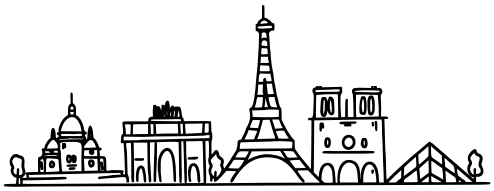
28-29 October 2024

Faculté Necker
Université Paris Cité



160 rue de Vaugirard
75015 Paris, France
Grand amphithéâtre
Métro Pasteur - Bus 70, 89

The final symposium of the Microbiota cross-cutting program of Inserm will bring to an end the program launched in 2017. It will revisit the main scientific breakthroughs of the scientific community structured by the program, and address the determinant role of microbiota in health and disease.

Keynote Speakers:
Yasmine BELKAID, Institut Pasteur, France
Eran SEGAL, Weizmann Institute, Israël

Invited Speakers:

Premysl BERCIK (McMaster University, Canada), Thomas CLAVEL (Aachen University, Germany), Maria Carmen COLLADO (National Research Council-Valencia, Spain), Mahesh DESAI (Luxembourg Institute of Health, Luxembourg), Sofia FORSLUND (Max Delbrück Center-Berlin, Germany), Andrew GEWIRTZ (Georgia State University, USA), Edoardo PASOLLI (University of Naples, Italy), Valentina TREMAROLI (University of Gothenburg, Sweden), Elena VERDU (Mc Master University, Canada)

Inserm Program Members and Organizing Committee:

Nicolas BARNICH, Ivo BONECA, Anne-Marie CASSARD, Nadine CERF-BENSUSSAN, Benoit CHASSAING, Mathias CHAMAILLARD, Sylvie CLAEYSEN, Karine CLÉMENT, Gérard EBERL, Serguei FETISSOV, Valérie GABORIAU-ROUTHIAU, Nathalie GRIVEL, Évelyne JOUVIN-MARCHE, Antonin LAMAZIÈRE, Agnès LEHUEN, François LEULIER, Philippe LESNIK, Olivier MEILHAC, Michel NEUNLIST, Harry SOKOL, Nathalie VERGNOLLE, Hubert VIDAL

With the support of the theme-based institutes of Inserm: Immunology, Inflammation, Infectious Diseases, Microbiology (I3M) and Pathophysiology, Metabolism, Nutrition (PMN)

Inserm

Link to register and submit poster abstract – free registration before September 15, 2024

Poster session

Group 1

1 A – Microbial mechanisms of action

Posters 1 to 12 (pp. 6-17)

Do conserved cell structures of archaea function as MAMPs ?	Camille Martin-Gallausiaux	1
Bacteriophage translocation across the intestinal barrier in Crohn's disease	Clara Douadi	2
AIEC LF82 cobB Deacetylase Targets the Nucleus to Enhance Adhesion	Flavie Dambrine	3
GUT BACTERIA WRESTLE WITH SUMO IN THE INTESTINAL ARENA	David RIBET	4
ChiA: a major player in the virulence of Crohn's disease-associated adherent and invasive Escherichia coli (AIEC)	Margot FARGEAS	5
IL4I1 induces gut and skin dysbiosis promoting melanoma development: modulating skin microbiota to restore anti-tumoral responses	Anna Llebaria Fabrias	6
Cytotoxic necrotizing factor-producing Escherichia coli enhance colorectal tumorigenesis in a preclinical mouse model of colorectal cancer with autophagy deficiency.	Coline Desseux	7
Action of an Escherichia coli toxin targeting Rho GTPase pathways in colorectal cancer	Diane LETOURNEUR	8
Clostridium filamentum, a newly discovered human gut species associated with metabolic health	Kassem Makki	9
Cancer-Associated Bacteria: Contribution of H. pylori and E. coli to DNA methylation changes and Gastric Cancer Pathogenesis	Emma Bergsten	10
Ruminococcus gnavus in Spondyloarthritis, story of a commensal killer	Simon Glatigny	11
Biochemical characterization of the Escherichia coli surfaceome: A focus on type I fimbriae and flagella	Devon KAVANAUGH	12

1 B – Bacterial adaptation to the intestinal environment

Posters 13 to 16 (pp.19–22)

Western diet impact EHEC colonization in M-ARCOL:a gut microbiota mediated study	Etienne-Mesmin Lucie	13
Cross-feeding interaction between inflammation-associated human gut microbes	Yuhang HU	14
A Paneth cell-succinate-tuft cell circuit links inflammation and dysbiosis in the gut mucosa	Nathalie Coutry	15
Study of the impact of E. coli genetic diversity on its fitness in the healthy and inflamed gut environment, using CRISPRi screen approaches.	Amandine Maire	16

Group 2

2 A – Exposome impact on microbiota and consequences for the host

Posters 17 to 22 (pp. 24–29)

Synthetic compounds with endocrine-disrupting properties influence the growth of gut bacteria and alter microbial community dynamics based on bacterial physiology and structure of compounds.	Andrea Marchetto	17
Pre- and post-natal exposure to phthalate and dinch metabolites and gut microbiota in one-year old children	Aline Davias	18
Effect of radiation on the symbiosis between the 'microbiota and host immune system' within the colonic ecosystem: Impact of diet as a therapeutic strategy	Calixte COTTINEAU	19
Atypical gut microbial ecosystem from athletes with very high exercise capacity	Frédéric Derbré	20
Consequences of antibiotic treatment at a young age on development of murine inflammatory arthritis	DE LIMA-ANTOINE Lara	21
Impact of titanium dioxide nanoparticles on colorectal carcinogenesis: focus on intestinal microbiota and colibactin-producing Escherichia coli	Charline Juban	22

2 B – Food and microbiota interactions and impact on the host

Posters 23 to 29 (pp. 31–37)

Obesogenic diet increases atherosclerosis through promoting microbiota dysbiosis	Nirmala Mouttoulingam	23
Gut microbiota in sex-specific effects of protein malnutrition in juvenile mice	Lucas Rebiffé	24
Severe Acute Malnutrition : a novel mouse model for therapeutic food investigations	Julie TOMAS	25
Early life microbiota alterations induced by maternal dietary emulsifiers intake prevent goblet cell-associated antigen passages, leading to long lasting consequences on intestinal and metabolic health.	Clara Delaroque	26
Identification of emulsifier sensors involved in the pathogenic potential of Crohn's disease associated Adherent Invasive Escherichia coli	Héloïse Rytter	27
L-serine, a key amino acid involved in the pro-carcinogenic effects of colibactin-producing E. coli	Amandine Devaux	28
Direct impact of dietary plant-based glycolipids on human gut microbiota and inflammation: first evidence from in vitro models	Cécile Vors	29

2 C – Therapeutic strategies for correcting disease-associated dysbiosis

Posters 30 to 33 (pp. 39–42)

MBRAs to model microbiome response to tryptophan and alcohol in ALD	Wanchao Hu	30
Saccharomyces boulardii ameliorates antibiotic-induced dysbiosis	Zhan Huang	31
Development of a probiotics and plant extracts combination targeting Adherent-Invasive Escherichia coli strains associated with Crohn's disease	Fanny De Clercq	32
Yeast β-glucan exert prebiotic activity increasing microbial diversity and short-chain fatty acids in the colonic microbiota of type II diabetic patients	Marciane Magnani	33

Group 3

3 A – Biomarkers

Posters 34 to 36 (pp. 44–46)

The human blood harbors a phageome which differs in Crohn's disease	Quentin LAMY-BESNIER	34
Determination of biomarkers associated with neoadjuvant treatment response focusing on colibactin-producing Escherichia coli in patients with mid or low rectal cancer	Christophe Taoum	35
In-situ bacterial and fungal microbiota influences Crohn's disease recurrence	Léonard DUBOIS	36

3 B – Microbiota influence on the host (except on the nervous system)

Posters 37 to 51 (pp. 48–63)

Microbial-derived metabolites promote NKT22 responses in colitis associated colorectal cancer	Alberto Baeri	37
Impact of a quorum sensing molecule on intestinal barrier function in IBD	Raphaelle Liquard	38
Impact of the perturbation and resilience of gut microbiota on cholesterolemia	Carolina Neves	39
Development of an organoid model from frozen chicken intestinal duodenum section	Tracy PARADIS	40
MyD88 signaling in hematopoietic cells controls host-Segmented Filamentous Bacteria symbiosis	Valérie Gaboriau-Routhiau	41
Impact of Staphylococcus aureus nasopharyngeal carriage on local mucosal and systemic immune responses	Malgorzata Mnich	42
Roseburia intestinalis modulates gut peptide (PYY) expression in a new a multicellular model including enteroendocrine cells	Thomas Gautier	43
Impact of intestinal miRNAs on gut health in IBD patients	Camille Remy	44
Taxonomic and functional analysis of gut microbiomes from patients with autoimmune diseases under low-dose IL-2 treatment	Grete Kvedaraviciute	45
Role of the human intestinal microbiota in individualized response to influenza vaccination	Maeva Duquesnoy	46
miRNA-microbiota dialogue in the neonatal period and long-term effects on gut health	Louis Berthet	47
DEFECTIVE AUTOPHAGY COMBINED WITH WESTERN DIET CAUSE DISRUPTED INTESTINAL HOMEOSTASIS, AIEC EMERGENCE AND INCREASED HOST SUSCEPTIBILITY TO AIEC INFECTION	Hanh Hoang	48
Cause-to-effect relationship between prefrail aging microbiota and intestinal inflammation	Guillaume Le Cosquer	49
MAIT cells monitor intestinal dysbiosis and contribute to host protection during colitis	Francois Legoux	50
Exploring systemic immune responses and faecal microbiome associations in the Milieu Intérieur healthy donor cohort	Auxence Desrentes	51

Group 4

4 – Microbiota and nervous system interactions

Posters 52 to 66 (pp. 65–80)

In-depth exploration of the oral microbiome reveals qualitative and quantitative alterations in multiple sclerosis	Laureline Berthelot	52
Role of the gut microbiome and Gastrointestinal disorders in autism spectrum disorder	Justine Marchix	53
Gut Microbiota's Role in Physical Activity on Testicular Cancer-Related Fatigue	Hwayoung NOH	54
Defects in the interaction between the microbiota and the intestinal epithelial barrier: a new player involved in the digestive disorders observed in patients with chronic pelvic pain	Mathéus MOREAU	55
The Gut Microbiota Influences Hypothalamic Blood-CSF Barrier Structure and Function	Rastelli Marialetizia	56
Microbiota-gut-brain axis in glioblastoma development and therapeutic resistance	Océane MARTIN	57
Characterization of gut microbiota alteration associated with eating disorders	David RIBET	58
THE ENTERIC NERVOUS SYSTEM: A TARGET OF FECAL EXTRACELLULAR VESICLES IN AUTISM	Martial CAILLAUD	59
Microbiome shapes postnatal development of the choroid plexus and brain volume	Ana Blas Medina	60
Immunoneutralization of enterobacterial ClpB protein protects mice against activity-based anorexia	Benjamin Thomas	61
Targeted proteomic approach to identify oxytocin-like bacterial proteins in human gut microbiota as putative biomarkers of autism spectrum disorders	Lisa Wallart	62
IDENTIFICATION OF OXYTOCIN-ANTIGEN MIMETIC PROTEIN IN LACTOBACILLUS AND ITS VALIDATION IN AN ANIMAL MODEL OF AUTISM	Emilie LAHAYE	63
Discovery of novel cellular mechanisms of vascular barrier enhancement in response to bacterial metabolites originating from healthy gut microbiota	Lola Savouré	64
GASTROINTESTINAL ALTERATIONS IN A MOUSE MODEL OF THE OKUR-CHUNG NEURODEVELOPMENTAL DISORDER	H Rebholz	65
Multi-omics analysis of gut microbiota unveils microbial functions alterations associated to Parkinson's disease.	Rémy Villette	66

Group 1

1 A - Microbial mechanisms of action

Posters 1 to 12

Microbiota – A key Determinant in Health and Diseases – 28-29 October 2024

Poster number: 1

Title: Do conserved cell structures of archaea function as MAMPs ?

Presenting Author: Camille Martin-Gallausiaux

Authors and Affiliations
Camille Martin-Gallausiaux, Robert Smithii, Catherine Werts, S. Griblado
Institut Pasteur
Institut Pasteur, 28 Rue du Docteur Roux – 75015, Paris

Abstract
Archaea are present in a wide variety of environments on Earth, including extreme environments, oceans, soil, or animals. Several archaea are human commensals, present on the skin and the gastrointestinal microbiota. Archaea have cell structures share functional similarity with their bacterial counterpart such as peptidoglycan (PG), flagellum, pilus, or S-layer. However, these archaeal cell structures have distinct genetic and molecular architectures.
Our knowledge of the interactions of these archaeal structures with the innate immunity of the host is very limited. C. Janeway proposed that multicellular organisms discriminate self from non-self by recognising structural molecules common to many microorganisms. In this project, we ask whether archaeal cells, like bacteria, have conserved microbe-associated molecular patterns (MAMPs) that are recognised by innate immune receptors.
To address this question, we selected 12 species spanning across the tree of archaea, that provide a diversity of cell structures and different environments (mesophiles/extremophiles,host/non-host associated). We assessed the ability of these archaea to activate the human TLR and NOD receptors by testing both whole cells and molecules released during culture. We show that archaea do not activate TLR4.. Next, we investigated whether archaeal flagella trigger TLR5 activation in a similar way to bacteria. None of the archaea, including flagellated species and isolated flagella, induced TLR5. On the contrary, most of the archaea tested activated the TLR2 receptor, although at a low level compared to bacteria. Finally, we evaluated the activity of archaeal PG on NOD receptors, which recognise bacterial PG motifs. The test of archaeal cells, purified archaeal PG and digested PG showed no activation of NOD1 and NOD2 receptors. This lack of detection may be related to the structural differences between archaeal and bacterial PG.
Overall, our study shows that despite the great diversity of archaeal cell structures, only a limited number of them serve as MAMPs in humans This suggests that there has been no repurposing of TLRs and NODs to recognise archaeal structure, as it has happened with Fungi and Viruses Apart from the yet unidentified MAMPs that stimulate TLR2, archaea are not recognised by receptors that recognise cell structures in bacteria. By comparing archaeal species from different environments, we were also able to show that the 'immunosilence' of archaea is not the result of co-evolution with the host, but possibly a more general feature of this domain of life. Our results suggest that the concept of pattern recognition works differently when applied to archaea.

Poster number: 2

Title: Bacteriophage translocation across the intestinal barrier in Crohn's disease

Presenting Author: Clara Douadi

Authors and Affiliations
C. Douadi et al. (16 authors, including V. Carrière, S. Thenet and L. De Sordi)
Sorbonne Université, INSERM, Centre de Recherche St Antoine, 75012 Paris, France
27 Rue Chaligny - 75012 Paris, France

Abstract
Crohn's disease (CD) is associated with alterations in gut barrier function and in the microbiota, largely composed of bacteria and bacteriophages (phages). We investigated the interaction of phages with the intestinal barrier under both physiological and inflammatory conditions, focusing on whether phages of varying sizes and structures can translocate from the gut to the bloodstream and whether they induce deleterious effects.

Purified phages (T4, M13 and ΦX174) were applied to Caco-2/TC7 intestinal epithelial cells or HUVEC endothelial cells, cultured on transwell filters, or on mouse gut samples mounted in Ussing chambers. EGTA or pro-inflammatory cytokines were used to increase paracellular permeability. We performed metagenomic viral analysis of blood and stool samples from CD patients and healthy subjects (HS).

All tested phages can translocate across intestinal epithelium and endothelium without disrupting the integrity of these barriers or triggering an inflammatory response. Notably, only ΦX174 translocation was significantly increased upon barrier dysfunction, as shown by a significant correlation with the paracellular permeability. Phages also translocated across mouse intestinal tissues. Using fluorescent phages, we showed their internalization within intestinal epithelial cells and endothelial cells by endocytosis. We revealed that viral sequences shared between blood and stool samples are more abundant in CD patients than HS.

Our results highlight how distinct phages can cross the intestinal barrier with translocation influenced by phage morphology, size and barrier integrity. They contribute to the understanding of phage dynamics in CD and support the potential safety of phages as therapeutic agents.

Poster number: 3

Title: AIEC LF82 cobB Deacetylase Targets the Nucleus to Enhance Adhesion

Presenting Author: Flavie Dambrine

Authors and Affiliations
Flavie Dambrine, Florian Coudray, Nicolas Barnich, Jérémy Denizot
M2iSH Université Clermont Auvergne, Inserm U1071
28 place Henri Dunant, 63000 Clermont-Ferrand

Abstract
Adherent Invasive Escherichia coli (AIEC) pathobionts, isolated from the ileal mucosa of patients with Crohn's disease, differ from strict pathogens in that they do not elicit an acute inflammatory response in murine models or in cultured intestinal epithelial cells. This characteristic may allow AIEC to persist in the intestinal mucosa, facilitating chronic colonization. These findings suggest that AIEC have evolved mechanisms to mitigate the host's inflammatory response, thereby avoiding clearance. Many of these mechanisms are likely regulated by epigenetic processes, particularly through post-translational modifications of histone proteins, such as acetylation. We recently showed that histone acetylation are central players in the control of AIEC entry within host cell.
This preliminary study aimed to identify and characterize a bacterial protein that could influence the structure of eukaryotic chromatin (nucleomodulin), with a specific focus on histone acetylation, which is known to regulate the expression of pro-inflammatory genes. Through the analysis of AIEC genomic data, we identified a bacterial gene encoding a lysine deacetylase with a putative nuclear localization sequence (NLS). Metagenomic analysis further revealed that the cobB gene is significantly enriched in the microbiota of Crohn's disease patients compared to healthy controls. Overexpression of the AIEC-LF82 cobB gene in Caco-2 intestinal epithelial cells demonstrated that cobB can translocate to the nucleus and induce substantial deacetylation of histone H3. Additionally, we observed that AIEC LF82 adhesion is enhanced in cobB-overexpressing cells, accompanied by a reduced inflammatory response to E. coli infection, as compared to cells transfected with an empty vector. This suggests that cobB may induce cellular modifications that favor AIEC adhesion while attenuating inflammation.
In conclusion, we have identified a bacterial protein capable of modulating the host cell epigenome to promote AIEC adhesion and suppress the inflammatory response during E. coli infection. Further research is required to elucidate the role of the cobB gene in AIEC pathobiont pathogenesis.

Poster number: 4

Title: GUT BACTERIA WRESTLE WITH SUMO IN THE INTESTINAL ARENA

Presenting Author: David RIBET

Authors and Affiliations
LOISON Léa, EZZINE Chaima, MONTBRION Nadine, BÔLE-FEYSOT Christine, DÉCHELOTTE Pierre, COËFFIER Moïse, RIBET David
Univ Rouen Normandie, INSERM, Normandie Univ, ADEN, UMR 1073 “Nutrition, Inflammation and Microbiota-Gut-Brain axis”, CHU Rouen, Department of Nutrition, F-76000 Rouen, France
Université de Rouen - 22 Bd Gambetta - 76000 ROUEN - FRANCE

Abstract
SUMOylation is a ubiquitin-like post-translation modification playing essential roles in intestinal physiology. Several pathogens were shown to interfere with host intestinal SUMOylation. We demonstrated for example that Listeria monocytogenes secretes a toxin that target host SUMOylation in order to promote bacterial replication. Along the same line, we recently highlighted that the gut opportunistic pathogen Staphylococcus warneri interferes with host SUMOylation and promotes intestinal inflammation.

In contrast to these pathogenic bacteria, the effect of symbiotic bacteria from the gut microbiota on intestinal SUMOylation remains poorly characterized. We recently unveiled that branched chain fatty acids (BCFAs), produced by the gut microbiota, increase protein SUMOylation in intestinal cells in a pH-dependent manner. We demonstrated that these metabolites inactivate intestinal deSUMOylases and promote the hyperSUMOylation of nuclear matrix-associated proteins. We further showed that BCFAs inhibit the NF-κB pathway, decrease pro-inflammatory cytokine expression, and promote intestinal epithelial integrity. BCFAs thus dampen host inflammatory responses via the modulation of host SUMOylation.

Together, our results illustrate that both pathogenic and symbiotic intestinal bacteria target host SUMOylation, albeit in opposite ways, in order to regulate intestinal physiology.

Poster number: 5

Title: ChiA: a major player in the virulence of Crohn's disease-associated adherent and invasive Escherichia coli (AIEC)

Presenting Author: Margot FARGEAS

Authors and Affiliations
Margot FARGEAS1, Frederic FAURE1-2, Clara DOUADI3-4, Caroline CHEVARIN1, Aurélien BIRER1, Adeline SIVIGNON1, Michael RODRIGUES1, Jérémy DENIZOT1, Elisabeth BILLARD1, Nicolas BARNICH1*# and Anthony BUISSON1-2*#
1. Université Clermont Auvergne/Inserm U1071, USC INRAE 1382, Microbes, Intestin, Inflammation et Susceptibilité de l'Hôte (M2iSH), Clermont-Ferrand, France. 2. Université Clermont Auvergne, Inserm, 3iHP, CHU Clermont-Ferrand, Service d'Hépato-Gastro Entérologie, Clermont-Ferrand, France. 3. Sorbonne Université, Inserm, Centre de Recherche Saint-Antoine, Paris, France. 4. Paris Center for Microbiome Medicine (PaCeMM) FHU, AP-HP, Paris, France.
Laboratoire M2iSH, 28 place Henri Dunant, Clermont-Ferrand, FRANCE

Abstract
Crohn's Disease (CD)-associated adherent-invasive E. coli (AIEC) are able to invade intestinal epithelial cells and to survive and replicate within macrophages. We investigated the role of the bacterial protein ChiA and its associated polymorphisms in the interaction between AIEC and the intestinal mucosa. Here we report that a higher abundance of the chiA gene is specifically observed among the metagenome of CD patients ($p<0.01$) and that ChiA is needed to achieve maximal colonization of ileal and colonic mucosa in mouse model. We observed that the pathogenic polymorphism of ChiA, carried by 42.40% of AIEC bacteria, increases its binding to CHI3L1rh and to mucin and that the strength of ChiA-mucin interaction was 300-fold stronger than that of ChiA-CHI3L1rh. We reveal that ChiA is able to degrade mucin to fuel its growth. Our results demonstrate that the number of LF82, the AIEC reference strain, associated with intestinal epithelial cells is significantly higher ($p<0.5$) when ChiA with a pathogenic polymorphism is added to infection conditions. Thus, the pathogenic polymorphism of ChiA seems to have a stronger impact on mucus degradation than on the binding capability of AIEC to adhere to the intestinal epithelium. In mice suffering from DSS-induced colitis and co-infected by LF82 and by its corresponding chiA-negative mutant LF82ΔchiA, we observed that ChiA could favor an efficient invasion of AIEC bacteria through intestinal crypts. Indeed, in the deeper areas of colonic crypts collected by laser microdissection, we detected exclusively LF82 compared to the upper parts of crypts where the two bacteria are found. We also observed that ChiA, especially its pathogenic polymorphism, gives to LF82 an advantage to enter within Peyer's patches, macrophages and mesenteric lymph nodes. Concerning macrophages infection by AIEC, ChiA confers an advantage for LF82 to enter within macrophages at the early stages of infection compared to LF82ΔchiA, in a co-infection context. All together, these data support the role of ChiA in the virulence of AIEC and show that ChiA could be a promising target to reduce AIEC colonization in CD patients.

Poster number: 6

Title: IL4I1 induces gut and skin dysbiosis promoting melanoma development: modulating skin microbiota to restore anti-tumoral responses

Presenting Author: Anna Llebaria Fabrias

Authors and Affiliations
Anna Llebaria-Fabrias, Malvina Seradj, Charlène Dauriat, Renée Lengagne, Benoît Chassaing and Armelle Prévost-Blondel
INSERM U1016 – CNRS UMR8104 – Université Paris Cité – Institut Cochin
27 Rue du Faubourg Saint Jacques, 75014, Paris

Abstract
IL4I1 is a secreted L-phenylalanine oxidase expressed in most solid tumors. We have reported that IL4I1 expression is associated with a reduced survival in human primary melanoma and demonstrated its pro-tumoral role in the RET spontaneous melanoma murine model. Interestingly, IL4I1 not only dampens anti-tumoral immune responses, but also exerts a bactericidal activity in vitro. Considering that commensal bacteria influence anti-tumoral immunity and response to immunotherapy, we investigated the effects of IL4I1 on melanoma-associated microbiota and their consequences on tumor aggressiveness with the aim to identify bacterial candidates susceptible to control melanoma development.

First, we compared the kinetic of tumor progression in RET and RET-IL4I1KO pups fostered by a mother of the same genotype or a mother from the other genotype. RET-IL4I1KO pups fostered by a RET mother developed melanoma faster than the control group and exhibited reduced infiltration by CD8+ T cells in the tumor microenvironment. Conversely, being fostered by a RET-IL4I1KO mother induced a delay of tumor development in RET pups associated with a decrease of tumor-associated macrophages. Together, these results show that IL4I1 contributes to melanoma aggressiveness via an impact on microbiota and reveal the presence of pro-tumoral bacteria in RET mice and anti-tumoral bacteria in RET-IL4I1KO mice.

To evaluate if IL4I1 expression alters microbiota, 16S rRNA gene sequencing of feces and skin from RET and RET-IL4I1KO mice was performed. RET mice exhibited a reduced alpha diversity, evidencing an IL4I1-induced dysbiosis in both compartments. Well aligned with this observation, principal coordinate analysis of Bray Curtis distances of microbiota from RET and RET-IL4I1KO mice revealed strain-dependent clustering, demonstrating an alteration of microbiota composition induced by IL4I1. Taxonomical analysis and the comparison of relative abundance of bacteria in RET and RET-IL4I1KO mice enabled the identification of gut- and skin-derived bacterial candidates susceptible to influence melanoma development. Two of these candidates, more abundant in RET-IL4I1KO mice, have already been tested in vivo. Indeed, topical application with the first one was able to delay the growth of subcutaneously transplanted melanoma associated to changes in the number and function of tumor-infiltrating CD4+ and CD8+ T cells. Skin or gut microbiota modulation with the second candidate elicited an anti-tumoral effect whatever the administration route. Interestingly, its protective proprieties were more profound when applied locally at the skin level.

Overall, our results demonstrate that IL4I1 promotes tumor development by impacting microbiota and reinforces the importance of modulating the tumor-associated microbiota to boost anti-tumoral responses.

Poster number: 7

Title: Cytotoxic necrotizing factor-producing Escherichia coli enhance colorectal tumorigenesis in a preclinical mouse model of colorectal cancer with autophagy deficiency.

Presenting Author: Coline Desseux

Authors and Affiliations
Coline Desseux1, Alison Da Silva1, Julien Delmas1, Anaëlle Tassini1, Pierre Sauvanet1, Nicolas Barnich#, Guillaume Dalmasso1, Hang Nguyen1,*
1M2iSH, UMR 1071 Inserm, Université Clermont Auvergne, INRAE USC 1382, CNRH, 63001 Clermont-Ferrand, France. *Correspondence: hang.nguyen@inserm.fr #Deceased.
28 Place Henri Dunant

Abstract
This work is dedicated to the memory of Nicolas Barnich.
Background and Aim: In patients with colorectal cancer (CRC), intestinal dysbiosis has been observed, with abnormal colonization of the colonic mucosa by pathogenic Escherichia coli strains producing a cyclomodulin named cytotoxic necrotizing factor (CNF). Cyclomodulins are bacterial toxins capable of altering the cell cycle of the infected cell. One of the mechanisms involved in host defence against pathogens and in carcinogenesis is autophagy. The role of autophagy in the host response to infection with CNF-producing E. coli, designated as CyPEC, has not yet been described. Thus, the aim of this study was to investigate the role of autophagy in colorectal carcinogenesis in the context of CyPEC infection. Methods: Mice predisposed to CRC development with autophagy deficiency specifically in intestinal epithelial cells (ApcMin/+/Atg16l1ΔIEC mice) and their control littermates with functional autophagy (ApcMin/+ mice) were infected with the clinical CyPEC strain 21F8 or with its mutant 21F8Δcnf that does not produce CNF. Tumor size and number were determined using a dissecting microscope. The mouse colons were collected and used for histological score assessment, and to analyse the levels of markers of autophagy, cell proliferation, apoptosis and inflammation by immunoblot, immunohistochemical staining and ELISA. Results: We showed that in ApcMin/+ mice, infection with either 21F8 or 21F8Δcnf did not have an impact on the number and the size of colonic tumours. However, in ApcMin/+/Atg16l1ΔIEC mice, infection with the CyPEC 21F8 strain led to increases in the number and the size of colonic tumours, compared with the uninfected condition. This increase appeared to be CNF-dependent as it was not observed upon infection with the 21F8Δcnf mutant. The increase in tumorigenesis in ApcMin/+/Atg16l1ΔIEC mice upon 21F8 infection versus uninfected condition was associated with increased pro-inflammatory cytokine production, enhanced cellular proliferation and decreased apoptosis in colonic epithelial cells. Conclusion: Our results suggested that autophagy deficiency combined with colonization by CyPEC strains could be a risk factor for the development of CRC.

Keywords: Escherichia coli; CNF; cyclomoduline; colorectal cancer; autophagy.

Poster number: 8

Title: Action of an Escherichia coli toxin targeting Rho GTPase pathways in colorectal cancer

Presenting Author: Diane LETOURNEUR

Authors and Affiliations
LETOURNEUR Diane 1, MONDY Juliette 1, NIGRO Giulia 2, BERGSTEN Emma 1,3, OBADIA Thomas 4, LEMICHEZ Emmanuel 1* and METTOUCHI Amel 1*
1 Institut Pasteur, Université Paris Cité, CNRS UMR 6047, INSERM ERL1306, Unité "Toxines Bactériennes", F-75015 Paris, France 2 Unité Stroma Inflammation et Réparation tissulaire & Unité Microenvironnement et immunité, Département d'Immunologie, Institut Pasteur, Paris, France 3 Pathogenèse de Helicobacter, Département de Microbiologie, Institut Pasteur, Paris, France 4 Institut Pasteur, Université Paris Cité, Bioinformatics and Biostatistics Hub, Paris, France.
25 rue du Docteur Roux, 75015 Paris

Abstract
Colorectal carcinogenesis is a multistep process involving a combination of host genetic susceptibility, lifestyle and environmental stressors, including microbiota dysbiosis and colonization by pathobionts. Considerable progress was recently made with the discovery of a mutational signature in colorectal tumor (CRC) samples, induced by the colibactin genotoxin (Clb) synthesized by some strains of Escherichia coli. A few studies described enrichment of E. coli encoding both Clb and the CNF1 toxin at the mucosa of patients suffering from CRC. Our unpublished data confirm this trend and show that such E. coli pathobionts are also detected in fecal microbiota of CRC patients.
The small GTPase Rac1 is an essential driver of cell proliferation and transformation that undergoes somatic gain-of-function alterations due the Rho/Rac-targeting bacterial deamidase activity of CNF1 toxin of E. coli. The flux of active Rac1 is under scrutiny of host HACE1 E3 ubiquitin ligase-mediated proteasomal degradation, maintaining cellular homeostasis.
We investigated CNF1 effects on the gut epithelium using a mouse intestinal organoid model. We observed exacerbation of DNA damages by CNF1, bringing mechanistical insights into how CNF1 toxin-producing bacteria could contribute to cancer onset and progression.

Poster number: 9

Title: Clostridium filamentum, a newly discovered human gut species associated with metabolic health

Presenting Author: Kassem Makki

Authors and Affiliations
Kassem Makki, Maria-Elena Martino, Andrea Quagliariello, Per-Olof Bergh, Muhammad-Tanweer Khan, Valentina Tremaroli, Fredrik Bäckhed
Laboratoire CarMeN, INSERM U.1060, INRAe U. 1397, Université Claude Bernard Lyon 1, Pierre Bénite, France and The Wallenberg Laboratory, Sahlgrenska Academy, University of Gothenburg, Sweden
Laboratoire CarMeN, INSERM U.1060, INRAe U. 1397, Université Claude Bernard Lyon1, Pierre Bénite, France

Abstract
The human gut contains trillions of microbial cells forming a complex network that can impact host physiology. Approximately 70% of gut bacteria identified in metagenomic studies are uncultured or poorly described, and therefore identification and characterization of human gut species is paramount for understanding microbial diversity and interactions with the host.
In this study, we isolated a previously unidentified anaerobic Clostridium species, with proposed name Clostridium filamentum ETTB (Clostridium sp. DSM 115107), from the stools of a healthy individual, and characterized it using in silico, in vitro, and in vivo analyses to explore potential functions, ecology, and dynamics.
Whole-genome sequencing revealed that C. filamentum ETTB clusters closely with Clostridium saudiense JCC, which was isolated from a fecal sample of a subject with morbid obesity. However, C. filamentum ETTB has a genome size that is 1 Mbp smaller compared to C. saudiense JCC. Notably, C. filamentum lacked genes involved in carbohydrate metabolism, transcription, and signal transduction present in C. saudiense, and contained genes involved in cell motility, such as the fliC gene.
Through metagenomic screening, we found that C. filamentum ETTB is present in the gut of both infants and metabolically healthy adults in industrialized (Swedish) and non-industrialized (Hunter-gatherers – Hadza) populations. Importantly, we explored the abundance of C. filamentum in a Swedish cohort with prediabetes and type 2 diabetes and found lower abundance in these individuals compared to controls with normal glucose tolerance. The abundance of C. filamentum correlated positively with gene richness, and negatively with body fat and HOMA-IR. High proportions of C. filamentum also correlated with lower circulating levels of secondary bile acids associated with insulin resistance (e.g. deoxycholic acid) and higher levels of 6α-hydroxylated bile acids, known to induce TGR5 and GLP-1 secretion, an important pathway linked to glucose regulation.
Supplementation of C. filamentum ETTB to mice on Western diet prevented liver fat accumulation, reduced white adipose tissue, and lowered intestinal inflammation. These phenotypes were linked to modulation of hepatic bile acid metabolism and changed bile acids levels the mirrored the correlations observed in humans.
In conclusion, we identified a new clostridial species that underwent reductive evolution and specialization, adapting to the human gut and likely promoting metabolic health partly by influencing bile acid metabolism.

Poster number: 10

Title: Cancer-Associated Bacteria: Contribution of H. pylori and E. coli to DNA methylation changes and Gastric Cancer Pathogenesis

Presenting Author: Emma Bergsten

Authors and Affiliations
BERGSTEN Emma1,2 (Post-doc), ARIMONDO Paola 3, KONTIZAS Lefteris 4, NAHORI Marie-Anne 1, MICHEL Valérie 2, MEYER Juliette5, VOLANT Stevenn 5, LEMICHEZ Emmanuel1, SGOURAS Dyonissios 4, TOUATI Eliette2* and METTOUCHI Amel1
1Bacterial Toxins, Department of Microbiology, CNRS UMR 6047, INSERM U1306, Institut Pasteur, Université Paris Cité, France. 2Infection Genotoxicity and Cancer, Department of Microbiology, CNRS UMR 6047, Institut Pasteur, Paris, France. 3EpiCBio, Epigenetic Chemical Biology, Department Structural Biology and Chemistry, CNRS UMR 3523, Institut Pasteur, Paris, France. 4 Laboratory of Medical Microbiology, Hellenic Pasteur Institute, Athens, Greece. 5 Bioinformatics and Biostatistics Hub, Institut Pasteur, Paris 75015, France. *Co-senior authors
Institut Pasteur, 28 rue du Dr Roux 75015 Paris

Abstract
Gastric and colorectal cancers are heterogeneous and multifactorial diseases influenced by genetic, epigenetic, and environmental factors, including microbial colonization. Helicobacter pylori, a leading cause of gastric cancer, is currently the only carcinogenic bacteria recognized by the WHO. DNA methylation pattern alterations are a phenomenon now recognized as a driver mechanism in cancer development and progression.
H. pylori, by altering the gastric environment, induces microbiota dysbiosis through the entire gastrointestinal tract. Notably, an increase in the Escherichia genus abundance has been observed in both stomach and gut microbiota of gastric cancer patients, and pathogenic strains of Escherichia coli have been implicated in the initiation of colorectal cancer. We hypothesize that gastric cancer may result from the synergistic or sequential impact over time of several pathobionts, such as E. coli, acting in partnership with H. pylori.
To investigate this hypothesis, we developed a model of human gastric epithelial cells chronically infected at low multiplicity of infection with H. pylori and E. coli. We explore early mechanisms promoting tumorigenesis, and their impact on gene expression, with a focus on alterations of DNA methylation patterns. Initial findings suggest that co-infection has a more pronounced impact than mono-infections in inducing de novo DNA methyltransferase activities. Ongoing experiments using DNA methylation arrays and RNA sequencing, along with the use of DNA methyltransferase inhibitors, will allow us to identify genes whose promoters are affected by aberrant methylation, impacting their expression levels. Bioinformatic analyses of our data together with publicly available methylome datasets in gastric cancer and premalignant lesions, including intestinal metaplasia, will allow the identification of essential pathways dysregulated by the co-infection of human gastric epithelial cells with H. pylori and E. coli.

Poster number: 11

Title: Ruminococcus gnavus in Spondyloarthritis, story of a commensal killer

Presenting Author: Simon Glatigny

Authors and Affiliations
Jacoutot M, Beaufrère M, Karpman P, Frison E, Robert V, Said-Nahal R, Gautreau G, Glatigny S, Breban M
UMR1173 INSERM, Université Paris-Saclay, Montigny-le-Bretonneux, France; 2 INFLAMEX, Laboratoire d'Excellence, Université Paris Diderot, Sorbonne Paris Cité, Paris, France;
2 avenue de la source de la bièvre, 78180 Montigny le bretonneux

Abstract
Introduction. Spondylarthritis (SpA) is a chronic inflammatory disorder characterized by osteoarticular and extra-articular manifestations, including inflammatory bowel disease (IBD). It is established that intestinal microbiota dysbiosis plays a role in IBD pathophysiology. We recently demonstrated that intestinal dysbiosis occurred during SpA. Thus, relative abundance of Ruminococcus gnavus is significantly increased in SpA patients. In this study, our goal was first to isolate R. gnavus from SpA patients and healthy controls (HCs). Second, we tested if R. gnavus strains from SpA patients were more proinflammatory than those from HCs. Finally, we evaluated if R. gnavus strains were selected by resistance to oxygen during SpA.
Methods. R. gnavus colonies were isolated from colonic biopsies and/or stools from SpA patients and HCs. Isolated R. gnavus strains were sequenced. Proinflammatory functions of R. gnavus strains were evaluated by their ability to induce mortality and tumor necrosis factor (TNF) production in monocytes isolated from SpA patients. Aerotolerance experiments were performed to test selection of R. gnavus by the proinflammatory environment of the gut during SpA.
Results. We successfully isolated R. gnavus colonies from HCs and SpA patients. Upon sequencing, we identified 33 different strains isolated from 13 SpA patients and 4 HCs. Interestingly, strains did not overlap between SpA patients and HCs. Mechanistically, R. gnavus strains isolated from SpA patients induced the greatest mortality and TNF production in patients' monocytes. Finally, R. gnavus strains isolated from SpA patients were not characterized by greater aerotolerance.
Conclusions. Our work demonstrates a broad R. gnavus diversity in stool and biopsies from SpA patients and HCs. Moreover, R. gnavus strains isolated from SpA patients induced greater mortality and TNF production in monocytes from SpA patients. Further studies in preclinical murine models of SpA will be required to better define the role of R. gnavus during SpA.

Poster number: 12

Title: Biochemical characterization of the Escherichia coli surfaceome: A focus on type I fimbriae and flagella

Presenting Author: Devon KAVANAUGH

Authors and Affiliations
DW Kavanaugh, A Sivignon, Y Rossez, Z Chouit, C Chambon, L Beal, M Hébraud, Y Guerardel, H Nguyen, N Barnich
M2iSH, UMR 1071 Inserm, Université Clermont Auvergne, INRAE USC 1382, CNRH, 63001 Clermont-Ferrand, France
Unité de Glycobiologie Structurale et Fonctionnelle (UGSF), Université de Lille, 59655 Villeneuve d'Ascq, France
Plateforme d'Exploration du Métabolisme, composante protéomique (PFEMcp), F-63122 Saint-Genès Champanelle, France
INRAE, UR 0370 Qualité des Produits Animaux (QuaPA), F-63122 Saint-Genès Champanelle, France
INRAE, Université Clermont Auvergne, UMR 0454 Microbiologie Environnement Digestif Santé (MEDiS), F-63122 Saint-Genès Champanelle, France

Abstract
The Escherichia coli surfaceome consists mainly of the large surface organelles expressed by the organism to navigate and interact with the surrounding environment. The current study focuses on type I fimbriae and flagella, which extend the furthest from the cell surface and likely represent the first point of contact with the surrounding environment. These large polymeric surface organelles are composed of hundreds to thousands of subunits, with their large size often preventing them from being studied in their native form. Recent studies are accumulating which demonstrate the glycosylation of surface proteins or virulence factors in pathogens, including E. coli.
Extracted E. coli surface proteins resolved by SDS-PAGE and stained with Alcian blue revealed varying staining profiles among the strains tested. Positive staining bands indicate the presence of an acidic / mucopolysaccharide protein conjugate. Further, using biochemical and glycobiological techniques, including biotin-hydrazide labelling of glycans and chemical and glycosidase treatments, we demonstrate i) the presence of well-defined and chemically resistant FimA oligomer in all tested strains of pathogenic and non-pathogenic E. coli, ii) the major subunit of type I fimbriae, FimA, in pathogenic and laboratory strains is recognized by concanavalin A, iii) ConA detection of FimA is only present after depolymerisation, indicating a sterically protected structure, iv) standard methods to remove mannose residues (PNGase F for N-glycans or a broad-specificity mannosidase) fail to remove the glycan structure, despite the treatments resulting in altered pili migration in SDS-PAGE, v) PNGase F treatment results in a novel 32 kDa band recognized by anti-FliC antiserum.
The current results support a novel model of type I pili structural composition, incorporating the presence of both, ConA-reactive and reducing agent-resistant, FimA subunits. While the exact identity of the glycan(s) and their site of attachment are yet to be confirmed, the current findings highlight a potential additional layer of complexity of the surface (glyco)proteome of the non-pathogenic or adhesive and invasive E. coli strains studied.

Group 1

1 B – Bacterial adaptation to the intestinal environment

Posters 13 to 16

Poster number: 13

Title: Western diet impact EHEC colonization in M-ARCOL:a gut microbiota mediated study

Presenting Author: Etienne-Mesmin Lucie

Authors and Affiliations
O'Sullivan D, Gahan CGM, Blanquet-Diot S, Etienne-Mesmin L
UMR MEDIS, Université Clermont Auvergne, France
28 place Henri Dunant, 63000 Clermont-Ferrand

Abstract
Abstract: Enterohemorrhagic Escherichia coli (EHEC) is a major food-borne pathogen causing human diseases ranging from diarrhea to life-threatening complications, among which O157:H7 is the most frequently serotype isolated. Recent accumulating evidence demonstrates that Western diet can enhance susceptibility to enteric infection in mice, but to date the effect of diet on EHEC colonization and the role of human gut microbiota remains unknown. In this study, our research aimed to investigate the effects of Standard diet (SD) versus Western diet (WD) on EHEC colonization in the human Mucosal ARtificial COLon (M-ARCOL) and the associated changes in gut microbiota composition and activities. After selection of donors using simplified fecal batch experiments (n=9), two M-ARCOL bioreactors were inoculated with human fecal samples (n=4) and ran in parallel, one receiving a Standard diet, the other a Western diet, and infected with EHEC O157:H7 reference strain EDL933. EHEC colonization was dependent on both donor and type of diet in luminal samples, but EHEC bacteria was maintained for a longer period in mucosal samples without elimination, suggesting a possible favorable niche environment for the pathogen. Western diet also impacted gut microbiota composition, as well as short chain fatty acid and bile acid profiles, without any direct link with EHEC survival.

Keywords: Enterohaemorrhagic Escherichia coli; colonization; Western diet; in vitro gut model; gut microbiota; mucus.

Poster number: 14

Title: Cross-feeding interaction between inflammation-associated human gut microbes

Presenting Author: PhD. Yuhang HU

Authors and Affiliations
Yuhang HU, Loïc BROT, Harry SOKOL, Nathalie ROLHION
Centre de Recherche Saint-Antoine, INSERM, Sorbonne Université
27 rue de Chaligny, 75012 Paris, France

Abstract
The human gut harbours a large microbial community in which diverse microbial species interact with each other. This large community is shaped by positive and negative interactions ranging from competition to cooperation, which contribute together to eubiosis in the gut. In comparison to the gut microbiome in healthy population, dysbiosis in microbiota of inflammatory bowel disease (IBD) patients is often highlighted. We hypothesize that the interplay between microorganisms (competition and cooperation) in the gut is perturbed in IBD patients, with impact on host metabolism and immune response and therefore disease development and chronicity. As interactions are mostly based on secreted molecules, we started by screening the effects of culture supernatants between IBD-associated microbes and we surprisingly observed that the supernatant from a pro-inflammatory bacterium (species A) affects positively the fitness of an anti-inflammatory bacterium (species B). Coculture and membrane-separation experiments indicated that this interaction is unidirectional and contact-independent. We found that the molecules responsible for the effect of species A supernatant are heat-resistant, enzymes-resistant and less than three kilodaltons. Identification of the molecules of interest will now be achieved with metabolomics and genetic screens. The impact of the interaction on microbial community and on host health will further be studied, using SHIME® and in vivo models respectively. Collectively, our work identified a commensalism in the microbes associated with inflammation. Investigation in this interaction will help us understand better the force shaping the microbial community and its relationship with the host's health.

Poster number: 15

Title: A Paneth cell-succinate-tuft cell circuit links inflammation and dysbiosis in the gut mucosa

Presenting Author: Nathalie Coutry

Authors and Affiliations
Nathalie Coutry, Julie Nguyen, Salima Soualhi, François Gerbe, Victoria Meslier,
IGF, Inserm U1191, CNRS UMR5203.
141 Rue de la Cardonille, 34000 Montpellier.

Abstract
Gut dysbiosis is characterized by an imbalance in microbiome composition and underlies the development and the severity of multiple diseases both within and outside the gastrointestinal tract. Intestinal epithelial Paneth cells play a key role in the control of innate immunity and gut microbiome integrity. This highly specialized cell type contains secretory granules filled with antimicrobial peptides (AMP) which are released into the crypt lumen to protect the host against pathogens and to shape gut microbiome composition. Given the importance of Paneth cells, deregulation of their function greatly impacts the host-microbiome communication and compromises gut homeostasis. Indeed, Paneth cells are highly vulnerable to genetic mutations or environmental perturbations and impairment in their function leads to gut dysbiosis and intestinal inflammation. However, the cellular and molecular mechanisms involved in gut dysbiosis initiation are still unclear and remain to be identified.
Paneth cell differentiation requires the transcription factor Sox9, and we found that Sox9 deletion in adult Paneth cells (Sox9LoxP/LoxP ;Villin-CreERT2 mice leading to Sox9 deletion in intestinal epithelial cells) leads to a profoundly altered differentiation with mixed features of Paneth and goblet cells, abnormal secretory granules and decreased AMP production. With the help of this relevant model, we addressed the impact of dysfunctional Paneth cells on intestinal physiology. We show that gut dysbiosis initiation involves a three-step mechanism. First, initial defaults in Paneth cells induce mild microbiome reshaping and an amplification of succinate-producing species. Succinate then activates tuft cells, epithelial sentinels which specifically express SucnR1 receptor, and which initiate a type 2 immune response via IL-25 secretion. Activated type 2 innate lymphoid cells and type 2 cytokines, in turn, aggravate Paneth cell defaults through altered RegIII expression, thus promoting strong dysbiosis and chronic inflammation.
This study highlights a new mechanism responsible for gut dysbiosis in a context of dysfunctional Paneth cell involving a crosstalk between Paneth and tuft cells. It also reveals an essential role of Paneth cells to maintain a balanced microbiome, and therefore to preserve from an inadequate and permanent activation of tuft cells and the development of a deleterious dysbiosis. This Paneth cell-succinate-tuft cell circuit may also contribute to chronic gut dysbiosis and inflammation observed in patients with altered Paneth cells such as obese and Crohn’s disease patients.

Poster number: 16

Title: Study of the impact of E. coli genetic diversity on its fitness in the healthy and inflamed gut environment, using CRISPRi screen approaches.

Presenting Author: Amandine Maire

Authors and Affiliations
Amandine Maire, Nathalie Rolhion, David Bikard
Synthetic Biology, Microbiology Department, Pasteur Institute
25-28 rue du Docteur Roux 75015 Paris, France

Abstract
Crohn's disease (CD) is characterized by a chronic inflammation of the gut affecting all parts of the digestive tract. Among other factors, the gut microbiota is known to play a role in this chronic inflammation and some specific bacteria are associated with those diseases. For instance, some strains of E. coli, the AIEC (adherent and invasive E. coli) are known to bloom in the gut of CD patients and exacerbate inflammation. There is wide genetic diversity within the E. coli species, illustrated by the fact that certain strains, such as AIEC, are pathobiont and survive better in an inflammatory environment than other commensal E. coli strains.

Therefore, the goal of my PhD project is to better understand how different strains of E. coli interact with other bacteria and with the host to maintain themselves in the healthy or inflamed gut environment using CRISPRi screen approaches.

We thus have implemented a CRISPRi screens in three strains of E. coli, a commensal and two pathobiont, an AIEC and a UPEC one, and optimized the experiment in two in vitro and in vivo microbiota models. First performing the in vitro CRISPRi screen, using human gut microbiota cultivated in MiniBioReactor Arrays (MBRAs), we are focusing on interactions of different E. coli strains with human microbiota. Additionally, we are using the OMM12 mouse model to study the genetic factors involved in the interactions with the host in a healthy or inflamed context. From the first saucerful in vivo experiments we already identified several genes that are involved in the ability of E. coli to colonize the gut. Among those genes we found some involved in nutrient and carbon source uptake, in response to several environmental stresses, as well as genes involved in cellular motility.

Group 2

2 A – Exposome impact on microbiota and consequences for the host

Posters 17 to 22

Poster number: 17

Title: Synthetic compounds with endocrine-disrupting properties influence the growth of gut bacteria and alter microbial community dynamics based on bacterial physiology and structure of compounds.

Presenting Author: Andrea Marchetto

Authors and Affiliations
Andrea Marchetto (a), Aline Davias (b), Rémy Slama (b), Patricia Lepage (a), Zehra Esra Ilhan (a)
(a) Paris-Saclay University, AgroParisTech, Micalis Institute, Domaine de Vilvert, Jouy-en-Josas, France
(b) University Grenoble Alpes, Inserm U1209, CNRS, UMR5309. Environmental Epidemiology Applied to Reproduction and Respiratory Health Team, Institute for Advanced Biosciences, Grenoble, France

Abstract
Persistent exposure to endocrine-disrupting chemicals (EDCs) has been linked to adverse physiological effects in humans. Despite the essential role of the gut microbiota in maintaining homeostasis, its interactions with EDCs are poorly understood. This study investigated the impact of 38 common EDCs (13 phenols, 9 phthalates, 8 per- and polyfluoroalkyl substances (PFASs)) and 8 EDCs used as pesticides, individually or in synthetic mixtures, on single bacteria or feces-derived microcosms under anaerobic in-vitro conditions. EDCs were selected from exposure patterns observed in the French couple-child cohort SEPAGES, reflecting real-world concentrations and potential cumulative impacts (10-1000 µM). Synthetic mixtures (5 phthalates and 4 phenols or 4 PFASs) were designed by clustering exposure data from the SEPAGES cohort or literature. A total of 42 strains were chosen as representative of core pediatric and adult gut species across six phyla (Actinomycetota, Bacteroidota, Bacillota, Pseudomonadota, Verrucomicrobiota, and Fusobacteriota). Feces-derived communities were obtained from anaerobic cultivation of stool samples from five children. Monoculture experiments showed that the impact of EDCs on the growth of microorganisms were influenced by chemical category, phylogeny, and physiological traits. Notably, Bacteroidota strains were the most affected by all EDC categories, Pseudomonadota strains were the least sensitive and Actinomycetota displayed selective sensitivity to PFAS. Within Bacteroidota, Bacteroides strains tolerated EDCs more than the non-Bacteroides strains. Based on the cell wall structure, Gram-positive bacteria were significantly less sensitive to EDCs than Gram-negative bacteria (2way ANOVA p= 0.05). The chemical structure of EDCs also played a role: phenols and PFASs inhibited the growth of more strains than phthalates. Additionally, alkyl chain length (e.g., parabens and PFASs) and functional group variations (e.g., bisphenols) significantly influenced the bacterial growth (2way ANOVA p= 0.05). EDC mixtures induced new sensitivity patterns, diverging from single-compound predictions. Mixtures containing PFASs or triclosan were particularly toxic to Bacteroidota. Concerning feces-derived communities, EDC exposure led to shifts in population dynamics mostly with PFASs and phenols. Among tested compounds, 4-hydroxybenzoic acid, bisphenol B, triclosan, triclocarban, perfluorooctane sulfonic acid, and perfluorodecanoic acid (PFDA) had the highest impact on alpha and beta diversity, with PFDA drastically reducing richness and promoting a sharp increase in the relative abundance of Escherichia/Shigella genus. These changes mirrored monoculture screening results, confirming the impact of specific EDCs on gut microbial populations. Our results suggest that EDCs may impact gut bacteria and communities, indicating a potential exposure-related disruption of gut bacterial homeostasis.

Poster number: 18

Title: Pre- and post-natal exposure to phthalate and dinch metabolites and gut microbiota in one-year old children

Presenting Author: Aline Davias

Authors and Affiliations
Aline Davias1, Sarah Lyon-Caen1, Matthieu Rolland1, Nina Iszatt2, Cathrine Thomsen2, Azemira Sabaredzovic2, Amrit Kaur Sakhi2, Celine Monot3, Yamina Rayah3, Zehra Esra Ilhan3, Claire Philippat1, Merete Eggesbø4, Patricia Lepage3, Rémy Slama1.
1Environmental Epidemiology applied to Development and Respiratory Health team, Institute for Advanced Biosciences, Inserm U1209, CNRS UMR 5309, University Grenoble Alpes, 38000 Grenoble, France.
2Division of Climate and Environmental Health, Norwegian Institute of Public Health (NIPH), 0213 Oslo, Norway.
3Université Paris-Saclay, INRAE, AgroParisTech, Micalis Institute, F-78350, Jouy-en-Josas, France.
4Department of Clinical and Molecular Medicine, NTNU, Trondheim, Norway.
Inserm U1209, CNRS UMR 5309, University Grenoble Alpes, 38000 Grenoble, France.

Abstract
The gut microbiota is a collection of symbiotic microorganisms in the gastrointestinal tract. Its sensitivity to chemicals with widespread exposure, such as phthalates, is little known. We aimed to investigate the impact of perinatal exposure to phthalates on the infant gut microbiota at 12 months of age. Within SEPAGES cohort (Suivi de l'Exposition à la Pollution Atmosphérique durant la Grossesse et Effet sur la Santé), we assessed 13 phthalate metabolites and 2 di(isononyl) cyclohexane-1,2-dicarboxylate (DINCH) metabolites in repeated urine samples collected in pregnant women and their offspring. We obtained stool samples from 356 children at 12 months of age and sequenced the V3-V4 region of the 16S rRNA gene, allowing gut bacterial profiling. We used single-chemical and mixture (BKMR, Bayesian Kernel Machine Regression) models to examine associations between phthalates and DINCH metabolites, and gut microbiota indices of α-diversity (specific richness and Shannon diversity) and the most abundant phyla and genera relative abundances. After correction for multiple testing, di(2-ethylhexyl) phthalate (ΣDEHP), diethyl phthalate (DEP) and bis(2-propylheptyl) phthalate (DPHP) metabolites 12-month urinary concentrations were associated with higher Shannon α-diversity of the child gut microbiota in single-chemical models. The multiple-chemical model (BKMR) suggested higher α-diversity with exposure to the phthalate mixture at 12 months, driven by the same phthalates. There were no associations between phthalate and DINCH exposure at other time points and α-diversity after correction for multiple testing. ΣDEHP metabolites concentration at 12 months was also associated with higher Coprococcus genus. Finally, ΣDEHP exposure at 12 months tended to be associated with higher phylum Firmicutes, an association not maintained after correction for multiple testing. Infancy exposure to phthalate might disrupt children's gut microbiota. The observed associations were cross-sectional, so that reverse causality cannot be excluded. The potential impact of these perturbations on children's health requires further investigation.

Poster number: 19

Title: Effect of radiation on the symbiosis between the 'microbiota and host immune system' within the colonic ecosystem: Impact of diet as a therapeutic strategy

Presenting Author: Calixte COTTINEAU

Authors and Affiliations
C. COTTINEAU, M. GEIGER, C. DEMARQUAY, V. BUARD, F. MILLIAT, A. SEMONT
Institut de radioprotection et de sûreté nucléaire - Santé - Service de
31, avenue de la Division. Leclerc. 92260 Fontenay-aux-Roses

Abstract
Radiotherapy is an essential treatment for pelvic cancers. However, it can affect the healthy tissues surrounding the tumor, causing toxic effects on radiosensitive organs such as the intestine or colon. These radiation-induced toxic effects lead to 'Pelvic Radiation Disease' (PRD), which limits the benefit/risk balance of the treatment, affects the patients' quality of life, and for which there is no curative treatment. In humans, a link between the state of the microbiota after irradiation and the development of side effects related to intestinal tract dysfunction is suggested and requires further investigations. The intestinal microbiota, in symbiosis with the host, plays a crucial role in the proper functioning of the digestive tract, notably by modulating the inflammatory response. Our hypothesis is that an alteration in the symbiosis within the colonic ecosystem, especially between the microbiome and the host's immune system, could contribute to the development of PRD. The objective of this work is to study, using diet, the impact of this alteration on the colonic epithelial barrier in a preclinical model of PRD.
To explore this hypothesis, a preclinical model of PRD was developed to reflect clinical protocols and the associated digestive toxicity. In this model, Sprague-Dawley rats were irradiated at the colorectal area with fractionated doses of 3x10Gy or 3x14Gy, generating moderate and severe toxicity, respectively. An initial study analyzing correlation of lesions with the temporal evolution of the microbiome and metabolome, revealed bacterial metabolic pathways potentially involved in the development, persistence or reduction of radiation-induced lesions. Our current study aims to analyze the influence of microbiota state on the colonic epithelial barrier after irradiation by modulating it through specific diets. We have chosen Western diet (pro-inflammatory state) or Mediterranean diet (anti-inflammatory state), to explore if diet could alter, maintain, or restore symbiosis.
A one-month longitudinal follow-up revealed differences in fecal appearance, transit, and cecum size depending on the diet, indicating a potential effect of diets on the microbiome. Preliminary histological analyses have showed a reduction in the severity of radiation-induced colonic epithelial lesions in rats following a Mediterranean diet. Experiments aimed at exploring the microbiota (16S-RNA sequencing), the metabolome, and the immune system (single-cell RNAseq) will help better understanding how symbiosis within the colonic ecosystem influences the development of radiation-induced digestive toxicity. This study will advance the understanding of PRD mechanisms in a preclinical model and potentially contribute to improve the quality of life of patients in the future

Poster number: 20

Title: Atypical gut microbial ecosystem from athletes with very high exercise capacity

Presenting Author: Frédéric Derbré

Authors and Affiliations
Martin D, Bonneau M, Orfila L, Hazon M, Cuzol A, Monbet V, Derbré F
Laboratory “M2S", UR7470, University of Rennes 2/ENS Rennes
Avenue Robert Schuman 36170 Bruz

Abstract
Although gut microbiota is known to act as a bridge between dietary nutrients and body's energy needs, the interactions between gut microbiota, host energy metabolism and exercise capacity remain uncertain. Here, we characterized the gut microbiota ecosystem in a cohort of 50 healthy normo-weight humans with heterogeneous exercise capacities (from inactive to elite endurance athletes). While our data support that the bacterial ecosystem appears to be modestly altered between individuals with low to high exercise capacities and close food habits, we report that gut bacterial α-diversity, density, and functional richness are significantly reduced in athletes with very high exercise capacity. By using fecal microbiota transfection (FMT), we report that the engraftment of gut microbiota from the athletes with very high exercise capacity improves insulin sensitivity and muscle glycogen stores into transfected mice. All these findings open promising research perspectives: 1) to improve the management of the gut microbiota ecosystem of elite athletes and patients performing adapted physical activity for therapeutic purposes, and 2) to personalize FMT in patients treated for non-communicable diseases by including exercise capacity in the clinical criteria for donor selection.

Poster number: 21

Title: Consequences of antibiotic treatment at a young age on development of murine inflammatory arthritis

Presenting Author: DE LIMA-ANTOINE Lara

Authors and Affiliations
DE LIMA-ANTOINE Lara; POSTAL Barbara; TOURNEUR-MARSILLE Julien; EVEILLARD Laurye-Anne; VIENNOIS Emilie; MEINZER Ulrich.
Université Paris Cité
16 Rue Henri Huchard 75018

Abstract
Introduction: Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. The causes of this disease remain poorly understood. Several cohort studies have suggested that exposure to antibiotics, particularly when administered in early childhood, may be associated with the development of JIA. The mechanisms by antibiotic exposure influence the pathophysiology of inflammatory arthritis remain poorly understood.

Objective: To describe the mechanisms linking antibiotic exposure in early childhood and the development of arthritis, using a mouse model of inflammatory arthritis.

Methods: We use a mouse model of arthritis, interleukin-1 receptor knockout (IL-1Ra KO) mice, which spontaneously develop inflammatory arthritis at 4-6 weeks of age. Mice were treated in drinking water with a broad-spectrum antibiotic cocktail (Ampicillin, Streptomycin, Vancomycin and Metronidazole) at different life stages (0-2, 2-4 and 4-5, 4-6 weeks).

Results: Antibiotic treatment resulted in a significant increase of lipopolysaccharide (LPS) and a decrease in flagellin (FLA) concentrations in the stools of mice IL-1 Ra KO, independent of age and or duration (1 or 2 weeks) of treatment. In adult mice, arthritis severity was correlated with high levels of LPS in stool ($p = 0.0032$) and serum ($p = 0.0005$). In young mice, which presented earlier and more severe onset compared with adult mice, a severe arthritis was associated with LPS increase ($p = 0.046$) and FLA decrease ($p = 0.004$) in stools. The analysis of stool samples from JIA patients compared with controls (age = 5.15 years ± 3.08) show that the presence of JIA is also associated with an increase in LPS in the stools ($p = 0.0169$).

Conclusion: These results demonstrate, in a mouse model, that treatment with broad-spectrum antibiotics is associated with altered fecal concentrations of LPS and FLA. This alteration could contribute to the modulation of the severity of arthritis depending on the age of treatment. The exact underlying mechanisms remain to be elucidated.

Poster number: 22

Title: Impact of titanium dioxide nanoparticles on colorectal carcinogenesis: focus on intestinal microbiota and colibactin-producing Escherichia coli

Presenting Author: Charline Juban

Authors and Affiliations
Charline Juban, Thomas Sauvaitre, Amandine Devaux, Gwenaëlle Roche, Célia Ledieu, Catherine Godfraind, Oscar Awitor, Nicolas Barnich, Christophe Massard, Mathilde Bonnet, Delphine Boucher
M2iSH, U1071 Université Clermont Auvergne/Inserm/USC-INRAé 1382, Clermont-Ferrand, France.
Centre Biomédical de Recherche et Valorisation 28, place Henri Dunant, BP 38 - 63001 CLERMONT-FERRAND

Abstract
Colorectal cancer (CRC) is the third most common cancer worldwide, and the second leading cause of cancer mortality. Genetic, host susceptibility, immunological and environmental factors all contribute in the initiation, development or/and clinical expression of the disease. Among the environmental contaminants, titanium dioxide (TiO2) particles are of particular concern given their potential carcinogenic effects and their ubiquity in everyday consumer products. TiO2 nanoparticles may interact with the intestinal microbiota and facilitate the emergence of pathobionts such as colibactin-producing Escherichia coli (CoPEC), which abnormally colonise the colonic mucosa of CRC patients.
The aim of this project is to investigate the impact of titanium dioxide on colon carcinogenesis, with a particular focus on its effects on interactions between intestinal epithelial cells and the gut microbiota, including CoPEC.
In vitro, exposure of 5 different CoPEC strains isolated from CRC patients to equivalent doses to those reaching the intestine (0.1 and 1 mg.kg-1) for 24 hours resulted in a reduction in their doubling time compared to a laboratory strain. Scanning electron microscopy observations coupled with energy dispersive spectroscopy revealed adsorption events for TiO2 nanoparticles in the CoPEC 11G5 strain, while structural changes in pili were observed. In consequence of these modifications, exposure to this compound also increased the strain's ability to adhere to and proliferate in intestinal epithelial cells.
In vivo, APCmin/+ mice predisposed to develop CRC were exposed to TiO2 as a food additive (E171) at a human-equivalent dose of 10 mg per kg of body weight twice a week for 27 days. Macroscopic and histological observations showed that some of the exposed individuals exhibited more advanced tumour development than the control group. The "sensitive" mice also exhibited greater dysbiosis than the "non-sensitive" and "unexposed" individuals with several overrepresented taxa that are also more abundant in CRC. Thus, in an ongoing study, APCmin/+ mice are exposed to TiO2 and/or 11G5 CoPEC strain for 56 days to determine whether TiO2 enhances both 11G5 colonisation and/or CRC development.
These results collectively indicate that exposure to TiO2 may play a role in the aetiology of CRC by altering the structure and function of the intestinal microbial ecosystem. This could promote the emergence of pathobionts such as CoPEC, in addition to inducing changes that enhance their colonisation.

Group 2

2 B – Food and microbiota interactions and impact on the host

Posters 23 to 29

Poster number: 23

Title: Obesogenic diet increases atherosclerosis through promoting microbiota dysbiosis

Presenting Author: Nirmala Mouttoulingam

Authors and Affiliations
Ludivine Laurans, Nirmala Mouttoulingam, Harry Sokol, Soraya Taleb
Paris Centre de Recherche Cardiovasculaire
56, Rue Leblanc 75015 Paris

Abstract
Introduction: Despite novel therapies, cardiovascular diseases such as atherosclerosis remain the leading cause of death worldwide. Several factors such as diet, particularly, the obesogenic high-fat diet (HFD), could alter gut microbiota and systemic inflammation, which are known to impact atherosclerosis. However, the causal links remain to be established.
Hypothesis: the obesogenic diet HFD through shaping gut microbiota has an impact on the development of atherosclerosis.
Objective: study the impact of HFD-driven microbiota dysbiosis effects on atherosclerosis and decipher its underlying mechanisms.
Methods: We used the low-density lipoprotein knock-out (ldlr-/-) mice that develop atherosclerosis when fed a high-cholesterol (HC) diet. To study the specific role of gut microbiota shaped by the diet, we performed fecal microbiota transplantation (FMT). Microbiota was harvested from Ldlr-/- mice fed different diets: chow diet (CD), HC diet, HFD, combined HFD+HC, or low fiber (LF) diet. This last diet has a low content of fibers equivalent to HFD. All, microbiota-recipient ldlr-/- mice were fed the same atherogenic diet. In addition, some microbiota-donor mice were supplemented with soluble fibers such as fructooligosaccharides (FOS). Microbiota was analyzed using 16S rRNA sequencing from fecal samples. Harvested hearts and aortas were used to analyze atheromatous plaques and plaque inflammatory contents.
Results: Our results show that gut microbiota shaped by HFD but not HC diet compared to CD, led to a significant increase in atherosclerotic plaques along with an increase in T cell accumulation within the plaques. Moreover, the pro-atherogenic effect of HFD-shaped microbiota was related to LF intake as evidenced by fiber supplementation that could reverse HFD-shaped microbiota effects. Furthermore, our work reveals a significant increase in gut immune cell trafficking mostly lymphocytes, imprinted by HFD- and LF-shaped microbiota, from the gut to the periphery, which exerts a pro-atherogenic role.
Conclusion: Our work unravels the missing pathological link between the HFD, particularly due to a low fiber level, gut microbiota dysbiosis, gut immune cell trafficking, and atherosclerosis.

Poster number: 24

Title: Gut microbiota in sex-specific effects of protein malnutrition in juvenile mice

Presenting Author: Lucas Rebiffé

Authors and Affiliations
Lucas Rebiffé, Amélie Joly, Tiphaine Fargeot, Filipe De Vadder, François Leulier
Institut de Génomique Fonctionnelle de Lyon, ENS Lyon, CNRS UMR 5242, UCBL
32-34 Avenue Tony Garnier, 69007 Lyon

Abstract
Malnutrition affects 148 million children under the age of 5 worldwide, posing a major public health challenge. Protein undernutrition, in particular, results in stunted growth, metabolic issues, delayed maturation of the gut microbiota, and reduced microbial diversity. Managing undernourished children is complicated as growth and metabolism are interconnected, with boys and girls showing different susceptibilities to malnutrition. We demonstrated, using a mouse model, a sexually dimorphic response to protein malnutrition, where males experienced significant growth retardation and metabolic disturbances, while females were minimally affected. Given the role of gut microbiota as a key mediator between diet and host physiology, we aimed to investigate how protein malnutrition alters microbiota composition and contributes to the observed sexual dimorphism.

Thus, juvenile mice were fed either a control diet (CD, 20% protein) or an isocaloric low-protein diet (LPD, 5% protein) for five weeks post-weaning. Shallow shotgun metagenomic analysis of fecal samples revealed two major findings. First, protein malnutrition caused a sex-independent response characterized by microbiota immaturity, including a significant increase in Bifidobacteriales (from 0.3% to 2.5% relative abundance, $p < 0.0001$). Second, some species exhibited sex-specific changes; for example, Mucispirillum schaedleri increased in females but decreased in males on the LPD ($p = 0.0114$).

To explore the microbiota's role in this sexually dimorphic response, we developed a model of antibiotic-induced microbiota depletion. This led to a significant drop in microbial load in CD mice (106 vs 103 16S DNA copies per µg of total DNA, $p < 0.0001$). Preliminary results suggested that gut microbiota contributes more to bone growth in males than in females.

Our findings indicate that protein malnutrition causes sexually dimorphic changes in microbiota composition, with differential microbiota contributions to male and female growth on a control diet. Using this model of protein undernutrition and microbiota disruption, we plan to further investigate how specific bacterial strains influence the macroscopic phenotype of malnutrition. Future experiments with gnotobiotic mice will allow us to precisely modulate the microbial community, shedding light on the intricate microbiota-host interactions that underlie the response to protein malnutrition.

Poster number: 25

Title: Severe Acute Malnutrition : a novel mouse model for therapeutic food investigations

Presenting Author: Julie TOMAS

Authors and Affiliations
Fanny Hidalgo-Villeda, Matthieu Million, Catherine Defoort, Thomas Vannier, Ljubica Svilar, Margaux Lagier, Camille Wagner, Cynthia Arroyo-Portilla, Lionel Chasson, Cécilia Luciani, Vincent Bossi, Jean-Pierre Gorvel, Hugues Lelouard, and Julie Tomas.
Aix Marseille University, CNRS, INSERM, CIML, Turing Centre for Living Systems, Marseille, France
Centre d'Immunologie de Marseille-Luminy, Parc Scientifique et Technologique de Luminy Case 906 13288 Marseille Cedex 09

Abstract
Today, nearly one in three persons globally suffers from at least one form of malnutrition: undernutrition, micronutrient deficiency, overweight or obesity. Early emergence of malnutrition has disastrous consequences later in life and must be assessed at very early stages to fully understand the pathogenesis and associated side effects (recurrent infections and noncommunicable diseases). To overcome the limits of clinical research in malnourished children, we developed a mouse model of Severe Acute Malnutrition (SAM) that faithfully recapitulates key features of the malnourished states of humans. The availability of this mouse model allows the simultaneous assessment of physiological, metabolic, immune and microbiome dysregulations at mucosal sites.
At weaning, male mice received either a regular control diet (Ctrl diet) or the isocaloric SAM diet during four weeks. We investigated the innate and adaptive immune profile of the small intestine using flow cytometry and confocal microscopy. We determined the composition and spatial organization of the intestinal microbiota by 16S rRNA gene sequencing and fluorescence in situ hybridization. Short chain fatty acids were analyzed by gas chromatography-mass spectrometry.
In our mouse model, the diet responsible for SAM alters mouse growth (WL-Z score -4.96±1.43, P-value<0.0001) and leads to atrophy of Peyer's patch and villi (207.50±24.99µm vs 157.81±20.80µm, P-value<0.001). An inflammatory state characterized by increased intestinal permeability and secretion of fecal lipocalin-2 (P-value<0.0001) is observed. SAM mice have half the number of lysozyme-expressing dendritic cells in Peyer's patches (P-value<0.001) and show an imbalance in the Th17/Treg balance. Analysis of the gut microbiota composition of SAM mice reveals notably a reduction in the butyrate producing bacteria, in genera Akkermensia and Candidatus Arthromitus. This microbiota is also unusually close to the epithelium and butyrate concentration is halved (P-value<0.01). The consumption of a standard diet two weeks after the induction of SAM resulted in a fast zoometric and intestinal physiology recovery but to an incomplete restoration of the intestinal microbiota, metabolism, and immune system. These data highlight that restoration of immune and microbial defenses lags behind anthropometric recovery as observed in children suffering from SAM. This murine model will not only help to dissect SAM pathogenesis but also to implement therapeutic foods with specific compounds restoring proper microbiota and immunity.
Taking advantage of our easy-to-use SAM mouse model, we are now focusing on microbiota-targeted therapy and how enteric infections and vaccination are affected by malnutrition.

Poster number: 26

Title: Early life microbiota alterations induced by maternal dietary emulsifiers intake prevent goblet cell-associated antigen passages, leading to long lasting consequences on intestinal and metabolic health.

Presenting Author: Clara Delaroque

Authors and Affiliations
Clara Delaroque, Erica Bonazzi, Marine Huillet, Sandrine Ellero-Simatos, Fuhua Hao, Andrew Patterson, Benoit Chassaing
Microbiome-Host Interactions, INSERM U1306, Institut Pasteur
institut Pasteur, 25-28 rue du docteur Roux, 75015 Paris, France

Abstract
Early life microbiota settlement is key in driving proper development of both the host and its microbiota. Microbiota disturbance during this critical window has been repeatedly observed to drive increase susceptibility to chronic inflammatory disease and metabolic deregulations. Nevertheless, the influence of maternal diet, especially exposure to microbiota-disrupting agents such as dietary emulsifiers, on offspring microbiota, metabolism, and immune system remain unknown. Here, we hypothesized that microbiota alteration in dams subjected to dietary emulsifiers, additives used by the food industry and for which our team previously reported their ability to detrimentally impact the microbiota, might be transferred to the offspring in a way that could drive long-lasting consequences on immunity and metabolism. We tested this hypothesis using mice breeding pairs treated with select dietary emulsifiers. After birth, half of the obtained offspring were cross-fostered with untreated dams in order to decipher microbiota-dependent effects. After weaning, mice were kept under emulsifiers-free regimen and treated with either a high-fat diet regimen or DSS in order to investigate susceptibility to diet-induced obesity and chronic intestinal inflammation, respectively. Feces were collected longitudinally for intestinal microbiota investigation, both compositionally and functionally, and tissues were harvested for macroscopical, histological and molecular analysis.
We importantly observed that maternal exposure to dietary emulsifiers induces early-life alterations in the offspring microbiota, characterized by changes in composition and increased pro-inflammatory potential. Such perturbations during this critical pre-weaning developmental window were associated with long-lasting increased susceptibility to diet-induced metabolic dysregulations and intestinal inflammation. Importantly, restoring early-life microbiota composition and pro-inflammatory potential through cross-fostering with unexposed dams proves effective in preventing intestinal inflammation and mitigating long-term disease susceptibility. Mechanistically, we observed that offspring from emulsifier-treated dams harboured compromised intestinal goblet cell-associated antigen passages (GAP), known to promote tolerance to intestinal bacteria. Reinstating normal GAP in these offspring, through tyrphostin treatment, was sufficient to fully protect against the trans-generational impact of emulsifier consumption on intestinal and metabolic health.
To conclude, our study underscores a significant role played by maternal intake of dietary emulsifiers on intestine-microbiota interactions in the subsequent generations in a way that drive increased susceptibility to inflammatory diseases and metabolic deregulations later in life. Our observations underscore the need to carefully consider maternal exposure and dietary recommendations to ensure the long-term health of future generations.

Poster number: 27

Title: Identification of emulsifier sensors involved in the pathogenic potential of Crohn's disease associated Adherent Invasive Escherichia coli

Presenting Author: Héloïse Rytter

Authors and Affiliations
Héloïse Rytter1, Charlène Dauriat1, Caroline Chevarin2, Nicolas Barnich2, Benoit Chassaing1
1Microbiome-Host Interactions, Institut Pasteur, Université Paris Cité, INSERM U1306, Paris, France.
2M2iSH, UMR 1071, INSERM, University of Clermont Auvergne, INRAE USC 1382, Clermont-Ferrand 63001, France
25 rue du Docteur Roux

Abstract
The intestinal microbiota is playing a central role in the promotion of various chronic inflammatory diseases. As an example, highlighting this notion, we previously reported that consumption of synthetic dietary emulsifiers can directly detrimentally impacts the microbiota in a way that led to microbiota encroachment and chronic intestinal inflammation. While the microbiota is the direct target of emulsifier, not all microbiota members are impacted. We previously reported that Adherent-Invasive Escherichia coli (AIEC), a pathovar of E. coli at play in a subset of Crohn disease patients, is a bacterial prototype being directly targeted by such class of food additives. Importantly, in vitro RNA-seq approaches reported that emulsifier exposure directly induces the expression of clusters of genes involved in AIEC virulence and their ability to induce inflammation.
Here, we initially performed an emulsifier sensitivity screen of 50 AIEC strains isolated from colonic biopsies, and we observed that emulsifier sensitivity is both strain- and additives-specific. Such observations further confirmed that emulsifiers can directly impact the pathogenic potential of various AIEC strains, but the molecular mechanism at play remains unknown.
Through high-throughput transposon-based screening approach, we constructed 5500 insertion mutants and tested their sensitivity to dietary emulsifier. Such an approach importantly identified AIEC mutants that became resistant to emulsifier-induced increased pathogenic potential normally observed in AIEC WT strains. Construction of isogenic mutants identified 5 genes playing a central role in dietary emulsifier sensing, with the observation that their deletion led to bacterial insensitivity toward dietary emulsifiers. Ongoing in vivo experimentations are investigating if the depletion of these "emulsifier sensors" is sufficient to abrogate colitis development normally observed in AIEC mono-colonized mice subjected to emulsifier regimen. Moreover, the prevalence of these sensors is currently being screened in metagenomic collections from deeply phenotyped cohorts of IBD patients, with the ultimate goal of patient stratification based on their emulsifier sensitivity status.

Poster number: 28

Title: L-serine, a key amino acid involved in the pro-carcinogenic effects of colibactin-producing E. coli

Presenting Author: Amandine Devaux

Authors and Affiliations
A. Devaux1, G. Roche1, B. Diémé2, M. Lagrée2, M. Rodrigues1, C. Jousse2, N. Barnich1, R. Villéger1, M. Bonnet1. 1University of Clermont Auvergne, M2ISH, Clermont-Ferrand, France. 2University of Clermont Auvergne, MetaboHUB, Clermont-Ferrand, France.
M2iSH Laboratory
28 place Henri Dunant 63000 Clermont-Ferrand

Abstract
The colonic tissues are abnormally colonized by colibactin-producing Escherichia coli (CoPEC) in colorectal cancer (CRC) patients. Colibactin is a genotoxin produced by enzymes encoded by the pks genomic island. Metabolomic studies have shown that CoPEC infection results in reprogramming of intestinal epithelial cell metabolism, leading to a decrease of L-serine concentration. The aim is to investigate whether L-serine allows CoPEC to better persist in the gastrointestinal tract and/or exert their pro-carcinogenic functions. In vitro, we have shown that CoPEC uses L-serine from the enterocyte via the activation of serine-utilization-operon, which provides to CoPEC a competitive growth advantage in comparison to a commensal strain or its mutant (11G5-Δpks). To highlight the specific role of L-serine, APCmin/+ mice were fed with a L-Serine Depleted (SD) diet. SD diet induced an early and transient decrease in CoPEC 11G5 bacterial colonization associated with a decrease of the DNA damages. In addition, the pro-carcinogenic potential of CoPEC on MC38 grafted-tumors is significantly lower with the SD diet than with the control diet. The impact of L-serine utilization on CoPEC virulence was verified both in vitro and in vivo with a 11G5-ΔtdcA mutant, unable to metabolize L-serine. Competition experiments in which mice were co-infected with WT 11G5 and the 11G5-ΔtdcA mutant confirmed the advantage of the bacteria using L-serine. Altogether, these data support that CoPEC would use the host L-serine, by activation of its serine operon utilization, to persist, to maximize its competitive fitness advantage over a commensal strain and to promote its genotoxic and pro-carcinogenic effects. This work allows us to elucidate the mechanisms of action of CoPEC in colonic carcinogenesis and identify potential novel therapeutic targets.

Keywords: Colorectal cancer, E. coli, colibactin, L-serine

Poster number: 29

Title: Direct impact of dietary plant-based glycolipids on human gut microbiota and inflammation: first evidence from in vitro models

Presenting Author: Cécile Vors

Authors and Affiliations
Naimi S1,2, Meugnier E3, Hautier MC3, Durand A3, Vitalis O4,6, Chick K3,4,6, Meiller L5,6, Sauvinet V5,6, Michalski MC3,5,6, Chassaing B1,2, Vors C3,5,6
1 Microbiome-Host Interactions, Institut Pasteur, Université Paris Cité, INSERM U1306, Paris, France ; 2 Mucosal microbiota in chronic inflammatory diseases, Institut Pasteur, INSERM U1016, CNRS UMR 8104, Université Paris Cité, Paris, France ; 3 CarMeN laboratory, INSERM U1060, INRAE UMR 1397, Université Claude Bernard Lyon 1, 69310 Pierre-Bénite, France; 4 Service de Biochimie et Biologie Moléculaire, Hôpital Lyon Sud, Hospices Civils de Lyon, Pierre-Bénite 69310, France; 5 Centre de Recherche en Nutrition Humaine Rhône-Alpes, Univ-Lyon, INSERM, INRAE, Claude Bernard Lyon1 University, Hospices Civils de Lyon, 69310 Pierre Bénite, France ; 6 Lyon GEM Microbiota Study Group, Lyon, France

Abstract

Confidential

Group 2

2 C – Therapeutic strategies for correcting disease-associated dysbiosis

Posters 30 to 33

Poster number: 30

Title: MBRAs to model microbiome response to tryptophan and alcohol in ALD

Presenting Author: Wanchao Hu

Authors and Affiliations
Wanchao Hu, Sabrine Naimi, Benoit Chassaing, Dragos Ciocan, Anne-Marie Cassard
INSERM U996
17, avenue des Science 91400 Orsay, France.

Abstract
Background and Aims: Intestinal microbiota (IM) plays a causal role in the severity of alcohol-associated liver disease (ALD). Using IM transplantation in mice, we proved that the dysbiosis of alcohol use disorder (AUD) patients with severe alcohol-associated hepatitis (sAH) could be modified, leading to an improvement in alcohol-induced liver injury by increasing tryptophan metabolites to activate aryl hydrocarbon receptor (AhR) signaling pathway. However, the effect of tryptophan on IM in AUD patients, as well as its interactions with alcohol, remain to be elucidated. For this purpose, we used an in vitro approach with Minibioreactor arrays (MBRAs) that allows for the study of IM in a continuous-flow culture with well-controlled factors.

Method: Fecal samples from AUD patients with sAH (n=2) or with noAH (n=2) were transferred to MBRAs chambers. After 24 hours of adaptation in the initial medium, treatments with different tryptophan concentrations (low: 8mg/L, normal: 24mg/L and high: 72mg/L) were initiated for 48 hours. Subsequently, alcohol was introduced in the system for 5 days (50mM ethanol/Day). Finally, alcohol was removed and the cultures were maintained for an additional 5 days. IM analysis was conducted by 16s sequencing. AhR activity of tryptophan derivatives in supernatants was determined using two reporter lines: intestinal epithelial cells (HT-29) and hepatocytes (HepG2) labelled with Lucia-AhR.

Results: After 24h of stabilization, MBRA effectively maintains each fecal community. Tryptophan had no effect on the alpha and beta diversity of the IM from sAH and noAH patients. However, normal tryptophan level decreased the relative abundances of Escherichia – Shigella and increased Bacteroides in noAH IM, decreased Proteobacteria and increased Bacillus in sAH IM. In the absence of alcohol, tryptophan changed more number of bacteria in noAH IM (43 species) than in sAH IM (8 species). However, with alcohol conditions, tryptophan had minimal effect on the noAH IM. Compared to low tryptophan, normal and high tryptophan levels increased the AhR activity.

Conclusion: Our results suggest that maintaining a normal tryptophan level in patients with noAH could be essential to prevent dysbiosis and high concentrations of tryptophan may have a beneficial effect on the IM of sAH patients. Tryptophan holds potential as a novel therapeutic agent for ALD treatment but these results must be confirmed in vivo.

Poster number: 31

Title: Saccharomyces boulardii ameliorates antibiotic-induced dysbiosis

Presenting Author: Zhan Huang

Authors and Affiliations
Zhan Huang, Harry Sokol, Nathalie Rolhion
Centre de Recherche Saint-Antoine, INSERM, Sorbonne Université
75012 Paris, France

Abstract
Saccharomyces boulardii CNCM I-745 (Sb) is the most widely prescribed probiotic yeast for the prevention and the treatment of antibiotic-associated diarrhea, yet its protective effects on intestinal microbiota remain insufficiently elucidated. Here, we employed in vitro models, including the static batch system MiPro and the continuous culture system SHIME®, to investigate the effects of Sb on antibiotic-induced dysbiosis of the human gut microbiome. We tested 2 doses of Sb against the gut microbiome of 8 healthy adults perturbed by either amoxicillin/clavulanic acid (AMC) or vancomycin in MiPro. Protective effects of Sb supplementation were observed mainly in AMC-induced dysbiosis. Supplementation of Sb, especially at a high dose, reduced the AMC-induced decline in bacterial load, without effects on α-diversity. Using quantitative microbiome profiling based on 16S ribosomal RNA amplicon sequencing and quantitative PCR, we found that Sb supplementation in AMC-treated conditions favored the growth of some beneficial genera, e.g. Bacteroides, Faecalibacterium, and Eubacterium, which in turn increased the production of propionate and indole-3-propionic acid and promoted the conversion of primary into secondary bile acids. To determine the effects of AMC and Sb on the gut microbiome in a dynamic way, we then used the SHIME® system that mimics the microbiological properties of the proximal and distal parts of the colon under environmental conditions similar to those found in vivo. Sb was delivered during a 1-week AMC treatment and the following 2-week washout. Sb supplementation showed no marked effects on bacterial load during the AMC treatment but induced a faster recovery of the bacterial load (particularly regarding Firmicutes) and promoted the production of acetate and propionate in the distal colon compartments during the washout. Taken together, these data show that the supplementation of S. boulardii CNCM I-745 can ameliorate antibiotic-induced dysbiosis of the human gut microbiome by promoting beneficial microbes and production of beneficial metabolites.

Poster number: 32

Title: Development of a probiotics and plant extracts combination targeting Adherent-Invasive Escherichia coli strains associated with Crohn's disease

Presenting Author: Fanny De Clercq

Authors and Affiliations
Fanny De Clercq1; Charlotte Leclaire1; Jeremy Denizot2; Sophie Holowacz3; Nathalie Boisseau4; Nicolas Barnich2; Adeline Sivignon2
1 Université Clermont Auvergne, Inserm, INRAe, M2iSH, F-63000 Clermont-Ferrand, France 2 Université Clermont Auvergne, IUT Clermont Auvergne, Inserm, INRAE, M2iSH, F-63000 Clermont-Ferrand, France 3 Groupe PiLeJe, Paris, France 4 Université Clermont Auvergne, AME2P, F-63000 Clermont-Ferrand, France
Clermont-Ferrand, France

Abstract
Abnormal colonization of the ileal mucosa by Adherent-Invasive Escherichia coli (AIEC) is observed in Crohn's disease (CD) patients. To date, no curative treatment for this disease exists, highlighting the need to develop new therapies targeting the origin of the inflammation, in particular the intestinal microbiota and more specifically AIEC bacteria. The aim of this work was to conduct an in vitro screening of seventeen probiotic strains (Bifidobacteria and Lactobacilli) and three plant extracts (green tea, walnut and liquorice) to assess their anti-virulence properties against AIEC bacteria.
Intestinal epithelial Caco-2/TC7 cells were incubated with various concentrations of probiotics or plant extracts and then infected with the AIEC reference strain LF82. IL-8 secretion by intestinal cells was quantified by ELISA and AIEC LF82 adhesion level to the cells was measured. Six Lactobacillus strains and one Bifidobacterium strain effectively prevented IL-8 secretion and/or reduced adhesion of AIEC LF82 to TC7 cells. Plant extracts did not succeed to prevent inflammatory response and adhesion but affected the growth of AIEC LF82, which was also observed with four Lactobacillus strains tested.
The effect of two Lactobacillus strains, one Bifidobacterium strain and the three plant extracts on AIEC colonization was studied in vivo. Probiotic bacteria (109) and plant extracts (1 mg) were daily administered by gavage to AIEC-infected mice treated with dextran sulfate sodium (DSS). The three probiotics as well as green tea and walnut extracts significantly reduced the severity of colitis and faecal lipocalin-2. Lactobacillus strains and green tea decreased the colon-associated AIEC load. Based on these promising results, three probiotics/extracts combinations were established and tested in the DSS/LF82 mouse model. The combination of two Lactobacillus strains and walnut strongly reduced of the score of colitis, protected intestinal mucosa from injuries and eliminated AIEC bacteria from the intestine in half of the mice whereas all the untreated mice remained heavily colonized by AIEC bacteria. Further studies are needed to gain a more accurate insight into the mechanisms of action of these probiotic/extract combinations, but these data clearly show that select probiotics, associated with specific plant extract could represent a promising strategy to limit AIEC colonization in CD patients.

Key words : Adherent-Invasive Escherichia coli, Crohn’s disease, probiotic, plant extract

Poster number: 33

Title: Yeast β-glucan exert prebiotic activity increasing microbial diversity and short-chain fatty acids in the colonic microbiota of type II diabetic patients

Presenting Author: Marciane Magnani

Authors and Affiliations
Jéssika Rodrigues Clementino, Louise Iara Gomes de Oliveira, Alexandra Ivo Medeiros, Victoria Mesa, Hubert Vidal, Katia Sivieri, Marciane Magnani
Federal University of Paraíba, Brazil; São Paulo State University, Brazil; Universidad de Antioquia, Colombia; CarMeN Laboratory, INSERM U1060, INRAE U1397, Université Claude Bernard Lyon-1, France
Laboratory of Microbial Processes in Foods, Federal University of paraíba, Campus I, University City, 58051-900

Abstract
Gut microbiota (GM) dysbiosis plays an important role in the symptoms of type 2 diabetes mellitus (T2DM). Yeast β-glucan is a fermentable polysaccharide with prebiotic properties related to its chemical structure. β-glucan obtained from spent brewer's yeast (YBG) is an environmentally friendly active component with positive effects in several models of metabolic disorders. This study evaluated the effects of YBG on the GM of T2DM individuals using the Human Gut Microbial Ecosystem Simulator (SHIME®). Production of short-chain fatty acid and ammonium ions (NH_4^+) were determined during the colonic fermentation. Secretion of IL-10 and IL-6 promoted by YBG treatment was evaluated using coculture (Caco-2 and THP1 cells) and measured by ELISA. The study included 5 volunteers (3 men and 2 women; 45 to 50 and years) recruited following ethical protocols. Dynamic colonic fermentation was performed using SHIME®, and YBG treatment (7.5 g/d) was administered daily for 7 days. The microbiota was evaluated thought 16S rRNA gene sequencing (V3-V4 region; primers 341F and 806R) using the Illumina MiSeq platform. QIIME2 program version 2019.7 was used for bioinformatics analyzes. The data set resulted in an average of 21464 raw reads. SCFA were determined by chromatographic analyses and NH_4^+ using a selective ion meter. YBG treatment positively impacted ($p < 0.005$) the microbial communities during colonic fermentation in SHIME® compared to control, increasing diversity indexes (Shannon 2.97 vs 1.12 and Simpson 10.89 vs 2.40, respectively), and richness (Chao 1 61.75 vs 10.5) ($p=0.028$). The most abundant phylum identified in the GM of T2DM individuals before the YBG treatment was Firmicutes, followed by Proteobacteria. YBG treatment decreased the abundance of Firmicutes and Proteobacteria and increased the abundance of Bacteroidetes and Actinobacteria phyla. After 7 days of YBG treatment, genera considered undesirable and indicators of dysbiosis such as the genera Escherichia-Shigella and Enterococcus were suppressed in GM. On the other hand, treatment with YBG stimulated the growth of the genera Bacteroides, Alistipes, Acidaminococcus, Prevotella, Sutterella, Parabacteroides, Bifidobacterium, Subdoligranulum and Faecalibacterium, mostly considered important producers of SCFA. The concentrations of SCFA (butyric, acetic and propionic), recognized as important for improving glucose homeostasis, increased after treatment with YBG in relation to the control ($p<0.05$). YBG did not change in the concentration of NH_4^+ ($p>0.05$). Treatment with BG increased ($p<0.05$) the IL-10 while deceased IL-6 concentration. Therefore, these results suggest that BG may improve symptoms associated with T2DM in adult individuals through modulation of GM composition and function.

Group 3

3 A – Biomarkers

Posters 34 to 36

Poster number: 34

Title: The human blood harbors a phageome which differs in Crohn's disease

Presenting Author: Quentin LAMY-BESNIER

Authors and Affiliations
Quentin LAMY-BESNIER (1,2), Ilias THEODOROU (1), Maud BILLAUD (1), Hao ZHANG (1), Loïc BROT (2), Antoine CULOT (3), Guillaume ABRIAT (3), Harry SOKOL (1,2,4,5), Marianne DE PAEPE (1), Marie-Agnès PETIT(1,*), and Luisa DE SORDI (2,5,*)
(1) Université Paris-Saclay, INRAE, AgroParisTech, MICALIS Unit, 78352 Jouy en Josas, France
(2) Sorbonne Université, INSERM, Centre de Recherche Saint-Antoine, 75012 Paris, France
(3) Rime Bioinformatics SAS, Palaiseau, France
(4) AP-HP, Saint Antoine Hospital, Gastroenterology Department, 75012 Paris, France.
(5) Paris Center for Microbiome Medicine (PaCeMM) FHU, Paris, France
(*) Corresponding author

Abstract
Viral communities (viromes) are integral components of various body microbiomes. The virome from fresh colon resections of IBD patients was recently shown to modulate innate immunity, suggesting implications for health. However, the virome of other environments, such as the blood, despite its potential as a disease biomarker and implications for health, remains poorly studied. We conducted virome shotgun sequencing on 29 blood and fecal samples obtained from healthy individuals and CD patients. The limitations of blood, a supposedly sterile environment (low quantity of viruses, high risks of contamination) were addressed by designing specific protocols and analysis pipelines. We provide the first comprehensive characterization of the human blood virome, showing that it contains diverse phages, which mostly infect Proteobacteria. We also demonstrate that globally, ~20% of contigs present in the blood are also found in the intestinal virome. We further explore other origins for the blood phages, including the oral environment. Besides, we reveal that the blood virome is significantly different in CD patients compared to healthy individuals, contrary to the fecal virome which does not differ significantly between the two groups. Finally, we found that CD patients had significantly more phages present in both blood and fecal samples, suggesting that their altered intestinal permeability could lead to the passage of viral particles to the blood. Collectively, these results unveil the presence of phages in human blood, suggest that their origin is partially intestinal, and underscore differences in the blood virome composition between CD and healthy individuals. These findings enhance our understanding of the microorganisms present in human blood and open the door for further studies on this environment in the context of disease.

Poster number: 35

Title: Determination of biomarkers associated with neoadjuvant treatment response focusing on colibactin-producing Escherichia coli in patients with mid or low rectal cancer

Presenting Author: Christophe Taoum

Authors and Affiliations
Christophe Taoum[1], Delphine Boucher[2], Guillaume Carrier[1], Gwenaëlle Roche[2], Mickael Rodrigues[2], Marine Latone[2], Marta Jarlier[1], Pierre-Emmanuel Colombo[1], Philippe Rouanet[1], Mathilde Bonnet[2]
1 : ICM Val d'Aurelle, 208 Avenue des Apothicaires, 34090 Montpellier
2 : Laboratoire M2ISH, 28 Place Henri Dunant BP 38 63001 Clermont-Ferrand

Abstract
Neoadjuvant chemoradiotherapy (CRT) remains a cornerstone in the treatment of locally advanced rectal cancers. Since 2020, the standard of care has shifted to total neoadjuvant therapy (TNT), combining chemotherapy and CRT. Patient management largely depends on the response to neoadjuvant therapy (NAT). Those who achieve complete response determined by MRI reassessment can benefit from active surveillance strategies, known as the Watch and Wait (WW) approach which avoid major surgery. While this therapeutic strategy has improved tumor response rates, there are still few biomarkers available to predict the response to NAT. Several studies have highlighted that theintestinal microbiota could be a powerful biomarkers in colorectal carcinogenesis. Most studies have been done in colonic tumors and few on rectal tumors. Pro-carcinogenic bacteria, such as colibactin-producing Escherichia coli (CoPEC), are commonly found in the mucosa of the most aggressive colon cancer patients. This study aimed to assess whether the presence of CoPEC in stool samples is associated with the response to NAT in rectal cancer patients.
This work presents the analysis of 93 patients from the MICARE clinical trial (NCT04103567), which enrolled patients with mid or low rectal cancer requiring NAT. Stool samples were collected prior to NAT. Microbiota composition was assessed through 16S rRNA sequencing and CoPEC by cultural and molecular analysis. Neoadjuvant CRT response and tumor regression were evaluated using MRI and the Dworak system during pathological examination in case of surgery. We demonstrated that CoPEC prevalence in stool was 37.6% in rectal cancer. Our data indicate that the population of non-responders to NAT is twice as large in CoPEC-positive patients compared to the non-carriers. Moreover, patients managed with the WW strategy appeared to have a higher local recurrence rate in the presence of CoPEC. In fact, 40% of CoPEC-positive patients experienced local recurrence, compared to 12.5% for CoPEC-negative patients. Ongoing analyses of the intestinal microbiota continue to reveal differences in bacterial populations at the genus and species levels. Even if these results must be confirmed on a larger population, they suggest a potential predictive role for CoPEC in poorly-response to NAT in rectal cancer. These clinical observations were confirmed by our preliminary data performed in vitro on epithelial cells. Indeed CoPEC infection reduced the cellular cytotoxicity induced by irradiation with modification of inflammation.
These results could contribute to the development of new classifications or predictive scoring systems based on both clinical and microbiological data in rectal cancer.

Poster number: 36

Title: In-situ bacterial and fungal microbiota influences Crohn's disease recurrence

Presenting Author: Léonard DUBOIS

Authors and Affiliations
Léonard DUBOIS, Philippe SEKSIK, Stéphane NANCEY, Maria NACHURY, Xavier TRETON, Anthony BUISSON, Franck CARBONNEL, Mathurin FUMERY, Laurent PEYRIN-BIROULET, Arnaud BOUREILLE, Xavier HEBUTERNE, Mélanie SERRERO, Edouard LOUIS, Pierre BLANC, Mathieu UZZAN, M
Centre de Recherche St Antoine - Sorbonne Univeristé
27 Rue Chaligny, 75012 Paris

Abstract
About 50 to 75% of Crohn's Disease patients (CD) will have to undergo partial bowel resection. While such surgery can improve the outcome of the disease, recurrence remains very frequent. Here, we investigate the role of resection on the mucosa-associated microbiota as well as the role of microbiota on the recurrence. Using 16S and ITS2 sequencing, we profiled the mucosa-associated microbiota of biopsies from CD patients before (n=140) and after (n=125) resection. Overall, resection decreased fungal alpha-diversity but not the bacterial one. Both fungal and bacterial beta-diversity were impacted by the resection, with a decrease of Bifidobacterium species and increase of Bacteroides species after surgery. Fungal microbiota composition was characterized by a dominance of the pro-inflammatory Malassezia species, whose prevalence increased after surgery. When considering post-resection samples only, the major effect on bacterial composition was the Rutgeerts score, a predictive score for endoscopic recurrence. The absence of recurrence was associated with species such as Bacteroides and Faecalibacterium prausnitzii while recurrence was associated with Fusobacterium nucleatum, Veillonella parvula and Akkermansia muciniphila. Interestingly, we were able to find strong bacterial signals for the whole range of the Rutgeerts scores scales (overall Rutgeerts score, Rutgeerts score of the ileum and of the anastomose), suggesting that the progression of the disease is associated with several changes in the bacterial composition. In addition, we investigated the community dynamics following resection and recurrence. The correlation network between bacterial species abundances highlighted the decreased modularity of the network after surgery and in the absence of recurrence. Moreover keystone species displaying high centrality in the network changed between time and recurrence. Altogether, these results provide a deeper understanding of the effects of ileal resection in the context of CD both at the species and community level.

Group 3

3 B – Microbiota influence on the host (except on the nervous system)

Posters 37 to 51

Poster number: 37

Title: Microbial-derived metabolites promote NKT22 responses in colitis associated colorectal cancer

Presenting Author: Alberto Baeri

Authors and Affiliations
F. Perillo, F. Strati, A. Baeri, F. Caprioli, F. Facciotti
Department of Biotechnology and Biosciences, University of Milan-Bicocca
Piazza dell'Ateneo Nuovo, 1 - 20126, Milano

Abstract
Patient suffering from inflammatory bowel diseases (IBD) manifest an increased risk of developing colorectal cancer (CRC), known as colitis-associated colon cancer (CAC). Interleukin 22 (IL22) is a cytokine with an important function in restoring IBD status since it is involved in the proliferation and survival of epithelial cells. However, given its ability to induce epithelial cell proliferation, IL22 also correlates with the development of tumoral lesions. IL22 is secreted by different immune cell types, including iNKT cells. However, the function of these cells in contributing or controlling intestinal inflammation and cancer is still highly debated.
Here, we studied the role of IL22-secreting iNKT cells during gut chronic inflammation and CAC development and the stimuli responsible for iNKT cells' IL22 secretion. Lamina propria mononuclear cells from a discovery cohort of IBD, CAC and CRC patients were isolated from surgical specimens obtained from the IRCCS Policlinico Hospital Milan. Multiparametric flow cytometry analyses, RNA and protein levels were evaluated, and mucus-associated microbiota composition was established through 16S rRNA gene sequencing. Stable human intestinal- and peripheral blood-derived iNKT cell lines and C57bl/6 mice were used to evaluate the molecular mechanisms involved in dictating iNKT cells to produce IL22. Metabolic analyses were performed to identify the molecules involved in this differentiation. Finally, immunofluorescence multiplexing analyses were performed on FFPE tissues of 20 CAC patients belonging to a validation cohort obtained from Istituto Oncologico Veneto, Padua. Collectively, we observed increased expression of IL22 and a higher NKT22 infiltration in CAC tissues, as well as an enrichment of Odoribacter, a gram-negative bacteria implicated in tryptophan metabolism and in Aryl hydrocarbon receptor (AhR) ligands production. We demonstrated that stimulation of iNKT cell lines with Odoribacter-derived metabolites induced IL22 production by iNKT cells and that this secretion is dependent on AhR function.
Metabolomic analyses revealed increased presence of few tryptophan metabolites in the Odoribacter supernatant. These metabolites were capable of increasing NKT22 differentiation both in vitro and in vivo models. The administration of Odoribacter Supernatant or the single purified metabolites were sufficient to increase tumorigenesis in C57bl/6 colorectal cancer mouse models but not in iNKT-deficient TRAJ18KO mice.
These data suggest that iNKT cells are the major IL22 producing cells in CAC patients, and are induced by the recognition of microbiota-derived metabolites implicated in tryptophan metabolism and Aryl hydrocarbon receptor (AhR) stimulation. NKT22-microbiota interaction in CAC patients could play a potential crucial role in tumor development.

Poster number: 38

Title: Impact of a quorum sensing molecule on intestinal barrier function in IBD

Presenting Author: Raphaelle Liquard

Authors and Affiliations
R.Liquard, S.Thenet ,V.Carrière, N.Sauvonnet, K.Oukacha, P.Seksik
Centre de recherche Saint-Antoine, UMRS 938; Institut Pasteur
27 rue Chaligny, 75012 Paris ; 28 rue du Dr Roux, 75015 Paris

Abstract
Implication of a bacterial quorum sensing molecule in the control of inflammation and intestinal barrier function in inflammatory bowel disease

Inflammatory bowel disease (IBD) is characterized by an altered intestinal barrier and an excessive immune response to the microbiota. Certain bacterial metabolites have been implicated in the maintenance of the intestinal barrier. Our team discovered several quorum sensing molecules of the N-acyl-homoserine-lactone (AHL) family in the human intestinal ecosystem and showed that the most abundant, 3-oxo-C12:2-HSL, is lost in IBD patients, suggesting a beneficial role in intestinal homeostasis. 3-oxo-C12:2-HSL exerts anti-inflammatory properties on immune cells, notably via a bitter taste receptor (TAS2R) and a protective role in tight junction integrity in intestinal epithelial cells under inflammation, but the underlying mechanisms remain unknown. Our aim is to identify the mechanisms of action of the 3-oxo-C12:2-HSL in epithelial cells and its molecular targets.
We use the Caco-2/TC7 cells, a human intestinal epithelial cell line, cultured on semi-permeable filters with induction of an inflammatory condition by adding Interferon-γ (IFNγ and Tumor Necrosis Factor-α (TNFα), in the presence of 3-oxo-C12:2-HSL.
Our results show that, in addition of maintaining tight junction integrity in Caco-2/TC7 cells, 3-oxo-C12:2-HSL attenuates apical secretion of MCP-1 chemokine induced by pro-inflammatory cytokines (IFNγ/TNFα), without marked effect on MCP-1 basal secretion or IL-8 secretion. This observation shows that 3-oxo-C12:2-HSL is able to mitigate impairment of the epithelial barrier in inflammatory conditions through different mechanisms. To identify signaling pathways relying effects of 3-oxo-C12:2-HSL in epithelial cells, we focused on TAS2Rs, previously involved in immune cells. Among TAS2Rs that can be activated by 3-oxo-C12:2-HSL, we show that TAS2R13 is one of the most highly expressed bitter taste receptors in Caco-2/TC7 cells and human intestinal tissues. Our first results using siRNA approach show that TAS2R13 appears to be involved in the effect of AHL on the maintenance of tight junctions under inflammatory conditions.
This work will provide essential data to understand the protective role of an intestinal microbiota molecule on host cells. As the level of 3-oxo-C12:2-HSL is decreased in IBD patients, knowing the mechanisms underlying the protective effects of this AHL on host cells may open the way to new therapeutic approaches in IBD.

Poster number: 39

Title: Impact of the perturbation and resilience of gut microbiota on cholesterolemia

Presenting Author: Carolina Neves

Authors and Affiliations
Carolina Neves, A. Vanduyse, ICANomics, E. Ramel, M. Larsen, P. KC, P. Lesnik
INSERM UMR_S 1166 - Sorbonne Université
Faculté de Santé Site Pitié-Salpétrière, 91 boulevard de l'Hopital, 75013 Paris

Abstract
Background

Hypercholesterolemia is a key risk factor for cardiovascular diseases. While environmental and genetic influences on cholesterol levels have been well established, recent research has highlighted the gut microbiota as an important regulator. Our laboratory was among the first to demonstrate that the microbiota can affect cholesterolemia. In hypercholesterolemic mouse models, experimental depletion of gut microbiota using antibiotics leads to increased plasma cholesterol levels, a change that can be reversed through microbiota re-implantation. However, the specific factors and mechanisms behind the restoration of basal cholesterolemia remain unknown. This study aims to identify the host and microbial factors involved in the mechanisms of cholesterolemia resilience.

Methods

We depleted the gut microbiota in hypercholesterolemic female LDL-R KO mice fed with a chow diet using broad-spectrum antibiotics. Subsequently, we conducted a longitudinal analysis of plasma cholesterol levels, transcriptomic analysis of the gut and liver, and lipidomic and metabolomic profiling of plasma and faeces. Finally, we monitored the recolonization of the gut microbiota by analyzing bacterial composition through 16S rRNA sequencing.

Results

We first confirmed that depleting the microbiota through antibiotic therapy increases plasma cholesterol levels and that re-implantation of the microbiota restores these levels to baseline. We demonstrated that cholesterol resilience occurs gradually between the 3rd and 7th days after discontinuing the antibiotic treatment. During the resilience phase, microbiota re-implantation was shown to reduce de novo cholesterol synthesis and promote its elimination by restoring initial bile acid concentrations. We also identified microbiota-dependent mechanisms involved in cholesterol resilience, marked by the return of dominant phyla such as Bacteroidota and Verrucomicrobiota, as well as specific genera like Bacteroides and Akkermansia. Additionally, we observed the restoration of certain bacterial metabolites, including propionate, acetate, and coprostanol, which were found to directly correlate with plasma cholesterol levels, suggesting their role in regulating cholesterol metabolism.

Conclusions

These results confirm that the gut microbiota plays a key role in modulating cholesterolemia. While certain bacterial phyla and metabolites emerged as potential candidates, further studies are needed to confirm their causal implications. If validated, these candidates could be explored as novel therapeutic agents for treating hypercholesterolemia and preventing cardiovascular diseases.

Poster number: 40

Title: Development of an organoid model from frozen chicken intestinal duodenum section

Presenting Author: Tracy PARADIS

Authors and Affiliations
Paradis, Bonhourre-Lasserre, Oliviero, Répérant, Le Douce, Bousarghin
Institut NuMeCan - Université de Rennes
Institut NuMeCan - 2 rue Henri Le Guilloux, 35 000 Rennes

Abstract
Intestinal microbiota and pathogen interactions: development of an organoid model from frozen chicken intestinal duodenum sections.

Tracy Paradis, Fanny Bonhoure-Lasserre, Nolwenn Oliviero, Jean-Michel Répérant, Jérôme Le Douce, Latifa Bousarghin

The intestinal lumen shelters a large community of microorganisms (viruses, protozoa and fungi) forming the intestinal microbiota. This microbiota contributes for biological process such as nutrient absorption, vitamin and metabolites production. This last decades, numerous studies have shown that it also plays an important role in gut colonization resistance against pathogens such as Salmonella, an intracellular zoonotic bacterium causing important world public health problem. Equilibrium between members of some gut phyla, such as Lactobacillus sp. and Bacteroidota seems to be critical to prevent colitis susceptibility induced by Salmonella. However, mechanisms by which members of gut microbiota prevent Salmonella colonization remain poorly described. Among the biological tools available to investigate these micro-organisms interactions, the use of intestinal organoids is an interesting alternative between the use of 2D in vitro cellular models, with limited poor cellular diversity and physiologically irrelevant environment, and the use of the ethically controversial animal models. These self-organized 3D multicellular ex vivo models are obtained from the culture of stem cells with self-renewal and differentiation properties. Because human organoids are often obtained from stem cells of patients, already presenting a pathological environment, and also because access to these human cells is difficult due to ethical issues, the use of animal intestinal organoids is preferentially chosen. The use of organoids from chicken intestine is therefore relevant to investigate gut microbiota role in Salmonella infection, indeed the consumption of infected chicken is one of the main sources of contamination of humans by Salmonella. Various models of avian intestinal organoids have already been developed. Here, we proposed the establishment of a new method to develop intestinal organoids of chicken duodenum. The originality of this model is based on the culture of intestinal crypt cells, obtained after freezing then thawing section of fresh duodenum. This methodology will offer a great perspective for reducing the use of animals in organoid generation, by creating duodenum sections biobank. It could also be used to understand the role of the intestinal microbiota in the intestinal colonization of Salmonella.

Poster number: 41

Title: MyD88 signaling in hematopoietic cells controls host-Segmented Filamentous Bacteria symbiosis

Presenting Author: Valérie Gaboriau-Routhiau

Authors and Affiliations
Marie Cherrier1, Renan Oliveira Correa1, Nadine Cerf-Bensussan1, Valérie Gaboriau-Routhiau1,2
1. Université Paris Cité, Institut Imagine, INSERM UMR1163, Laboratory of Intestinal Immunity, Paris, France
2. Université Paris-Saclay, INRAe, AgroParisTech, Micalis institute, Jouy-en-Josas, France
Institut Imagine, Laboratory of Intestinal Immunity, Paris

Abstract
The segmented filamentous bacterium (SFB) is a commensal member of the gut microbiota that is crucial to orchestrate the post-natal maturation of the host immune system and to establish a healthy state of physiological inflammation in the intestine, including notably a strong homeostatic Th17 cell response. Strikingly, this function was shown to be largely dependent on the intimate attachment of SFB to the ileal mucosa. Although this unusual innocuous partnership remains largely enigmatic, it suggests that hosts have evolved potent mechanisms to control SFB colonization and maintain a symbiotic relationship with SFB. However, the signaling pathways used by SFB to induce self-limiting immune responses and how such homeostatic responses ultimately control SFB colonization remain controversial. Using gnotobiotic approaches in immunodeficient and chimeric mice to avoid confounding effects of a complex microbiota on SFB and host responses, we observe that adaptive T or B cell-dependent immune responses are dispensable to control SFB growth in SFB-monocolonized mice. In contrast, MyD88 signaling in myeloid cells is critical for licensing interleukin (IL)-22 production by type 3 innate lymphoid cells (ILC3), which ultimately limits SFB expansion. Thus, our results emphasize the necessary and sufficient role of a hematopoietic MyD88/ILC3/IL-22 axis that directly controls SFB growth.

Poster number: 42

Title: Impact of Staphylococcus aureus nasopharyngeal carriage on local mucosal and systemic immune responses

Presenting Author: Malgorzata Mnich

Authors and Affiliations
Malgorzata MNICH, Pedro GONCALVES, Evangelia ELEFTHERIOU, Darragh DUFFY, James DI SANTO
Institut Pasteur
25-28 Rue du Dr Roux, 75015 Paris

Abstract
Staphylococcus aureus (SA) is a Gram-positive bacterium present in microbial communities of the skin, gastrointestinal tract, and upper respiratory tract (URT) but is considered a pathobiont due to its potential to cause infections. Recent evidence supports the notion that SA has evolutionarily adapted to colonize the human host, underscoring the importance of analyzing individual human samples to understand the molecular mechanisms of colonization as well as the correlates of protective immunity. To address these questions, we assessed SA-specific systemic and mucosal immune responses in a cohort of 1000 healthy individuals (Milieu Intérieur; www.milieuinterieur.fr). To determine SA carriage and its relative abundance, we performed droplet digital PCR using nasopharyngeal swab samples. After filtering out samples with low total bacterial counts, 971 samples were analyzed and based on a relative abundance threshold, we identified 88 high-level SA carriers and 263 low/intermediate-level SA carriers. Among individuals sampled at two time points, we could also identify persistent SA carriers. To investigate factors associated with SA carriage, we correlated SA levels with variables such as sex, age, smoking status, season of sampling, and CMV status. Additionally, we analyzed nasopharyngeal bacterial communities to identify the most prevalent bacterial genera across SA carriers. SA colonization can begin as early as birth, with transmission from mother to newborn but frequently occurs later in life. As such, SA-specific antibodies and memory T cells are found at all ages within the population. However, the commensal nature of SA may promote anti-inflammatory or regulatory immune responses, which can inhibit clearance of SA infection. This phenomenon, known as antigenic sin, complicates the development of an effective SA vaccine and the need to fully characterize pre-existing anti-staphylococcal systemic immune responses in healthy individuals with or without SA carriage. To address this point, we analyzed changes in RNA expression from PBMCs stimulated with heat-killed S. aureus, comparing these to unstimulated controls. Differential gene expression analysis identified several genes specifically associated with nasopharyngeal SA carriage. This study provides an in-depth comparison of the local and systemic immune responses in SA carriers and non-carriers. As SA currently remains on the WHO Global Priority Pathogens List, our findings highlight the importance of developing effective anti-staphylococcal treatments and offer valuable insights for future vaccine development efforts.

Poster number: 43

Title: Roseburia intestinalis modulates gut peptide (PYY) expression in a new a multicellular model including enteroendocrine cells

Presenting Author: Thomas Gautier

Authors and Affiliations
Thomas Gautier, Nelly Fahet, Zohreh Tamanai-Shacoori, Nolwenn Oliviero, Marielle Blot, Aurélie Sauvager, Agnes Burel, Sandrine David-Le Gall , Sophie Tomasi, Sophie Blat, Latifa Bousarghin
Institut Numecan
Intitut NuMeCan, 2 Rue Henri le Guilloux, 35000 Rennes

Abstract
For several years now, correlations have been emerging between the decline of certain bacterial species and the onset of metabolic diseases such as obesity and type 2 diabetes (T2DM). Previous research shows that the balance of species in the intestinal microbiota, called commensal bacteria, contributes to human health and disease. However, the mechanisms by which commensal bacteria interact with the host are still unclear. Among the species of interest, the commensal bacteria Roseburia intestinalis (R. intestinalis) and Bacteroides fragilis (B. fragilis) were found to be reduced in obesity and T2DM. In metabolic pathologies, the regulation of hormones produced by enteroendocrine cells is disrupted. Indeed, hormones such as PYY and GLP-1 (GCG) are significantly reduced in these patients. R. intestinalis and B. fragilis are considered like potential Next Generation Probiotics (NGP). The mechanisms by which these two bacteria protect and regulate the gut have yet to be elucidated. The aim of this study was to determine how metabolites produced by R. intestinalis and B. fragilis could regulate enteroendocrine cells. To date, a number of in vitro systems have been designed to investigate the host-R. intestinalis and host-B. fragilis interactions. In most of the intestinal models, the enteroendocrine cells, considered as a potential link between gut bacteria and several human diseases, were missing. In the present study, we have generated a new model by adding enteroendocrine cells (ECC) of L-type (NCI-H716) to the one that we have previously described including enterocytes, mucus, and M cells. After 21 days of culture with the other cells, enteroendocrine-differentiated NCI-H716 cells showed neuropods at their basolateral side and expressed their specific genes encoding proglucagon (GCG) and chromogranin A (CHGA). We showed that this model could be stimulated by Roseburia intestinalis and Bacteroides fragilis, but also by a pathogenic strain such as Salmonella Heidelberg. Moreover, using cell-free supernatants of B. fragilis and R. intestinalis, we have shown that R. intestinalis supernatant induced a significant increase in IL-8 and PYY but not in GCG gene expression, while B. fragilis had no impact. Our data indicated that R. intestinalis produced short chain fatty acids (SCFAs) such as butyrate whereas B. fragilis produced more propionate. However, these SCFAs were probably not the only metabolites implicated in PYY expression since butyrate alone had no effect. In conclusion, our new quadricellular model of gut epithelium could be an effective tool to highlight potential beneficial effects of bacteria or their metabolites, in order to develop new classes of probiotics.

Poster number: 44

Title: Impact of intestinal miRNAs on gut health in IBD patients

Presenting Author: Camille Remy

Authors and Affiliations
Camille REMY1, Maryline ROY1, Anne DUMAY1, Maeva DUQUESNOY2, Benoit CHASSAING2, Servane ALIROL1,3, Franck CARBONNEL4, Anne BUISSON5, Corinne GOWER-ROUSSEAU6, Jean-Pierre HUGOT1,3, Emilie VIENNOIS1
1INSERM, U1149, Center of Research on Inflammation, Université Paris-Cité, 16 rue Henri Huchard, 75018 Paris, France. 2Microbiome-Host Interactions, Institut Pasteur, Université Paris Cité, INSERM U1306, Paris, France. 3Hopital Robert Debré, Assistance Publique Hopitaux de Paris, Paris, France 4Hopital Kremlin Bicêtre, Assistance Publique Hopitaux de Paris, Paris, France 5Association François Aupetit Crohn RCH, Paris, France 6Pôle Recherche et Santé Publique – Hôpital Robert Debré – CHU de Reims, France
1§ Rue Henri Huchard, 75018 Paris

Abstract
Background: Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are characterized by a chronic inflammation of the digestive tract. Their etiology is likely multifactorial, related to a loss of tolerance towards the microbiota in genetically predisposed subjects. An altered dialogue between the microbiota and the host have been identified as a key element in the pathophysiology of IBD. MicroRNAs (miRNAs), small non-coding RNAs abundant in the intestinal lumen, are emerging as potential players in this dialogue. Based on our previous findings, we reported that an increase in miR-21 and let-7b during murine colitis can alter the microbiota and induce intestinal inflammation. In a small cohort study involving 18 IBD patients, we confirmed that both miRNAs were elevated in stool samples from these patients compared to healthy controls. Here, we hypothesize that fecal miR-21 and let-7b contribute to IBD pathophysiology through their interaction with the microbiota. Objective: The aim of this study was to evaluate the expression levels of miR-21 and let-7b in a large cohort of IBD patients, and to correlate them with disease activity and alterations of the microbiota. Method: miRNAs were extracted from fecal samples from adult and pediatric IBD patients. Quantification of miR-21 and let-7b was performed by RT qPCR and microbiota analysis by shotgun metagenomics. Results: Analysis of fecal miRNAs from 256 patients revealed a correlation between miR-21 and let-7b expression and fecal calprotectin levels, reflecting disease activity. This association was not influenced by gender, age nor type of IBD (CD or UC) but depended on the location and extent of lesions. Microbiota analysis showed an association between the relative abundance of specific bacterial taxa and disease activity, as well as a correlation between fecal miR21 and let-7b levels and certain bacteria. Conclusion: In conclusion, our study revealed an association between fecal miRNAs, microbiota changes and disease activity in IBD patients. These findings suggest that the interaction between microbiota and miRNAs, in particular miR-21 and let-7b, could play a role in IBD flares.

Poster number: 45

Title: Taxonomic and functional analysis of gut microbiomes from patients with autoimmune diseases under low-dose IL-2 treatment

Presenting Author: Grete Kvedaraviciute

Authors and Affiliations
Grete Kvedaraviciute, Gabriel Pires, Fabien Maury, David Klatzmann, Nicolas Tchitchek, Adrien Six
Sorbonne Université, INSERM, Immunology-Immunopathology-Immunotherapy (i3), Paris, France. AP-HP, Hôpital Pitié-Salpêtrière, Biotherapy (CIC-BTi) and Inflammation-Immunopathology-Biotherapy Department (i2B), Paris, France
INSERM UMRS 959 - Sorbonne Université Bâtiment CERVI, CHU Pitié-Salpêtrière 83 boulevard de l'Hôpital

Abstract
BACKGROUND:
Recent studies link gut microbiome dysbiosis to various immune system alterations. However, mechanisms of host-microbiome interactions, especially in autoimmune diseases involving immune system and gut microbiome dysregulation, remain unclear. We recently discovered that low-dose interleukin-2 (IL-2LD), a treatment for several autoimmune diseases, fosters a tolerogenic gut microbiota, enhancing autoimmunity and reducing gut inflammation. This calls for further characterization of the dialogue between the immune system and the gut microbiome under low-dose IL-2 treatment.

METHOD:
We collected over 500 gut microbiome samples from patients with autoimmune diseases such as Type 1 Diabetes (T1D), Systemic Lupus Erythematosus (SLE), and Multiple Sclerosis (MS) under low-dose IL-2 treatment and placebo. Taxonomic and functional profiling of metagenomic samples were performed using MetaPhlAn3 and HUMAnN3. Alpha diversity analysis, employing Shannon and Simpson indexes and Renyi's diversity curve, assessed the impact of IL-2LD on gut microbiome taxonomic diversity.

RESULTS:
We observed a statistically significant decrease in alpha diversity from Phylum to Order taxonomic ranks up to 250 days after the treatment in SLE and T1D patients treated with IL-2LD. We did not observe any significant changes in MS patients with same conditions. These findings were validated using randomization, leave-one-out, and bootstrapping methods.

IMPACT:
This research aims to elucidate the impact of IL-2LD treatment on the gut microbiome. Understanding IL-2LD's mode of action on the gut microbiome may identify new biomarkers and treatment strategies for autoimmune and inflammatory diseases.

Poster number: 46

Title: Role of the human intestinal microbiota in individualized response to influenza vaccination

Presenting Author: Maeva Duquesnoy

Authors and Affiliations
DUQUESNOY Maeva (PhD student)1, DELAROQUE Clara1, SZGAIRY Soha2 , Rytter Heloïse1 DAURIAT Charlène1, ROBERT Chloé1, TURJEMAN Sondra2, KOREN Omry2, CHASSAING Benoit1, 1 Microbiome-Host Interactions, Microbiology Department, Institut Pasteur, Université Paris Cité, Paris, France 2 Microbiome Research Laboratory, Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel
25 rue du docteur Roux, 75015 Paris

Abstract
Vaccination has been established as a cornerstone of public health, resulting in the global eradication of various lethal diseases. However, vaccination efficacy is not uniform and select populations exhibit morbidity and mortality from preventable diseases partially due to poor vaccine efficacy, such as observed with Rotavirus vaccine. Furthermore, vaccine immunogenicity is frequently suboptimal in populations at risk, such as obese individuals and pregnant women whom harbor decreased antibodies titers in response to various vaccines. Interestingly, these populations are also characterized by alterations in their intestinal microbiota. While there is growing evidences that the intestinal microbiota is playing a role in local and systemic immune response, its exact impact on vaccine efficacy has not yet been carefully investigated.
We investigated here the role played by the intestinal microbiota in dictating influenza vaccination efficacy. Germ-free mice were transplanted with fecal microbiota originating from either obese donors, pregnant women, or their healthy counterparts (lean and non-pregnant women donors). After microbiota stabilization, recipient mice were subjected to influenza vaccination. Fecal, blood samples and organs were harvested to investigate the intestinal microbiota, the intestinal inflammatory tone, as well as antibody production.
We observed that mice receiving microbiota from obese or pregnant donors harbored various metabolic changes compared to those receiving microbiota from lean or non-pregnant donors. These changes included increased fat deposition as well as colon shortening, indicative of low-grade intestinal inflammation. More importantly, mice colonized with microbiota from obese or pregnant donors harbored an impaired anti-flu antibody production following vaccination, with the observation of a highly donor-dependent response. In depth microbiota analysis of the recipient mice at both the compositional and functional levels are currently under investigation to decipher microbial signature that could contributes to compromised vaccine responses.
Collectively, these data suggest that the intestinal microbiota is a crucial contributor in individualized response to vaccination. Further studies are needed to mechanistically decipher the observed inter-individual variations and identify microbiota members impacting vaccine efficacy.

Poster number: 47

Title: miRNA-microbiota dialogue in the neonatal period and long-term effects on gut health

Presenting Author: Louis Berthet

Authors and Affiliations
Louis BERTHET1, Maryline ROY1, Camille REMY1, Emilie VIENNOIS1
INSERM, U1149, Center of Research on Inflammation, Université Paris-Cité
16 rue Henri Huchard, 75018 Paris, France

Abstract
New concerns suggest that the conditions of initial colonization of the newborn gut by commensal bacteria play a decisive role in infant development. Alterations in the microbiota occurring early in life seem particularly associated with a profound impact on intestinal health in adulthood, as indicated by numerous studies. For instance, several studies conducted in humans and mice indicate that individuals exposed to antibiotics early in life develop a pathological imprint for certain chronic disorders later in life, such as Inflammatory Bowel Diseases (IBD). However, the mechanisms by which the microbiota influences host intestinal homeostasis early in life remain poorly understood. At the host-microbiota interface, many elements suggest that microRNAs (miRNAs), small noncoding RNAs that regulate about 60% of the human transcriptome, play a major regulatory role. We have previously shown that the over- or under-expression of several distinct fecal miRNAs is associated with inflammation in IBD, impacting various key functions within the digestive system, such as barrier function, and the onset of dysbiosis. Their influence during the early stages of life, however, remains completely unexplored. This study aims to explore whether and how changes in miRNA-microbiota interactions during the neonatal period can lead to long-term impacts on gut health.
Therefore, we conducted an experiment evaluating the long-term impact of neonatal gavage administration of miRNAs previously identified by our team as pro-inflammatory. C57BL/6J mouse pups were gavaged once a day from 7 days old for 4 days with PBS, a control miRNA (control groups), miR-A, or miR-B (treated groups). We then collected feces and monitored the development of these mice until 51 days of life. Supplementation with miR-B in pups during their second week of life, led to an increase in several inflammatory markers in adulthood. Among these markers, myeloperoxidase and relative expression of Interleukin 6 in the colon, both inflammatory molecules produced by monocytes/macrophages, were significantly increased in our miR treated animals when compared to controls.
Analyses are still in progress to determine the extent of the gut microbial switch caused by the administration of our miRNA in the neonatal period and the mechanisms involved.
Overall, our findings are the first to identify a possible modulatory role of miRNA on the development of the host-microbiota interface.

Poster number: 48

Title: DEFECTIVE AUTOPHAGY COMBINED WITH WESTERN DIET CAUSE DISRUPTED INTESTINAL HOMEOSTASIS, AIEC EMERGENCE AND INCREASED HOST SUSCEPTIBILITY TO AIEC INFECTION

Presenting Author: Hanh Hoang

Authors and Affiliations
My Hanh Thi Hoang, Angéline Duval, Julien Delmas, Guillaume Dalmasso, Nicolas Barnich, Hang Thi Thu Nguyen
University Clermont Auvergne
49, Bd François-Mitterrand - CS 60032 63001 Clermont-Ferrand Cedex 1

Abstract
Background: Crohn's disease (CD) is a chronic inflammatory bowel disease, of which the etiology involves environmental, genetic and microbial factors. Dysregulated autophagy, Western diet and abnormal colonization of adherent-invasive E. coli (AIEC) have been revealed as risk factors for CD. Here, we investigated the effect of high fat, high sugar (HFHS) diet on autophagy, and that of combined HFHS diet and dysregulated autophagy on intestinal homeostasis, gut microbiota and host susceptibility to pathobiont exposition.
Methods: Mice deficient for the autophagy-related gene Atg16l1 specifically in intestinal epithelial cells (Atg16l1flox/floxCreVillin or Atg16l1△IEC) or wild-type mice (WT or Atg16l1flox/flox) were fed a control or HFHS diet for 16 weeks and infected with the AIEC LF82 strain or the commensal E. coli MG1655 strain. Mice were sacrificed at day 3 post-infection. Levels of autophagy markers (LC3-II, p62) and anti-microbial peptides (AMPs) were assessed by Western blot, qRT-PCR and immunofluorescent staining. E. coli strains were isolated using selective media and identified by mass spectrometry. Intestinal inflammation was assessed by quantification of pro-inflammatory cytokine and chemokine levels and histological scoring.
Results: In WT mice, HFHS diet induced autophagy defect in IECs, as shown by decreased LC3-II and increased p62 protein levels, decreased mRNA levels of several autophagy-related genes, and lack of autophagy induction in IECs upon infection with the AIEC LF82 strain. Combination of HFHS diet and intestinal autophagy deficiency led to markedly decreased AMP levels, increased intestinal inflammation, and enhanced E. coli colonization in the ileum. Most of the E. coli strains isolated from the ileal mucosa of HFHS diet-fed Atg16l1△IEC mice presented the pathogenic characteristics of AIEC (adhere to and invade IECs, survive and replicate in macrophages, and induce pro-inflammatory response). Combination of HFHS diet and intestinal autophagy deficiency also increased host susceptibility to AIEC LF82 infection, as shown by increased intestinal colonization by LF82 and LF82-induced intestinal inflammation.
Conclusion: HFHS diet induced dysregulated autophagy, and combination of genetic (defective autophagy) and environment (HFHS diet) factors causes abnormalities in IEC functions, gut dysbiosis with the emergence of AIEC strains, and increased host susceptibility to AIEC LF82 infection, exacerbating intestinal inflammation.

*This work is dedicated to the memory of Nicolas Barnich.

Poster number: 49

Title: Cause-to-effect relationship between prefrail aging microbiota and intestinal inflammation

Presenting Author: Guillaume Le Cosquer

Authors and Affiliations
Guillaume Le Cosquer1,2, Melissa Pannier1, Elise Pyhourquet1, Yohan Santin3,*, Bruno Guiard3,*, Angelo Parini3,*Nathalie Vergnolle1,4,*, Jean-Paul Motta1,*
1Institute of Digestive Health Research (IRSD), INSERM, Toulouse University, INRAe, ENVT, University Toulouse III Paul Sabatier (UPS), 31300 Toulouse, France 2Department of Gastroenterology and Pancreatology, Toulouse University Hospital (CHU Toulouse), Toulouse, France and Toulouse University, University Toulouse III Paul Sabatier (UPS), 31059 Toulouse, France 3 Institute of Metabolic and Cardiovascular Diseases (I2MC), INSERM, Toulouse University, University Toulouse III Paul Sabatier (UPS), 31432, Toulouse, France 4 Department of Physiology and Pharmacology, University of Calgary Cumming School of Medicine, 3330 Hospital Drive, NW Calgary, AB, T2N4N1, Canada * members of the IHU HealthAge INSPIRE/Open Science study group
INSERM IRSD U1220 , CHU PURPAN PLACE DU DOCTEUR BAYLAC, CS 60039 31024, TOULOUSE CEDEX 3

Abstract
Introduction
Although age-related alteration of the gut microbiome (microb-aging) is well studied, there is a lack of research investigating the gut microbiota during the early stages of prefrailty and understanding its behavior in close interaction with host tissue. A cause-to-effect relationship between alterations of microbiota during prefrail aging and intestinal disease has never been investigated.

Methods
We used intestinal tissues and fecal samples from a phenotypically well-characterized French mice aging cohort, INSPIRE-T. The cohort comprised male and female SWISS outbred mice that underwent health assessments to measure frailty, using the Valencia Score. Mice were categorized into groups of young (6 months, n=8), aged robust (24 months, n=8), and aged prefrail animals (24 months, n=8).
Fluorescence in situ hybridization (FISH) was performed with a universal bacterial 16S fluorescent rRNA probe, DAPI and wheat germ agglutinin labeled with fluorescein. The biofilm damage score was blindly evaluated for each mouse in the groups of interest (Motta et al., 2019).
To experimentally demonstrate a causal relationship between prefrailty-associated microbiota and local gut inflammation, we conducted fecal microbiota transplantation (FMT) in antibiotic-treated young mice (ampicillin, metronidazole, neomycin, and vancomycin). We used as transplant a pool of feces from young, robust, and prefrail mice. Four days post-transplantation, the colon was harvested for evaluation of macroscopic damage (blind Wallace scoring), and mucosal biogeography analysis.

Results
Young mice exhibited a mucosal microbiota organized as a dense biofilm community lining a layer of sterile mucus. In contrast, aged animals displayed a different spatial organization, featuring isolated bacteria within the mucus layer that escaped from the dense mucosal biofilm and bacterial translocation. Prefrail animals exhibited more signs of tissue-associated biofilm alterations than aged robust animals.
We did not find any significant macroscopic damage in the colon of mice transplanted with young fecal microbiota (total damage score of 1.7±0.44). On the opposite recipient animals of aged microbiota had significantly higher colon damage such as increased incidence of erythema, mucus release in the lumen, edema, and ulcers (1.7±0.44 vs. 3.6±0.73, P= 0.035). Further stratifying aged animals into robust and prefrail categories revealed a substantially higher damage score in the prefrail group

compared to robust animals (total score 5.4±0.98 vs. 2±0.98, ANOVA followed by Dunnett's test, P = 0.002).

Conclusion

These findings suggest a causal link between microb-aging in prefrailty and gut inflammation, advocating microbiota-directed therapies to reverse prefrail phenotype and thereby promote healthspan.

Poster number: 50

Title: MAIT cells monitor intestinal dysbiosis and contribute to host protection during colitis

Presenting Author: Francois Legoux

Authors and Affiliations
Yara El Morr#, Mariela Fürstenheim#, Martin Mestdagh, Katarzyna Franciszkiewicz, Marion Salou, Claire Morvan, Thierry Dupré, Alexey Vorobev, Bakhos Jneid, Virginie Premel, Aurélie Darbois, Laetitia Perrin, Stanislas Mondot, Ludovic Colombeau, Hélène Bugau
Inserm ERL1305, Institut Curie
Rennes, France

Abstract
Intestinal inflammation shifts microbiota composition and metabolism. How the host monitors and responds to such changes remains unclear. Here, we describe a protective mechanism by which mucosal-associated invariant T (MAIT) cells detect microbiota metabolites produced upon intestinal inflammation and promote tissue repair. At steady state, MAIT ligands derived from the riboflavin biosynthesis pathway were produced by aerotolerant bacteria residing in the colonic mucosa. Experimental colitis triggered luminal expansion of riboflavin-producing bacteria, leading to increased production of MAIT ligands. Modulation of intestinal oxygen levels suggested a role for oxygen in inducing MAIT ligand production. MAIT ligands produced in the colon rapidly crossed the intestinal barrier and activated MAIT cells, which expressed tissue-repair genes and produced barrier-promoting mediators during colitis. Mice lacking MAIT cells were more susceptible to colitis and colitis-driven colorectal cancer. Thus, MAIT cells are sensitive to a bacterial metabolic pathway indicative of intestinal inflammation.

Poster number: 51

Title: Exploring systemic immune responses and faecal microbiome associations in the Milieu Intérieur healthy donor cohort

Presenting Author: Auxence Desrentes

Authors and Affiliations
Auxence Desrentes1,2, Etienne Villain2, Vincent Bondet2, Jamie Sugrue2, Allyson Byrd3, Lluís Quintana-Murci4, Darragh Duffy1,2, Milieu Intérieur consortium
1 Cytometry and Biomarkers UTechS, Institut Pasteur, Université Paris Cité, Paris
2 Translational Immunology Unit, Institut Pasteur, Université Paris Cité, Paris
3 Department of Cancer Immunology, Genentech Inc., San Francisco
4 Human Evolutionary Genetics Unit, Institut Pasteur, Université Paris Cité, Paris

Abstract
The gut microbiome has been shown to have a significant impact on immune responses in multiple models. However, many of these studies have been performed in disease states, when both the immune response and the microbiome are perturbed. Few studies have examined the impact of the microbiome on healthy immune states. We asked the question of how faecal microbiome and systemic immune responses are associated in a healthy adult human context: the Milieu Intérieur cohort, a genetically homogeneous cohort of 1,000 healthy donors of French ancestry, equally distributed between males and females and between the ages of 20 and 69.
To do this we first defined systemic immune response phenotypes by calculating gene expression scores after whole-blood stimulation with diverse microbes in the donors of the Milieu Intérieur cohort. To characterise the microbiome, we used shotgun sequencing datasets obtained from paired faecal samples. To test for significant associations, we applied either linear regression models or PERMANOVA, on microbiome and blood immune phenotypes, while correcting for potential confounders: age, sex, day of sampling, genetics, BMI, smoking, diet, and frequency of major immune cell components.
While we found no consistent significant correlations between immune scores and alpha diversity measurements, for beta diversity, we saw significant correlations with specific immune responses after Influenza, BCG, and C. albicans stimulation. Analysis at the taxa level identified significant associations between the relative abundance of Lactobacillales and Influenza-induced IFNγ, IL-1Β, and TNF gene scores. An association was also found for TNF secretion at the protein level. In parallel, we observed significant associations between the relative abundance of Christensenellaceae and Poly:IC-induced IFN-I gene score, which was also found at the protein level for IFNα.
In summary, we identified significant associations between the relative abundance of specific faecal microbiome taxa with systemic immune responses. This included the identification of novel associations as well as confirmation of previously described associations in other contexts. Ongoing and future work will further dissect the immune pathways affected, and test specific hypotheses related to microbiome metabolite immune interactions.

Group 4

4 – Microbiota and nervous system interactions

Posters 52 to 66

Poster number: 52

Title: In-depth exploration of the oral microbiome reveals qualitative and quantitative alterations in multiple sclerosis

Presenting Author: Laureline Berthelot

Authors and Affiliations
Leo Boussamet, Emmanuel Montassier, Camille Mathé, Alexandra Garcia, Emilie Dugast, Sandrine Wiertlewski, Arnaud Nicot, Nicolas Vince, David-Axel Laplaud, Laureline Berthelot
CR2TI (Center for Research on Transplantation and Translational Immunology) UMR 1064, Inserm, Nantes University, Nantes, France

Abstract
Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) combining genetic and environmental factors. Among these, the gut microbiota appears as an important contributor, which can promote inflammation. In addition, several studies have shown that oral health may be related to systemic inflammation and neuroinflammation. As the dynamics of the oral microbiota remain largely unexplored in MS, we performed an in-depth characterization of the oral microbiota exploring not only bacterial but also fungal and viral content as well as bacterial gene contents. To investigate the microbiome content in our samples, we performed whole genome sequencing (GenoBird, Sysmics cluster) on salivary samples of 19 relapsing-remitting MS (RRMS) patients (8 treated with corticosteroids before sampling and 11 untreated) and 11 healthy controls. For each sample, taxonomy and gene content were obtained by aligning the sequencing reads to a database of genus specific genes using the Humann2 algorithm. In parallel, targeted analysis on virulence factors was performed using Pathofact algorithm. IgA response towards bacteria was investigated using ELISA. We were able to demonstrate a state of oral dysbiosis in MS individuals compared to healthy controls (beta diversity permanova, $p<0.05$). These changes included an increase in the proportion of Fusobacterium, Leptotrichia and Actinomyces genera (fdr<0.05), and a decrease in Aggregatibacter genus (fdr<0.1) as well as several Streptococcus species (fdr<0.1). Several bacterial metabolite pathways, including vitamin B12 production, nitrogen, and polyamine pathways were altered. Moreover, a targeted analysis of virulence factors (virulome) showed an accumulation of virulence factors in the oral compartment of MS patients (53 up-regulated fdr<0.05, 7 down regulated, fdr<0.05). These included intracellular survival factors, resistance to ROS and toxins. We further demonstrated that this accumulation of virulence factors was mostly due to Porphyromonas gingivalis, despite similar relative abundances of this bacterium shared between patients and controls. Finally, we showed corticosteroid treatment impacted the viral and fungal flora but not the bacterial one (Permanova, $p<0.01$; $p<0.01$; and p=NS, respectively). Among the identified altered bacterial genera, Porphyromonas was associated to an increased IgA reactivity in the saliva of MS patients, which also correlated with disease disability score (EDSS) of patients. This study highlights the importance of the oral microbiome in multiple sclerosis and suggests oral health as a new potential risk factor in this disease. The immune oral microbiome interface and the impact of the Porphyromonas related virulence factors should be further studied in MS.

Poster number: 53

Title: Role of the gut microbiome and Gastrointestinal disorders in autism spectrum disorder

Presenting Author: Justine Marchix

Authors and Affiliations
Marchix J., Le Dréan ME., Oullier T., Trottier C., Mondot S., Brouillet JZ., Le Berre-Scoul C., Durand T., Aubert P., Bessard A., Emond P., Chaffron S., Lamaziere A., Rainteau D., Thirion F., Richard J-R., Lejuste F., Leboyer M., Doré J., Davidovic L., Bo
Inserm, TENS, The Enteric Nervous System in Gut and Brain Disorders, IMAD, Université deNantes, 44035 Nantes, France.
INSERM U955 Neuro-Psychiatrie Translationnelle, Institut Mondor de Recherche Biomédicale, 94010 Créteil, France.
AP-HP, Département médico-Universitaire d'Addictologie et de Psychiatrie des Hôpitaux Henri Mondor, Université Paris Est Créteil, 94010 Créteil, France.
Fondation FondaMental, 94000 Créteil, France.
CNRS UMR 6004, Laboratoire des Sciences du Numérique de Nantes (LS2N), Université de Nantes, 44000 Nantes, France.
Centre National de la Recherche Scientifique, Institut de Pharmacologie Moléculaire et Cellulaire, 06560 Valbonne, France.
Department of Life Science, Université Côte d'Azur, 06103 Nice, France.
Université Paris-Saclay, INRAE, MGP Metagenopolis, Jouy-en-Josas, France; Université Paris-Saclay, INRAE, AgroParisTech, Micalis Institute, Jouy-en-Josas, France.
Institut Micalis, INRAE, AgroParisTech, Université Paris-Saclay, Jouy-en-Josas, France.
UMR 1253, iBrain, University of Tours, 37000, InsermTours, France.
Sorbonne Université, Saint Antoine Research Center, INSERM UMR 938, 75012 Paris, France.
IMAD, Université deNantes, 44035 Nantes, France.

Abstract
Background: Autism spectrum disorders (ASD) are neurodevelopmental disorders defined by impaired social communication and interactions as well as repetitive and stereotyped behaviors. Gastrointestinal (GI) disorders (diarrhea, constipation, bloating…) are highly prevalent comorbidities of ASD and appear to correlate with behavioral symptom severity. Also, alterations of the gut microbiota have been reported in children with ASD. However, it is still unclear how the gut microbiota can contribute to alterations of the gut-brain axis in ASD.
Therefore, we investigated the role of the gut microbiota of individuals with ASD, without or with GI disorders (ASD Gi- or ASD Gi+), on gut and brain functions.
Methods: We used fecal samples from a well-characterized cohort of autistic adults (FondaMental Advanced Centers of Expertise for ASD cohort, FACE-ASD). Male adult C57/Bl6 mice received the fecal microbiota of control (n=11) or ASD donors without or with GI disorders (ASD Gi-, n=10 or ASD Gi+, n=16). Three and five weeks following fecal microbiota transfer (FMT), behavioral and digestive functions were evaluated in recipient mice. Fecal microbiome and metabolomic profiles of donors and recipient mice were analyzed.
Results: The clinical analysis of the donors showed that the presence of GI disorders worsened their psychosocial profile based on EQ-5D and Dunn's questionnaires. Shotgun analysis of the fecal human microbiota did not reveal major changes in microbial composition among the three groups. However, individuals with ASD display a different microbial metabolism with altered levels of short chain fatty acids and tryptophan-derivative metabolites. The gut microbiome of recipient mice held human-associated bacteria up to five weeks following FMT. The changes in microbial composition was associated with the emergence of functional module including nitric oxide metabolism and tryptophan metabolism. The recipient mice of ASD Gi+ microbiota displayed an altered colonic motility according

to the donor transit disorders (constipation, diarrhea) which was driven by nitrergic signaling. Similarly, ASD Gi+ mice showed alterations of their social interactions according to donor transit type. Anxiety and stereotypies of the recipient mice were not altered by the presence of GI disorders as compared to ASD Gi-. Also, the gut-brain axis dysfunction in ASD Gi+ recipient mice were associated with an altered metabolomic profile, specific of the donor transit type.
Conclusion: Altogether, these data support a role for the gut microbiota in the gut-brain axis in ASD and call for further investigation of the GI disorder subtypes in ASD symptoms.

Poster number: 54

Title: Gut Microbiota's Role in Physical Activity on Testicular Cancer-Related Fatigue

Presenting Author: Hwayoung NOH

Authors and Affiliations
Hwayoung Noh, Marc J Gunter, Pekka Keski-Rahkonen, Aude Fléchon & Olivia Pérol
INSERM U1296 & Département Prévention Cancer Environnement, Centre Léon Bérard
28 rue Laennec, 69373 Lyon cedex 08

Abstract
Testicular germ cell tumor (TGCT) is the most common cancer in men aged 15-40 years, with its incidence rising globally. Approximately 33 ~ 50% of patients present with metastatic disease at diagnosis. Although TCGT survivors generally have a favorable prognosis, many, especially those who undergo chemotherapy, face short- and long-term sequelae, including cancer-related fatigue (CRF) as a primary issue. Physical activity (PA) has established effects on reducing CRF and other sequelae and improving health-related quality of life (HQoL) in cancer patients during treatments. However, its impact on TGCT survivors has not been extensively studied. Recently, emerging evidence strongly supports the crucial role of the gut microbiota and its metabolites in CRF and other sequelae of cancer patients or survivors, influencing gut-brain signaling pathways. This study, therefore, hypothesizes that the gut microbiota and its metabolites mediate the beneficial effects of PA on CRF and other sequelae in metastatic TGCT patients undergoing chemotherapy. The study aims to evaluate the mediating role of the gut microbiota and its metabolites in the context of a one-year supervised PA program on long-term CRF and other sequelae in metastatic TGCT patients undergoing first-line chemotherapy. The study will be conducted as a part of a national, multicentre, phase-III randomized controlled trial (STARTER trial), which assesses the impact of a one-year supervised PA program on CRF and other short- and long-term sequelae in metastatic TGCT patients receiving cisplatin-based chemotherapy combined with etoposide+/-bleomycin. We will apply a two-step statistical analysis approach: Step 1 will examine the impact of PA on chemotherapy-induced alterations in the gut microbiota and relevant metabolites, and Step 2 will assess the effects of the gut microbiota and relevant metabolites modulated by PA on CRF and other short- and long-term sequelae in metastatic TGCT patients undergoing chemotherapy. This study will provide comprehensive and novel insights into the impact of PA on CRF and other sequelae in TGCT patients undergoing first-line chemotherapy by demonstrating the role of the gut microbiota as a potential biological mechanism. The findings of this study could support the development of effective and personalized PA interventions to maintain or promote beneficial gut microbiota and its metabolites, potentially reducing sequelae and improving HQoL in TGCT survivors. The implications of this study may extend to other cancer populations as well.

Poster number: 55

Title: Defects in the interaction between the microbiota and the intestinal epithelial barrier: a new player involved in the digestive disorders observed in patients with chronic pelvic pain

Presenting Author: Mathéus MOREAU

Authors and Affiliations
Claire Cardaillac 1,2,3 ; Mathéus Moreau 2 ; Philippe Aubert 2 ; Stéphane Ploteau 1,3 ; Amélie Levesque 3,4 ; Thibault Riant 3 ; Charlène Brochard 2 ; Ylan Camby 1,2 ; Anais Mortier 1,2 ; Nicolas Cénac 5 ; Marie-Aimée Perrouin-Verbe, 2,3,4 ; Patrick Emond
1 Service de Gynécologie-Obstétrique, CHU de Nantes ; 2 INSERM U1235, The Enter
1 rue Gaston Veil, Fac de médecine, Nantes CEDEX 01, 44035, France

Abstract
Introduction: Functional digestive disorders associated with chronic pelvic-perineal pain (CPP) are disabling and poorly understood. The objectives of this study were to (1) characterize the digestive disorders of CPP women (2) characterize the gut microbiota and its metabolites in CPP women with (CPP+) and without (CPP-) digestive symptoms or healthy controls (HC) (3) evaluate the ability of fecal supernatant (FS) from CPP patients to reproduce digestive disorders in a mouse model (4) determine the ability of bacterial metabolites differentially expressed in CPP patients subgroups to modulate digestive functions.

Material and methods: ROME IV questionnaire and rectal barostat of CPP patients (n=40). 16S analysis (microbiota) and identification of bacterial metabolites by mass spectrometry from feces from a population of CPP+ (n=15), CPP- (n=15) and HC (n=16). Colonic enemas with SF from CPP+ (n=5), CPP- (n=5) and HC (n=5) of mice pretreated with antibiotics. Functional exploration of gut brain axis in vivo and ex vivo (motility, permeability) associated with high-throughput transcriptomic and immunohistological analysis. Analysis of the impact of treatment with bacterial metabolite of interest ex vivo and in vitro.

Results: 60% of CPP patients had transit disorders over the previous 3 months (10% diarrhea, 46,7% constipation, 43,3% mixt). A significant reduction of the pain threshold following rectal distension was found in CPP+ vs CPP- and HC. A change in the composition of the intestinal microbiota, an increase in its richness (number of ASV, p=0.046) and a decrease in its beta-diversity (PCOA, p=0.009) were found in the CPP+ population vs CPP- and HC. In addition, a significant decrease of bacterial metabolites – including tryptophan derivatives (picolinic acid, tryptophan, kynurenine) - was found in CPP+ VS CPP- patients. Colonic permeability was not altered, but mRNA expression of Muc2 and a network of 8 associated genes were underexpressed in mice treated with SF from CPP+ patients vs the other two groups. This colonic mucus alteration was also found in Muc2 immunohistochemistry. Picolinic acid, a candidate metabolite altered in CPP+ patients, didn’t induce changes in intestinal permeability on ex-vivo intestinal tissues, but increased the expression of mRNAs mentioned above. In addition, it induced muscle relaxation in a 5HT3R dependent mechanism in ex-vivo intestinal tissues.

Conclusion: The microbiota and metabolites in the feces of CPP+ patients could alter the mucus barrier and motility in a subgroup of CPP patients and contribute to the digestive disorders observed.

Key words: chronic pelvic pain; digestive disorders; gut microbiota; picolinic acid.

Poster number: 56

Title: The Gut Microbiota Influences Hypothalamic Blood-CSF Barrier Structure and Function

Presenting Author: Rastelli Marialetizia

Authors and Affiliations
Marialetizia Rastelli, Vincent Prevot, Sebastien G Bouret
a Development and plasticity of Neuroendocrine Brain , UMR-S 1172; Lille Neuroscience and Cognition Center (LilNCog), Université de Lille, CHU de Lille, INSERM
1, Place de Verdun 59000 Lille

Abstract
A complex neuronal network in the hypothalamus regulates appetite and energy expenditure. To maintain energy homeostasis, hypothalamic neurons must rapidly sense and integrate a variety of peripheral signals (e.g., hormones and nutrients). This is possible because of the close vicinity of hypothalamic neurons with the median eminence (ME), a circumventricular organ containing a specialized interface called the blood-cerebrospinal fluid (CSF) barrier. The ME blood-CSF barrier is characterized by fenestrated vessels, which are highly permeable to blood-borne molecules. It is also composed of tanycytes, which are specialized hypothalamic glial cells that line the floor of the 3rd ventricle and are joint together by tight-junction complexes to create a physical barrier with a typical honeycomb structure that prevents the diffusion of molecules from the ME parenchyma to the rest of the brain via the CSF. The gut microbiota is a complex and dynamic community of bacteria living within the gastrointestinal tract of the host. It is now well established that the gut microbiota plays an essential role in maintaining host energy homeostasis. Increasing amount of evidence also suggests that the gut microbiota may affect brain function and development, as well as blood brain barrier integrity. However, whether the gut microbiota influences the structure and function of the hypothalamic blood-CSF barrier is still unknown. To address this question, we examined the structure and function of the hypothalamic blood-CSF barrier using two complementary animal models with altered gut microbiota: the germ-free (GF) mice and mice in which the gut microbiota composition was altered during adulthood using oral administration of a cocktail of antibiotics (ABX). Immunohistochemical labeling and confocal microscopy was used to visualize the organization of the tight-junction protein zonula occludens-1 in relation to the blood-CSF barrier of the ME. Additionally, we assessed the diffusion function of the ME blood-CSF barrier by quantifying the penetration of Evans Blue dye in the hypothalamic parenchyma. The results indicate that the organization tanycytic honeycomb structure is disrupted in GF and adult ABX mice. The structural reorganization of the ME barrier was associated with the altered diffusion of the circulating Evans Blue dye into the parenchyma of the hypothalamus. Together, our results suggest that the gut microbiota plays an essential role in maintaining the structure and diffusion function of blood-CSF in the adult mouse hypothalamus.

Poster number: 57

Title: Microbiota-gut-brain axis in glioblastoma development and therapeutic resistance

Presenting Author: Océane MARTIN

Authors and Affiliations
LAVIELLE Sarah1, DELROT Gauthier1, LILLO Sebastian1, LEMAITRE Manon1, BOMONT Doriane1, PATERAS Ioannis2, NIKOLSKI Macha1, DAUBON Thomas1, MARTIN CB Océane1
1- University Bordeaux, CNRS, IBGC, UMR 5095, 33000 Bordeaux, France;
2- 2nd Department of Pathology, "Attikon" University Hospital, Medical School, National and Kapodistrian University of Athens, 124 62, Athens, Greece
University Bordeaux

Abstract
Glioblastoma (GB) is the most common subtype of glioma in adults. Despite treatments, this cancer still has a very poor prognosis. Recently, the crucial implication of the microbiome-gut-brain axis has been shown in several neurodegenerative diseases, but its role in GB is poorly studied. Therefore, our project aims to understand how modulation of gut physiopathology affects GB development and therapeutic resistance. We first focused on the effects of gut inflammation and microbiota. Then, we also assessed the intratumoral microbiota.
We orthotopically injected GB stem cells in different mouse models: DSS-treated mice to induce gut inflammation and antibiotics-treated mice to assess the effect of bacterial depletion. Tumor growth was assessed by bioluminescence, and the colon and brain were collected for histological assessment. Microbiota composition was determined by metagenomic analysis. Intratumoral microbiota was assessed by RNAscope, sequencing and culturomics methods.
Our results showed that DSS-treated mice had a higher GB growth than non-treated mice. Moreover, the recurrence after treatment was higher in mice bearing gut inflammation. Interestingly, we also observed on DSS-treated mice that the GB-bearing mice had lower intestinal inflammation than the control. GB growth was also associated with microbiota modifications and systemic metabolite changes, which were restored by treatments. Then, we observed that depletion of gut bacterial microbiota leads to decreased GB growth and a decreased infiltration of immune cells in the tumoral microenvironment. Finally, we were able to detect the presence of bacteria in the tumor, and we are currently characterizing the observed populations.
Altogether, our results support the bidirectional communication between the gut and the brain in the context of GB. Alteration of gut physiopathology strongly impacts GB development and therapeutic resistance. This connection suggests that targeting the gut microbiome could slow down GB progression and/or improve treatment efficacy.

Poster number: 58

Title: Characterization of gut microbiota alteration associated with eating disorders

Presenting Author: David RIBET

Authors and Affiliations
Achamrah N, Breton J, ... , Déchelotte P, Tavolacci MP, Ribet D.
Univ Rouen Normandie, INSERM, Normandie Univ, ADEN, UMR 1073 , Rouen, France
Université de Rouen - 22 Bd Gambetta - 76000 ROUEN - FRANCE

Abstract
Eating disorders are serious pathologies of adolescence and young adulthood, and represent a major public health issue. The etiology of eating disorders is complex and involves various biological, psychological and socio-cultural factors. The gut microbiota could be one of the factors involved in eating disorders. To gain a better understanding of the potential role of this microbiota in eating disorders, we compared the composition of the fecal microbiota of patients suffering from anorexia, bulimia or binge-eating disorder with that of healthy subjects.
We have included in our study 35 patients with anorexia nervosa, 18 patients with bulimia nervosa and 128 patients with binge eating disorder, as well as 73 matched healthy individuals. The composition of the gut microbiota was determined for each patient and correlated with the presence of comorbidities, such as functional gastrointestinal disorders or anxiety/depression.
We observed that each type of eating disorder is associated with a specific gut dysbiosis. We observed, for example, a decrease in the level of Agathobacter and Romboutsia in anorectic patients. Patients with binge-eating disorder exhibit, in contrast, a decrease in Akkermansia, Oscillibacter, Alistipes, Bilophila and Turicibacter, and an increase in Actinomyces, Streptococcus and Eggerthella. In addition, we identified several taxa such as the Acidaminococcus genus, whose levels correlate with the occurrence of anxiety/depressive-like symptoms in patients with eating disorders.
Our work demonstrates for the first time that each type of eating disorder is associated with a specific dysbiosis. We identified specific bacterial patterns that depend on the type of eating behaviour and psychological characteristics of the patients. The predictive value of these patterns on the duration of the pathology or on the probability of relapse remains to be determined. These results now pave the way for the study of the causal role of the microbiota in the development or chronicity of eating disorders.

Poster number: 59

Title: THE ENTERIC NERVOUS SYSTEM: A TARGET OF FECAL EXTRACELLULAR VESICLES IN AUTISM

Presenting Author: Martial CAILLAUD

Authors and Affiliations
B Ganachaud, M Caillaud, M Moreau, J Marchix, M Neunlist, H Boudin
1. Nantes Université, INSERM, TENS, The Enteric Nervous System in Gut and Brain
1 rue Gaston Veil, 44035 Nantes

Abstract
Autism Spectrum Disorders (ASD) are characterized by difficulties in social interaction and communication, and by restricted interests. Although ASD are associated with neuronal connectivity abnormalities in the brain, gastrointestinal disorders are frequently observed along with gut microbiota dysbiosis. In addition, transfer of microbiota from patients to mice results in behavioral and digestive symptoms relevant to ASD, suggesting a contribution of the microbiota in the pathophysiology of ASD. However, the mechanisms of action of the microbiota on the gut and brain are still largely unknown but may involve extracellular vesicles (EVs). EVs are signaling cargo that function as mediators of intercellular and inter-organ communication. Their potential role in microbiota-host interactions has never been studied in the context of ASD.
The hypothesis of this study is that fecal EVs (f-EVs), that contain EVs produced by gut microbiota, are mediators between the microbiota and the enteric nervous system (ENS). By targeting the ENS, EVs could contribute to the gastrointestinal disorders associated with autism. The aim was to study the impact of f-EVs on enteric neuron activity and connectivity.
We isolated f-EVs from the stool of controls and ASD patients and applied them to cultured rat enteric neurons. Their impact on neuronal activity and connectivity was assessed by Ca2+ imaging and synaptic protein expression/distribution, respectively. Acute treatment with f-EVs from ASD patients induced in enteric neurons an immediate increase of intracellular Ca2+ that was more sustained than with f-EVs from controls. A longer-term treatment for 48 h induced a more sustained rise in intracellular Ca2+ evoked by veratridine, an activator of voltage-gated sodium channels, for f-EVs from ASD patients than from controls. No difference was observed in the expression of the synaptic proteins synapsin 1 and PSD95, but we found an increase in the number of synaptic clusters containing PSD95 in enteric neurons treated with f-EVs from ASD patients compared to controls. PSD95 is a scaffolding protein involved in the recruitment of the neuronal nitric oxide synthase (nNOS), an enzyme responsible for nitric oxide (NO) production. Analyses of nNOS expression indicated that f-EVs from ASD patients, compared to controls, induced an increased nNOS expression and in the number of nNOS neurons.
In conclusion, we found that f-EVs from ASD patients modify enteric neuron activity and nNOS expression. These results suggest that the neuronal NO pathway might be a target of gut microbiota in ASD.

Poster number: 60

Title: Microbiome shapes postnatal development of the choroid plexus and brain volume

Presenting Author: Ana Blas Medina

Authors and Affiliations
Blas-Medina A., Josephides J., Ali-Mousa S, Mirabeau O, Travier L, Deczkowska A.
Brain-Immune Communication Unit, Institut Pasteur
Institut Pasteur Metchnikoff building 67-02-06 25-28 Rue du Dr Roux 75015 Paris,

Abstract
Postnatal development is a critical window of increased brain circuit remodeling coinciding with colonization of mucosal surfaces by microbial communities. A growing body of evidence suggests that perturbations of the microbiome-brain communication in the perinatal window are a risk factor for neurodevelopmental disease onset. Holding a strategic position to mediate such microbiome-brain crosstalk, the choroid plexus (CP) shapes brain function through the production of cerebrospinal fluid (CSF) and completes its maturation postnatally, yet the extent of microbial product influence on this process remains to be studied. Using a transcriptomic approach, we show that CP development was accelerated and altered between postnatal days 10 and 15 when microbial factors are absent, coinciding with the dysregulation of genes involved in extracellular matrix organization, cell proliferation, stress pathways, and glucocorticoid responses. Furthermore, our study revealed abnormalities in brain and third ventricle volume in adult germ-free mice, likely responding to changes in CSF flow or composition. Overall, our findings shed light on a new pathway of microbiome-brain communication, suggesting that the cognitive abnormalities observed in adult germ-free mice may be partially caused by alterations in postnatal CP development. Therefore, early interventions aimed at modifying the microbiome-CP crosstalk may help prevent neurodevelopmental disease onset.

Poster number: 61

Title: Immunoneutralization of enterobacterial ClpB protein protects mice against activity-based anorexia

Presenting Author: Benjamin Thomas

Authors and Affiliations
Benjamin Thomas 1, Emilie Lahaye 1, Lisa Wallart 1, Jean-Luc do Rego 2, Jean-Claude do Rego 2, Sergueï O. Fetissov 1
1 : INSERM 1239, Neuroendocrine, Endocrine and Germinal Differentiation and Communication Laboratory, University of Rouen Normandie, 76000, Rouen, France. 2 : Animal Behavioral Platform SCAC, University of Rouen Normandie, INSERM US51, CNRS UAR 2026, HeRacLeS, Institute for Research and Innovation in Biomedicine (IRIB), 76000 Rouen, France
25 rue Lucien Tesnière, Mont Saint Aignan

Abstract
BACKGROUND AND OBJECTIVES:
Anorexia nervosa (AN) is an eating disorder characterized by food self-deprivation and excessive physical activity. Development of effective biopharmacological treatment of AN is hampered by insufficient knowledge of its pathophysiology. Recently, a key role of ClpB, a 96 kDa heat-shock enterobacterial protein in the origin of AN was proposed, based on ClpB molecular mimicry with α-MSH, an anorexigenic neuropeptide. To further validate this hypothesis, in the present study we determined if immunization against ClpB can influence the development of activity-based anorexia (ABA) in mice, an animal model of AN.

METHODS:
4 groups of C57Bl6- male mice were used. 2 groups were immunized with 25 µg of E. coli ClpB in an adjuvant. Prior to immunization, to induce immune tolerance for ClpB, one group received ClpB protein (25 µg/mL) in drinking water for 10 days. In two control groups, mice received the adjuvant only or 0.9% NaCl. All mice were placed in individual Biodaq cages equipped with a running wheel and were exposed to an ABA protocol consisting of progressive decrease of food access to 4 h/day during the last 8 days. Plasma levels of ClpB, α-MSH and their reactive IgG were determined by ELISA. Surface plasmon resonance was used to measure IgG affinity for these molecules.

RESULTS :
As expected, ClpB immunized mice showed increased production of anti-ClpB and α-MSH-reactive IgG, characterized by their lower affinity. Importantly, the ClpB and α-MSH antibody production was abolished in mice orally tolerized with ClpB. Moreover, plasma levels of ClpB protein was increased only in ClpB-tolerized mice. Behavioral analysis revealed higher food intake and reduced food anticipatory physical activity in ClpB immunized mice as compared to the control groups resulting in a significant reduction of body weight loss during the 4 h- food restriction period.

CONCLUSIONS :
Taken together, these results demonstrate that immunoneutralization of bacterial ClpB efficiently protects mice from ABA suggesting a novel therapeutic strategy for AN.

Acknowledgement: The study was supported by the EU ERANET Neuron and ANR, France MiGBAN project, Nr 01EW1906A “Microbiome Gut-Brain Axis in Anorexia Nervosa” and by the Transversal Microbiota Program (PTM-2) of Inserm, France.

Poster number: 62

Title: Targeted proteomic approach to identify oxytocin-like bacterial proteins in human gut microbiota as putative biomarkers of autism spectrum disorders

Presenting Author: Lisa Wallart

Authors and Affiliations
Lisa Wallart 1, Emilie Lahaye 1, Julie Hardouin 2, Sarah Kadzielski 3, Dario Siniscalco 4,5, Geraldine Leader 6 and Sergueï O. Fetissov 1
1Regulatory Peptides - Energy Metabolism and Motivated Behavior Team, Neuroendocrine, Endocrine and Germinal Differentiation and Communication Laboratory, Inserm UMR1239, University of Rouen Normandie, 76000, Rouen, France; 2HeRacLeS-PISSARO, INSERM US 51, CNRS UAR 2026, University of Rouen Normandie, 76000, Rouen, France; 3Department of Pediatrics, Harvard Medical School, Boston, MA, USA; 4Department of Experimental Medicine, University of Campania, 80138 Naples, Italy; 5European Biomedical Research Institute of Salerno (EBRIS), 84125 Salerno, Italy; 6Irish Centre for Autism and Neurodevelopmental Research (ICAN), Department of Psychology, National University of Ireland Galway, University Road, Galway, Ireland.
25 rue Lucien Tesnière 76130 Mont-Saint-Aignan

Abstract
Background and objective: Autism (ASD) is a neurodevelopmental disorder that appears in early childhood lacking specific biomarkers and efficient treatment. The gut microbiota has recently become a topic of research of putative biomarkers in neuropsychiatric disorders including ASD. In this study, we hypothesized that the human gut microbiota produces proteins homologous to oxytocin (OT), a neuropeptide involved in regulation of social behavior and affected in ASD.
Method: We applied a targeted proteomic approach to identify microbiota-derived OT-like proteins in fecal samples of children with ASD and healthy controls (HCs). Total bacterial protein was extracted from cultured fecal microbiota samples and separated by 1- or 2-dimensional gel electrophoresis followed by immunodetection with polyclonal oxytocin antibodies. Positive spots were identified by mass-spectrometry (MS).
Results: By comparing the individual samples from both study groups, we found that all of them consistently displayed an OT-like immunopositive protein spot at about 70 kDa. Moreover, one OT-positive spot at about 55 kDa was present only in female HCs. The MS identification of OT-positive spots has yielded putative protein targets. The identified OT-like protein targets are currently validated for their specificity.
Conclusion: For the first time, we revealed a constitutive production of OT-like bacterial proteins in human gut microbiota suggesting their physiological role in the oxytocinergic system. Moreover, the presence of such OT-like bacterial proteins seems to be sex-specific and deficient in the microbiota of ASD patients suggesting that such proteins can become both biomarkers and therapeutic targets of ASD.
Acknowledgement: The study received support from “GEMMA” project (ID 825033) funded by the European Commission in the frame of the Horizon 2020 program (call H2020-SC1-BHC-03-2018) and Inserm PTM2 Program, France.

Poster number: 63

Title: IDENTIFICATION OF OXYTOCIN-ANTIGEN MIMETIC PROTEIN IN LACTOBACILLUS AND ITS VALIDATION IN AN ANIMAL MODEL OF AUTISM

Presenting Author: Emilie LAHAYE

Authors and Affiliations
Emilie Lahaye1, Marion Nicol1, Philippe Chan2, Arnaud Arabo3, Julie Maucotel3, Axelle Houssier3, Nicolas Chartrel1, Sergueï O. Fetissov1
1Neuroendocrine, Endocrine and Germinal Differentiation and Communication Laboratory, University of Rouen Normandie, INSERM 1239, 76000, Rouen, France. 2Proteomic Platform PISSARO, University of Rouen Normandie, INSERM US51, CNRS UAR 2026, HeRacLeS, 76000 Rouen, France. 3Center for Biological Resources, University of Rouen Normandie, INSERM US51, CNRS UAR 2026, HeRacLeS, 76000 Rouen, France.
25 Rue Lucien Tesnière

Abstract
Oxytocin (OT) is a neuropeptide playing a key role in promoting social interactions. Deficient OT signaling was associated with autism spectrum disorders (ASD). Recently we showed that immunoglobulin G (IgG) serves as an OT carrier protein modulating OT receptor activation. In this study, we tested our hypothesis that OT-binding IgG can be stimulated by homologous antigens produced by commensal gut bacteria and, therefore, can modulate social and anxiety-like behavior relevant to ASD.
Targeted proteomic approach using OT-antibodies was applied to the total proteome of Lactobacillus salivarius. Mass spectrometry-identified OT-like target proteins have been synthesized and used for immunization of BTBR mice, a genetic model of ASD. Effects of immunization on social and repetitive behavior was analyzed using 3-chambers and self-grooming tests, respectively, and on anxiety by the open-field and elevated plus maze tests. Plasma levels of OT-reactive IgG and hypothalamic concentration of OT peptide were measured by ELISA.
An about 50 kDa OT-like positive protein spot was consistently detected in the proteome of L. salivarius resulting in identification of 3 OT-like candidate proteins with molecular weight of 48, 43 and 50 kDa, among which only the 48-kDa protein displayed OT-like immunoreactivity. Immunization of BTBR with the corresponding recombinant proteins resulted in increased plasma levels of OT-reactive IgG by all 3 proteins but increased hypothalamic OT concentration only by the 48 kDa protein. Behavioral tests revealed significantly reduced repetitive and locomotor behavior effects of all 3 OT-like proteins but increased sociability and reduced anxiety only by the 48-kDa protein.
The study identified an oxytocin-antigen mimetic protein produced by Lactobacillus salivarius which can improve OT-like signaling and OT-mediated behavior suggesting its putative application as a new therapeutic strategy against ASD.
Acknowledgement: The study received support from “GEMMA” project (ID 825033) funded by the European Commission in the frame of the Horizon 2020 program (call H2020-SC1-BHC-03-2018) and Inserm PTM2 Program, France. L. salivarius strain was provided by Targedys SA, France.

Poster number: 64

Title: Discovery of novel cellular mechanisms of vascular barrier enhancement in response to bacterial metabolites originating from healthy gut microbiota

Presenting Author: Lola Savouré

Authors and Affiliations
Lola Savouré (1), Alix Decobert (1), Sylvie Demignot (1,2), Diego Garcia-Weber (1,2)
1: Centre de Recherche Saint-Antoine, Sorbonne Université, INSERM UMR_S 938, Paris, France (« Microbiota, Intestine and inflammation » team, Prs. Philippe SEKSIK / Harry SOKOL) Ecole Pratique des Hautes Etudes (EPHE), Paris Sciences et Lettres University (PSL), Paris, France 2:
27 rue de Chaligny 75012 Paris

Abstract
The intestinal microbiota plays a crucial role in the maintenance of host homeostasis. Its alteration underlies the development of several inflammatory diseases not only at the local intestine level, but also at distant sites in the body. It has been well established that proinflammatory metabolites, mainly produced by the altered microbiota, can cross the gut-vascular barrier, enter the systemic circulation and reach distant sites, thus promoting inflammation in many other organs. On the other hand, a growing body of evidence also shows the existence of many classes of anti-inflammatory bacterial metabolites, such as short-chain fatty acids (SCFA), usually released by members of the healthy microbiota, which are lost during dysbiosis. Interestingly, although some of these metabolites cross the gut-vascular barrier and reach the systemic circulation, their precise effect on the integrity of the different vascular endothelia is still poorly understood. In this sense, this project aims to identify precise bacterial metabolites of intestinal origin that limit the disruption of different vascular endothelia and to decipher the cellular signaling pathways that drive their barrier-enhancing effects in endothelial cells. We performed a screen of SCFA on primary HUVEC endothelial cells with the xCELLigence system and identified 3 SCFA with significant endothelial barrier-function enhancing properties under homeostatic conditions: butyrate, propionate and valerate. We have shown that cells treated with these metabolites enhance the formation of reticular adherens junctions. Our results also suggest that treatment with these SCFA limits endothelial disruption induced by the pro-inflammatory cytokine TNFα. We are currently investigating the cellular mechanisms that drive these TNFα-dependent and independent effects. This project will allow to propose new therapeutic tools to limit inflammation (bacterial metabolites) and also new therapeutic targets (cellular mechanisms) to treat inflammatory diseases.

Poster number: 65

Title: GASTROINTESTINAL ALTERATIONS IN A MOUSE MODEL OF THE OKUR-CHUNG NEURODEVELOPMENTAL DISORDER

Presenting Author: H Rebholz

Authors and Affiliations
Ballardin D1, Cruz Gamero JM1, Waqar W1, Matta S2, Abo-Shaban T2
Hill-Yardin E2 and Rebholz H1,3,4
Ballardin D1, Cruz Gamero JM1, Waqar W1, Matta S2, Abo-Shaban T2
Hill-Yardin E2 and Rebholz H1
1Université Paris Cité, Institute of Psychiatry and Neuroscience of Paris (IPNP), INSERM U1266, Paris, France, 2RMIT, Melbourne, Australia 3GHU-Paris Psychiatrie et Neurosciences, Hôpital Sainte Anne, Paris, France, 4Center of Neurodegeneration, Faculty of Medicine, Danube Private University, Krems, Austria

Abstract
Monoallelic de novo mutations in the gene CSNK2A1 encoding the catalytic subunit of the S/T kinase CK2 are linked Okur-Chung neurodevelopmental disorder (OCNDS). The symptom profile of OCNDS includes stereotypic movements, learning disabilities, sensory challenges and sociability deficits (1, 2). Gastrointestinal (GI) dysfunction, such as chronic constipation, diarrhea and bloating is common in various neurodevelopmental disorders and was implicated in the development/severity of ASD symptoms. OCNDS patients are particularly affected: at least 58% of them were reported to have GI issues, while a recent survey by the CSNK2A1 Foundation suggested an even higher prevalence of 87%.
It has been shown for several pathologies, including autism spectrum disorders that inflammation in the gut can influence brain function and behavior. We have studied a knockin mouse line harboring a hotspot mutation in the activation segment of CK2a, representing a third of all OCNDS patients, CK2aK198R, and found that it exhibits significant alterations in gut morphology (reduction in intestinal crypt area, reduced circular muscle thickness in the colon), reduction of endothelial mucus production (reduced number of mucus secreting Goblet cells), and an altered gut-associated lymphoid system (reduced number of Peyer's patches). Plasma cytokine concentrations were almost exclusively upregulated.
In the brain, microglial marker Iba1 showed a reduced ramification, indicative of activated microglia in the hippocampus of knockin mice. These results suggest that gastrointestinal alterations are part of the OCNDS pathology. Further studies are required to determine whether the gut microbiome and modulation thereof may open novel therapeutic avenues for OCNDS.

Poster number: 66

Title: Multi-omics analysis of gut microbiota unveils microbial functions alterations associated to Parkinson's disease.

Presenting Author: Rémy Villette

Authors and Affiliations
Rémy Villette(1), Polina Novikova(1,) Julia Ortis-Sunyer(1), Velma Aho(1) , Viacheslav Petrov(1), Oskar Hickl(1), Charlotte De Rudder(1), Benoit Kunath(1), Susheel Bhanu Busi(1), Sebastian Schade(2), Annette Janzen(3), Wolfgang Oertel(3), Cédric Laczny(1)
1 Luxembourg Center of Systems Biomedicine, University of Luxembourg, Belval, Luxembourg
2 Movement disorders and Parkinson's Disease, Paracelsus-Kliniken Deutschland GmbH, Osnabruck, Germany
3 Department of Neurology, Philipps-University Marburg, Marburg, Germany

Abstract
Objective: Microbiome composition has been associated with Parkinson's disease (PD) at multiple stages. However, these associations are mainly studied using genomics technologies where the functional capacities of microbes are not fully investigated. In this study, we aim at describing the microbiome functions associated with PD using multi-omics technologies.
Methods: Using integrated multi-omics analysis, we performed deep phenotyping of the gut microbiome in a cross-sectional cohort of 49 healthy control (HC), 28 iRBD and 46 PD patients. Stool samples were phenotyped using shotgun metagenomics (MG), metatranscriptomics (MT), metaproteomics (MP) and metabolomics (MB).
Results: The gut microbiome showed no clear differences between groups both in alpha and beta-diversity for MG and MT taxonomic composition but differences in MT functions and MB. Roseburia, Blautia and Eubacterium were however reduced in PD for MT taxonomy. We observed a decrease in glycerol which correlated with Roseburia abundance and an increase beta-glutamate for PD that was correlated with Akkermansia and Methanobrevibacter abundance. We observed an increase and a decrease in diversity of gene expression in PD for Methanobrevibacter and Roseburia, respectively. Interestingly, we found important changes in gene expression that were related to glutamate transformation, chemotaxis-flagellin assembly and methane metabolism. Finally, we witnessed a decrease in functional diversity for Roseburia, Eubacterium and Blautia, while Methanobrevibacter gained functional diversity.
Conclusions: MT and MB represented the most powerful omics to differentiate the gut microbiome between HC and PD. Microbial functions appeared to be altered in PD context, especially for Roseburia and Methanobrevibacter that seemed to have contrary links to PD.