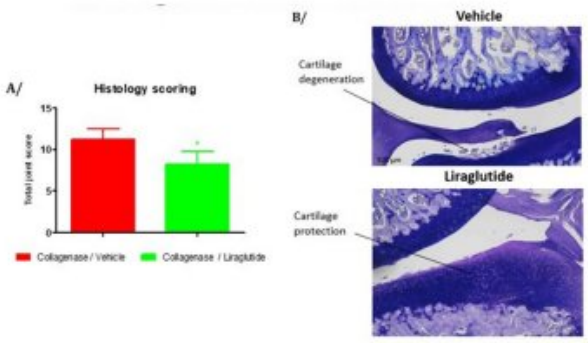


Human OA subchondral bone has peripheral and cholinergic nerves



Immunofluorescence of peripherin and ChAT in human OA subchondral bone after the 3DISCO clearing protocol and analysis with Imaris. The colocalization of both markers showed that some subchondral bone peripheral nerves marked by Prph (white) are also cholinergic, as they showed ChAT immunofluorescence (red) as shown on the right while some did not expressed ChAT (left). ChAT: choline acetyltransferase, Prph : peripherin.

Liraglutide has cartilage protection effects in collagenase-induced model in rats



In the rat collagenase OA model (500U in 25µl/ rat, n=8-10, intraarticular injections at day 1 and 4), repeated IA injections of formulated liraglutide or vehicle were performed once a week for 5 weeks

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Key facts

Team

• Researchers : 12
• Technicians : 7
• Postdoc fellows : 4
• PhD Students : 5

Translational approaches

• Patents : 1
• Clinical research grants : 3
• Industry partnerships : 2

International research links

• USA Birmingham, Alabama - Leeds, UK - Brazilia, Brazil - Carabobo, Venezuela - Ho Chi Min, Vietnam

Keywords

• Genetics
• oral medicine
• Environment
• Mineralization
• Physiopathology
• Tissue reconstruction

Biological Resources

• Cultures of oral mineralized tissue forming cells.
• Collection of Human Odontogenic Tissues.
• Cohort of Rare Facial and Buccal Malformation Center (national network and ERN)
• Transgenic mouse models of oral malformations.

Ariane Berdal Sylvie Babajko

Molecular Oral Physiopathology

Université de Paris 07
(Université Denis Diderot) Université de Paris 05
(Université Paris Descartes)
CHU Inserm U 1138
Jessica Zucman Rossi
Paris

Tranlational researches are conducted from involved genes to in vitro cell biology, animal models and clinics.

Research Brief :

Our group is dedicated to the oral-facial area, an exemplary composite skeleton where epithelial and neurectoderm-derived mesenchymal cells cooperate within a permanently challenged microenvironment. Post-natal physiology harbours specificity (dental cells, bone drug sensitivity and fate related to odontogenic growth and tumours) which determinants are studied in our group. Homeogene patterns were shown to imprint oral cells and impact their post-natal proliferation, differentiation and functions. This was illustrated in transgenic mice: the combinatorial Msx2, Dlx1, 3, 4, 6 interplay defined the frame of matrix protein expression and thus, regional enamel thickness. Msx1 and Msx2 controlled site-specifically osteoblast/osteoclast cross-talks and activity during physiology and healing. Msx/Dlx transcriptional role is explored on dental and bone genes. An endogenous antisense cis-RNA for Msx1 was discovered by us. Epigenetic and cell-autonomous mechanisms were evidenced and are presently analysed from sense and antisense promoters to an integrated level. Based on this detailed cell profiles, innovative biomaterials are tested as well some hormonal and toxic factors controlling skeletal morphogenesis. Correspondingly, human rare diseases are studied in our Reference Center. The team is involved in training programs which welcome scientists and health students in oral and mineralised tissue research.

• **Methodologies Used :**

Molecular in situ studies on mineralized tissues and cells.
2D and 3D analysis of the dento-maxillo-facial skeleton.
Oral and dental genetics - rare diseases
Experimental surgery and material investigation.
Molecular and cellular Biology.

Publications

Jedeon K., De la Dure-Molla M., Brookes S.J., Loiodice S., Marciano C., Kirkham J., Canivenc-Lavier M.C., Boudalia S., Bergès R., Harada H., Berdal A., Babajko S. (2013). Enamel defects reflect perinatal exposure to bisphenol A, Am. J. Pathol.,. 183(1), 108-18

1. de la Dure Molla M., Quentric M., Yamaguti P.M., Acevedo A.-C., Mighell A.J., Vikkula M., Huckert M., Berdal A., Bloch-Zupan A*..*co-last (2014). Pathognomomic oral profile of enamel renal syndrome (ERS) caused by recessive FAM20A mutations., Orphanet J. Rare Dis.,. 14(95), 84-922516-26*

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Jedeon K, Loiodice S, Salhi K, Le Normand M, Houari S, Chaloyard J, Berdal A, Babajko S. (2016). Androgen Receptor Involvement in Rat Amelogenesis: An Additional Way for Endocrine-Disrupting Chemicals to Affect Enamel Synthesis., Endocrinology. 157(11), 4287-96

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Claudine Blin

Osteoimmunology, niches and inflammation

Université Côte d'Azur
CNRS UMR7370
Laurent Counillon
Nice

Key facts

Team

• Researchers : 4
• Technicians : 1
• Postdoc fellows : 1
• PhD Students : 2

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 1

International research links

• USA, Germany, Spain, Netherlands, Italy, Denmark, Monaco

Keywords

• Osteoimmunology
• Chronic inflammation
• Rheumatic diseases, osteoporosis
• Hematopoietic niches
• Osteoclast
• Cell culture
• Cytometry
• Functional assays
• scRNAseq
• Murine models

Focusing on inflammation and bone destruction, our team proposes a novel vision not only on how immune cells control bone destruction, but also on how bone cells participate in immune responses. We are one the very few teams to consider osteoclasts in their diversity and as innate immune cells.

Research Brief :

Bone marrow is the site of bone remodeling, immune cell differentiation and memory lymphocyte maintenance. Interactions between bone, immune and precursor cells are essential and their deregulation is associated with inflammatory bone destruction. Our projects focus on the contribution of these interactions in the maintenance of bone and immuno-hematological system homeostasis.
Axe 1: Diversity, origin and immune function of osteoclasts.
We recently showed that bone-resorbing osteoclasts in inflammation differ from normal ones and that, as other monocytic cells, osteoclasts are innate immune cells driving tolerance or inflammation depending on their origin/environment. We are characterizing osteoclast diversity at the single cell level in terms of phenotype, function and origin, in order to evaluate new therapeutic approaches for bone destruction targeting only inflammatory osteoclasts while preserving the physiological ones.

Axe 2: Gut-bone axis in chronic inflammation.
Our projects are focused on the reciprocal gut-bone interaction in the regulation of inflammation and bone destruction. In chronic colitis, we identified in vivo reciprocal interaction between osteoclasts and Th17 cells that maintain inflammation. We are exploring the implication of other pathological immune cells and developping approaches to limit their emergence. Using human iPS-derived MSCs, we are also exploring how T cell-MSC interactions modulate T cell activation.

• **Methodologies Used :**

- Murine models of chronic inflammation and bone destruction
- Primary cultures of human / murine bone cells (osteoclasts, osteoblasts, MSCs) and immune cells (T cells, dendritic cells, monocytes, macrophages...)
- In vitro generation of murine and human CD4+ T cell subsets (including Th17 cells)
- Transcriptomic analysis, including scRNAseq, on bone and immune cells
- Generation of human iPS cells and their derivatives
- Flow cytometry and cell sorting of osteoclasts
- Flow cytometry for cell phenotyping (immune cells, MSCs, hematopoietic progenitor and stem cells)
- Functional assays to characterize immune cell responses (T cells, dendritic cells, monocytes...)
- Histological analysis on bone and other tissue

Publications

Mansour A, Abou-Ezzi G, Sitnicka E, Jacobsen SE, Wakkach A, Blin-Wakkach C (2012). Osteoclasts promote the formation of hematopoietic stem cell niches in the bone marrow, Journal of Experimental Medicine. 209(3), 537-49

Ciucci T, Ibáñez L, Boucoiran A, Birgy-Barelli E, Pène J, Abou-Ezzi G, Arab N, Rouleau M, Hébuterne X, Yssel H, Blin-Wakkach C, Wakkach A (2015). Bone marrow Th17 TNFa cells induce osteoclast differentiation, and link bone destruction to IBD, Gut. 64(7), 1072-81

Ibáñez L, Abou-Ezzi G, Ciucci T, Amiot V, Belaïd N, Obino D, Mansour A, Rouleau M, Wakkach A, Blin-Wakkach C (2016). Inflammatory osteoclasts prime TNFa-producing CD4+ T cells and express CX3CR1, Journal of Bone and Mineral Research. 31(10), 1899?1908

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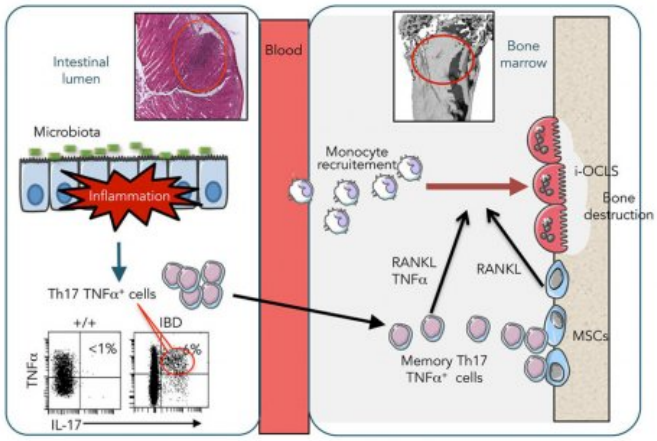
Madel MB, Ibáñez L, Wakkach A, de Vries TJ, Teti A, Apparailly F, Blin-Wakkach C. (2019). Immune Function and Diversity of Osteoclasts in Normal and Pathological Conditions, Front Immunol. Jun 19(10), 1408

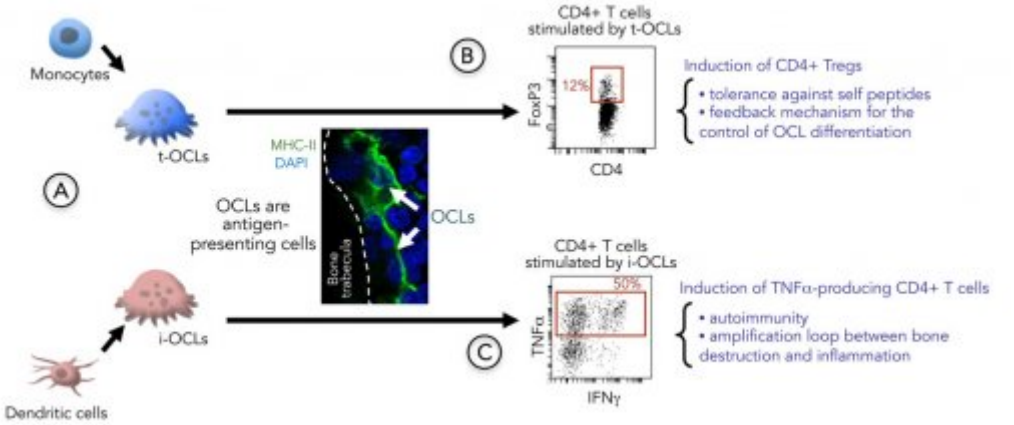
Madel MB, Ibáñez L, Ciucci T, Halper J, Rouleau M, Boutin A, Hue C, Duroux-Richard I, Apparailly F, Garchon HJ, Wakkach A, Blin-Wakkach C. (2020). Dissecting the phenotypic and functional heterogeneity of mouse inflammatory osteoclasts by the expression of Cx3cr1, eLife. May 13(9), e54493-73

Link between inflammation and bone destruction in Crohn's disease



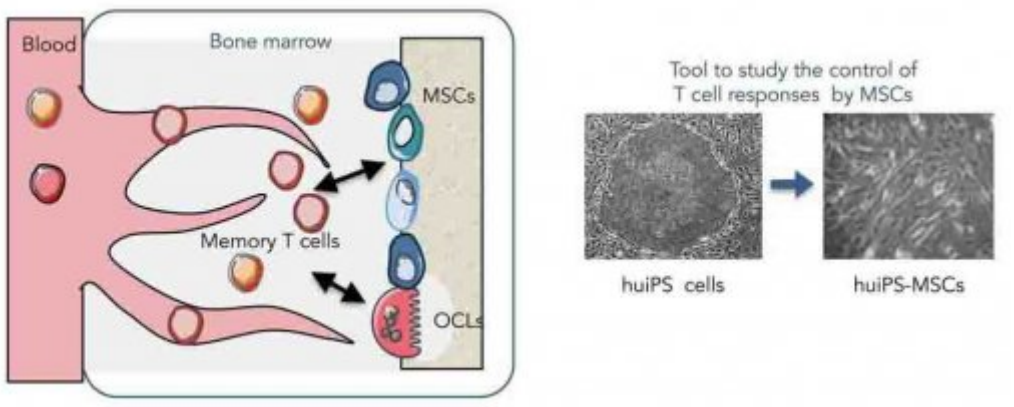
Bone destruction is a hallmark of inflammation. Gut inflammation generates TNFa-producing Th17 cells that migrate to the bone marrow where they dramatically increase osteoclast differentiation. (i) They produce osteoclastogenic factors (RANKL, TNFa), (ii) they stimulate MSCs to produce RANKL, and (iii) they increase in MSCs the expression of chemokines attracting OCL precursors. The resulting inflammatory osteoclasts (iOCL) differ from control ones and participate in inflammatory responses.

The immune function of osteoclasts



(A) Osteoclasts (OCLs) have different phenotypes according to their environment / origin and are antigen-presenting cells.
(B) In steady state, tolerogenic OCLs (t-OCLs) induce regulatory T cells, that can participe to the immune tolerance to avoid autoimmune reaction against self peptides issued from bone resorption.
(C) In an inflammatory context, inflammatory OCLs (i-OCLs) induce TNFa-producing CD4+ T cells that can participe to autoimmune reactions and link inflammation and bone destruction.

Interaction between memory CD4+ T cells and MSCs in the bone marrow



The bone marrow is a major reservoir for memory T cells. Maintenance of these cells in the bone marrow is controlled by bone marrow cells, in particular mesenchymal stromal cells (MSCs) and osteoclasts (OCLs). Establishment of clones of MSCs derived from induced-pluripotent stem (huiPS) cells represents an original model to study the mechanisms involved in these interactions in human in normal and pathological conditions.

Key facts

Team

- Researchers : 12
- Technicians : 5
- Postdoc fellows : 0
- PhD Students : 6

Translational approaches

- Patents : 0
- Clinical research grants : 2
- Industry partnerships : 5

International research links

- JAPON
- USA
- SINGAPOUR

Keywords

- ARTHRITIS
- INFLAMMATION
- CYTOKINES
- LYMPHOCYTES
- NETOSIS
- EXPERIMENTAL MODELS
- CLINICAL RESEARCH
- IMAGING
- IMMUNOTECHNOLOGIES
- CELL CULTURES

Biological Resources

- Animal models (including gene modified models of arthritis)
- cohorts of rheumatoid arthritis patients, and spondyloarthritis

Marie-Christophe Boissier

Pathophysiology, Targets and Therapies of Rheumatoid Arthritis

UNIVERSITE SORBONNE PARIS NORD INSERM
INSERM U1125
Marie-Christophe BOISSIER
BOBIGNY

Clinical and basic researchers work in perfect symbiosis, taking advantage of geographical proximity between lab and rheumatology department. We are developing a translational research through the development of both human and experimental models expertise.

Research Brief :

We seek to identify the conditions of onset, aggravation and therapeutic improvement of rheumatoid arthritis (RA) (also other inflammatory diseases such as spondyloarthritis, psoriasis, systemic diseases, bullous dermatoses), in humans and in murine models.
We study T lymphocytes, including regulatory T cells (Tregs), whose functional deficit is a major agent of the disease, and whose restoration is mandatory for the effectiveness of treatments. We examine their stability, receptors and molecules involved, and the influence of metabolic factors. We study memory effector T cells (Tem) in RA that are highly pro-inflammatory and we are deciphering the mechanisms leading to their persistence and hyperfunctionality. We are studying the neutrophils (PMN) and the role of NETs (neutrophil extracellular traps), DNA-protein complexes released by the PMN. They have a major role in inflammation and autoimmunity, especially against citrullinated antigens. We are studying the close relationship of PMNs with Tregs, and macrophages. This leads us to determine the role of cytokines, complement, TLRs, also B lymphocytes, in these interactions and their consequences.
We study the role of the exposome in RA, and develop a program to define the role of dust and silica in RA. We study metabolic factors using metabolomics and lipidomics tools. The factors identified are studied according to the clinical profile of each patient (stage of the disease, therapeutic phase, response to treatments)

Methodologies Used :

· Flow cytometry multiparametric (28 colors) / Cell sorting
· Animal models (including gene modified models of arthritis)
· Cell culture / In vitro Co-culture cell models
· Molecular biology (including RNAs seq, real time qRT-PCR Taqman)
· Immunostaining (ELISA, immunohistochemistry)
· Fluorescent microscopy / Metabolomics, lipidomic / Western-blot

Publications

Biton J, Khaleghparast Athari S, Thiolat A, Santinon F, Lemeiter D, Hervé R, Delavallée L, Levescot A, Roga S, Decker P, Girard JP, Herbelin A, Boissier MC, Bessis N (2016). In Vivo Expansion of Activated Foxp3+ Regulatory T Cells and Establishment of a Type 2 Immune Response upon IL-33 Treatment Protect against Experimental Arthritis, J Immunol. 197(), 1708

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F Santinon, M Batignes, M L Mebrek, J Biton, G Clavel, R Hervé,, D Lemeiter, M Breckler, F Busato, J Tost, M Ziol, MC Boissier, P Decker, ,L Semerano, N Bessis (2020). Involvement of Tumor Necrosis Factor Receptor Type II in FoxP3 Stability and as a Marker of Tregs Cells Specifically Expanded by Anti-Tumor Necrosis Factor Treatments in Rheumatoid Arthritis, Arthritis Rheumatol. 72(), 576

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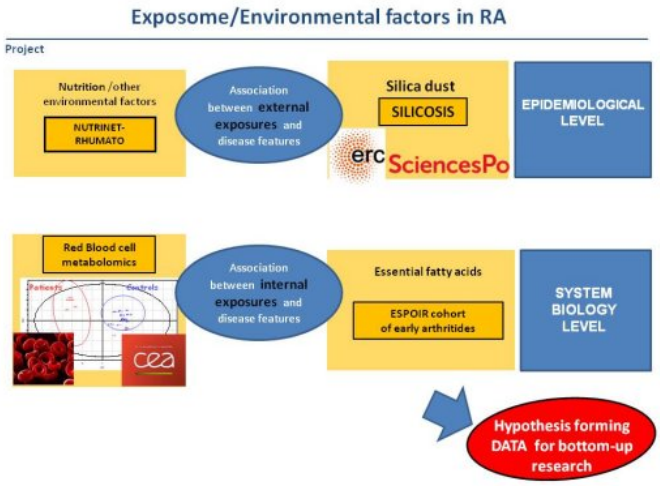
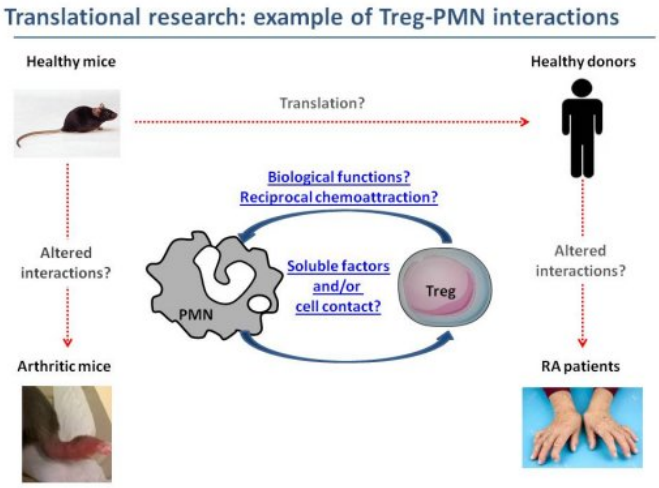
Exposome / Environmental factors in RA



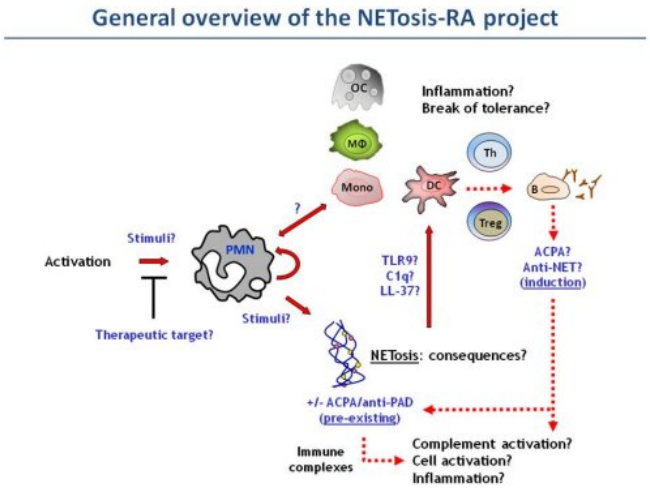
Role of exposome in Rheumatoid Arthritis (RA): (1) Silicosis is an integrated project on sociologic links with RA, mainly on sources of dust and work and behaviour influencing RA. (2) Nutrinet is a nationwide web-based prospective cohort on nutrition facts (150000 participants) ; we are studying rheumatic diseases in this cohort. (3) We are studying metabolomics in RA patients, in collaboration with CEA. (4) We are studying lipidomics in RA cohort ESPOIR, mainly omega3, 6, and 9 fatty acids.

Translational research : example of Treg PMN interactions



Interactions between polymorphonuclear cells (PMNs) and Tregs cells. They are studying in RA and in healthy donors, in humans (RA, spondyloarthritis) and in experimental models of arthritis. This examplified our specific approach of true translationnal research.

General overview of the NETosis RA project



Role of PMN in RA and murine models and their interactions with other cells, examplifying the rôle of NETs : monocytes, macrophages, Tregs, B cells, osteoclasts.

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Research teams with secondary association to PMN Institute

BioS EA 4691 Biomateriaux et Inflammation en Site Osseux

Sophie Gangloff

Biomatériaux et inflammation en site osseux

Université de Reims
Champagne-Ardenne
/ EA 4691 BIOS
Sophie Gangloff
Reims

Our multidisciplinary team covers the whole spectrum of bone biology coming from assessment of bone loss-related pathology through therapeutics development using in vitro, in vivo and translational approaches.

Key facts

Team

- Researchers : 11
- Technicians : 6
- Postdoc fellows : 2
- PhD Students : 9

Translational approaches

- Patents : 2
- Clinical research grants : 1
- Industry partnerships : 2

International research links

- United-States of America
- Belgium

Keywords

- Bone
- Cystic Fibrosis
- Fibrous dysplasia
- Stem cells
- Infection
- iPSC
- Human Primary Cells
- Bone cells differentiation
- In vivo
- Bacterial biofilms

Research Brief :

The laboratory « Biomaterials and inflammation in bone site » brings together faculties and hospital practitioners (dental surgeons - pharmacists - biologists).
Our multidisciplinary project aims to decipher mechanisms underlying bone-loss related pathologies with a broad spectrum of models including, rare genetic disorders, rare bone cancers, infections... to propose prevention and new therapeutic solutions to the patients.

To achieve these objectives, the laboratory conducts basic science researches : 1) to characterize biological processes (inflammation, infection, cell differentiation) affecting the bone homeostasis 2) to study the physiopathology of bone in context of rare bone diseases with a peculiar emphasis on cystic fibrosis-related bone disease, fibrous dyplasia of bone, osteosarcoma and osteonecrosis of the jaw 3) to deapen our understanding of periodontal disease thanks to more translationnal approaches.
Our objectives also relate to technological and methodological developments of mimetic models of bone regeneration/degeneration, infection with or without medical devices to evidence bacterial adaptation to bone environment and bacterial persistence mechanisms, and rare bone disease dedicated models to provide insights leading to therapeutics options.

- **Methodologies Used :**

In vitro: primary human cells and/or bacteria, stem cells (human primary, iPSCs) commitment, inflammatory or anti-inflammatory potential, antibacterial activity, bacteria/biofilm adhesion, cell/bacteria interaction
In vivo : inflammation/infection in mice (air pouch, LPS models), bone surgery (drill defect, induced membrane), BRONJ model, genetically modified mice.

Publications

Jourdain ML, Velard F, Pierrard L, Sergheraert J, Gangloff SC, Braux J (2019). Cationic antimicrobial peptides and periodontal physiopathology: A systematic review, J Periodontal Res. 54(6), 589-600

Braux J, Jourdain ML, Guillaume C, Untereiner V, Piot O, Baehr A, Klymiuk N, Winter N, Berri M, Buzoni-Gatel D, Caballero I, Guillon A, Si-Tahar M, Jacquot J, Velard F (2020). CFTR-deficient pigs display alterations of bone microarchitecture and composition at birth, J Cyst Fibros. 19(3), 466-475

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Moniot A, Braux J, Bour C, Guillaume C, Lamret F, Laronze-Cochard M, Allart-Simon I, Audonnet S, Renault S, Rédini F, Sapi J, Gangloff SC, Gérard S, Velard F (2021). Pyridazinone Derivatives Limit Osteosarcoma-Cells Growth In Vitro and In Vivo, Cancers. 13(23), 5992

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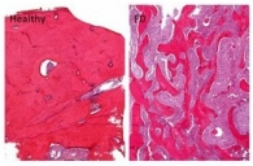
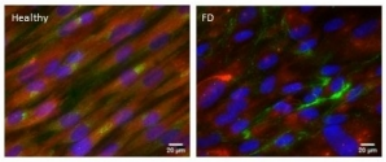
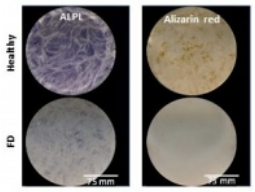
***In vitro* study of fibrodysplasia: specificity of mandibular osteoblasts**



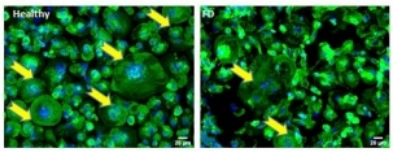
FD bone sample exhibits disorganized osteoid matrix (*)



In vitro, FD osteoblasts shows more Col1A1 (green) and osteocalcin (red) expression

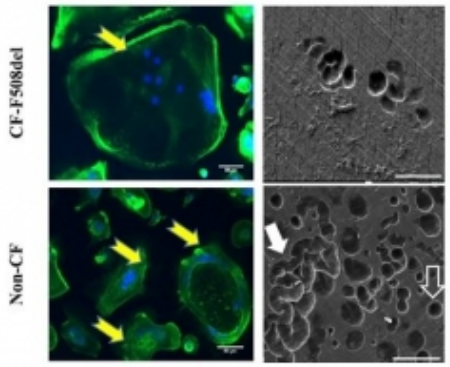


In vitro, FD osteoblasts shows less ALPL activity and less mineralization abilities

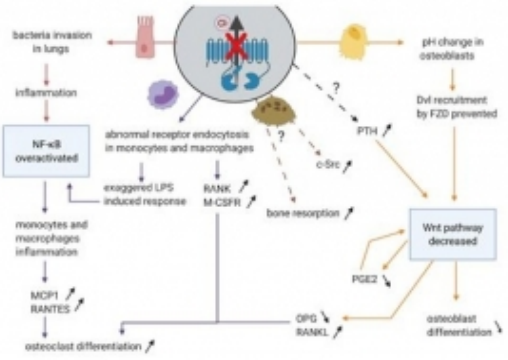


In vitro, FD osteoblasts supernatants impair oseoclastogenesis (yellow arrows)

Understanding Cystic Fibrosis-related Bone Disease

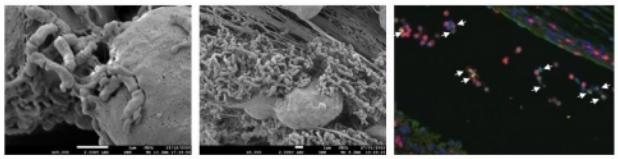


In vitro, patients' monocytes-derived osteoclasts (yellow arrows) are larger, less numerous and exhibit deficiencies in resorption abilities (white arrows)



Litterature-based hypotheses on how CFTR may rule bone homeostasis

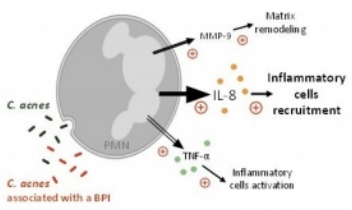
Deciphering Cutibacterium acnes infection-related inflammatory response in bone site



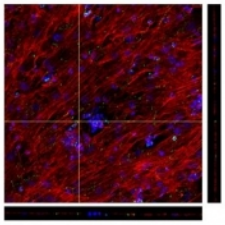
Neutrophils may phagocyte planktonic *C. acnes in vitro*

Neutrophils contact with *C. acnes* mature biofilm induce *NETosis*

Neutrophils (red) are recruited in air pouch model and engulf (arrows) *C. acnes* (green)



Schematic view of neutrophil response to *C. acnes* apart from bone site



In presence of osteoblasts (red), *C. acnes* (*green*) may be hidden inside to escape neutrophils

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Frédéric Mallein-Gerin

ROAD Regeneration of OsteoArticular and Dental tissues

Université Claude Bernard
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Dominique Sigaudo-Roussel
LYON

We combine basic and translational research with original topics at the international level (roles of LSD1 and integrin ?10?1 in cartilage pathophysiology, use of THPs able to guide cellular response for cartilage regeneration).

Key facts

Team

- Researchers : 7
- Technicians : 1
- Postdoc fellows : 1
- PhD Students : 1

Translational approaches

- Patents : 2
- Clinical research grants : 2
- Industry partnerships : 1

International research links

- Sweden
- Germany

Keywords

- mechanotransduction
- extracellular matrix turnover
- cartilage pathophysiology
- dental pulp pathophysiology
- tissue engineering
- proteomics
- transcriptomics
- bioreactors

Biological Resources

- Pre-clinical studies in animal
- Cell biobank

Research Brief :

1) We explore the role of the Lysine-Specific histone Demethylase 1 (LSD1)in OA by using a posttraumatic mouse osteoarthritis (PTOA) model (destabilization of medial meniscus, DMM). We cross LSD1-floxed mice with Col2-CreER mice (mice expressing the cre recombinase under the control of the type II collagen gene promoter, inducible with tamoxifen). Therefore, we create transgenic mice that enable us to study in a temporally and tissue-specific manner the function of LSD1 in OA.
2) The cellular response to mechanical stress results from a set of intracellular signaling cascades that lead to gene regulation. We study the impact of dynamic compression on the phosphorylation state of signaling molecules and on the transcriptome of chondrocytes in the presence or absence of integrin ?10?1, the most abundant integrin expressed at the surface of chondrocytes. This will, for the first time, determine how ?10?1 contributes to mechanotransduction in chondrocytes.
3) We develop an original approach for tissue engineering of cartilage based on the functionalization of collagen biomaterials with triple-helical peptides (THPs), a family of biomimetic peptides that adopt the triple helix conformation of native collagen. We use a novel photocrosslinking method, which preserves the collagen binding sites for cell receptors. We use these new biomaterials to orientate cellular response and to improve biomaterial's resistance and stability.

• **Methodologies Used :**

- Transgenic mice and DMM
- Production of THPs
- Tribo-bioreactor
- human cartilage tissue culture

Publications

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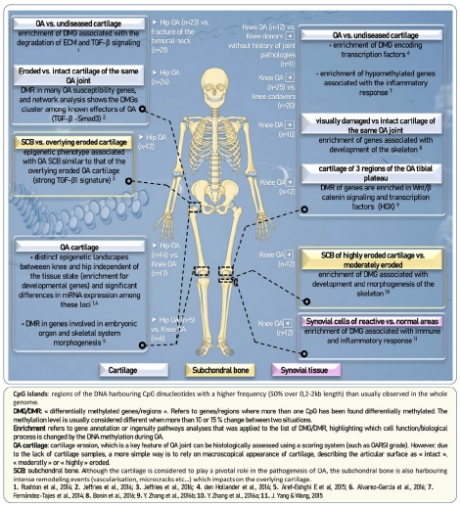
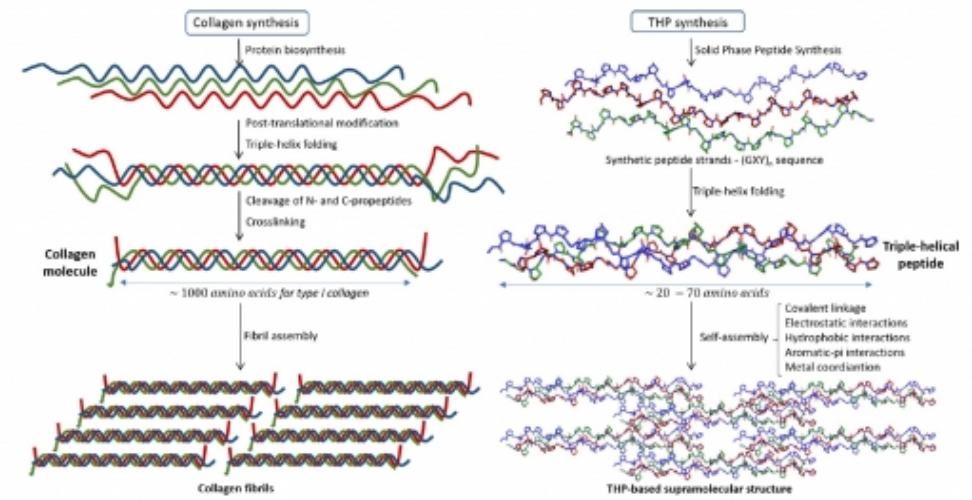
Comparative analyses of DNA methylation profiles of various OA joints



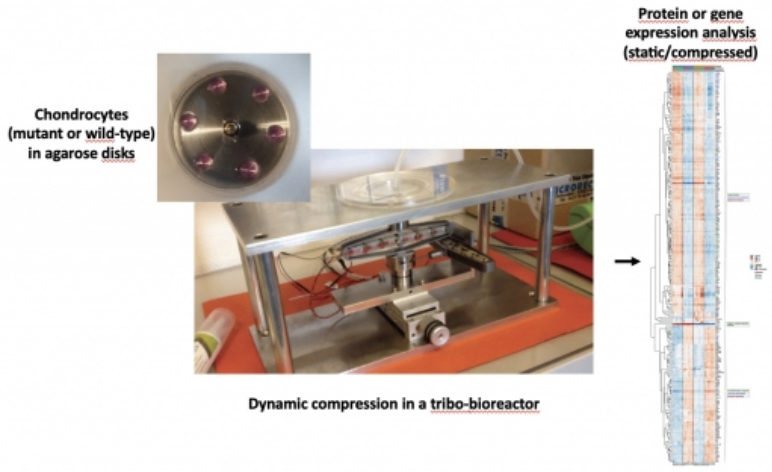
Among the epigenetic players involved in OA, we explore the role of the Lysine-Specific histone Demethylase 1 (LSD1).

Hierarchical assembly of native fibrillar collagen and synthetic pathway for THP production



We use triple-helical peptides to guide cell adhesion and differentiation of chondrocytes seeded in collagen biomaterials.

Development of a prototype tribo-bioreactor to study mechanotransduction in chondrocytes



Using this system, we analyze the impact of alpha10beta1 integrin in the response of chondrocytes to dynamic compression.

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Yannick Allanore Frédéric Batteux

Pathogenesis and innovative therapies in systemic sclerosis and other fibro-inflammatory diseases

Paris Cité University
INSERM U1016 CNRS UMR8104
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Paris

Key facts

Team

- Researchers : 7
- Technicians : 4
- Postdoc fellows : 3
- PhD Students : 3

Translational approaches

- Patents : 1
- Clinical research grants : 10
- Industry partnerships : 10

Keywords

- Systemic sclerosis
- Fibrosis
- Auto-immunity
- Animal models
- Genetic

High translational applications with really from bench to bedside and back

Research Brief :

Systemic sclerosis (SSc), a multisystem autoimmune connective tissue disease, has the highest mortality from all inflammatory rheumatological disorders and a heavy morbidity. Its pathogenesis is incompletely understood but it is thought to occur because of interactions between susceptibility genes and environmental factors. The interplay between microvascular damages and both innate and adaptative immune disturbances promotes activation of mesenchymal cells that induce fibrosis. Our group is committed to decipher SSc pathogenesis since many years. Our strategies include genetic susceptibility, polarization of innate and adaptative immune responses, role of reactive oxygen species in the interplay between various systems, epigenetic marks contributing to fibroblast dysfunction and chronic inflammation, with the ultimate goal to develop biomarkers and new therapies. We have established a huge databank of DNA, mRNA, serum, plasma, tissues and cells to perform translational research. Moreover, we have established a pre-clinical platform of SSc related and complementary animal models to investigate in vivo any relevant candidate as a potential treatment. These strategies are further applied in other fibro-inflammatory diseases with key interest in rheumatoid arthritis and endometriosis thanks to the expertise and recruitment at Cochin University Hospital.

- **Methodologies Used :**

Re sequencing
genotyping
cellular biology
molecular biology
animal models

Publications

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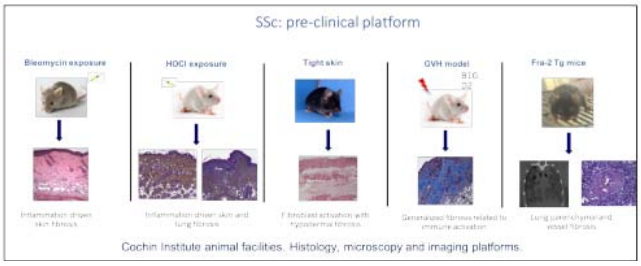
systemic sclerosis pre-clinical platform

- **Objectives:**
  - To decipher scleroderma pathogenesis
  - To investigate how chronic inflammation can promote fibrosis
  - To identify relevant biomarkers and innovative therapies
- **Tools:**
  - Large biobank from patients : DNA, RNA, serum, plasma, tissue and cells
  - A platform of preclinical mouse models
  - Close work with the clinical teams from Cochin Hospital
  - Active international networking with academics and pharmaceutical companies



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