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Poster 1

A Degradable Nanofibrous Scaffold Of Poly(E-Caprolactone-Co-Lactide)For Annulus Fibrosus Regeneration

Mansoor CHAABAN

A Degradable Nanofibrous Scaffold Of Poly(E-Caprolactone-Co-Lactide) For Annulus Fibrosus Regeneration

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The intervertebral disc herniation is a significant cause of low back pain, accounting for up to 32% of cases. Previously, we showed the potential of an implant made of poly(ε-caprolactone) (PCL) for AF defect closure. However, the slow in vivo degradation of PCL might hinder AF regeneration. Here, we hypothesized that accelerating PCL degradation kinetics by incorporating a lactide polymer known for its rapid degradation enhances AF regeneration.

A Poly(ε-caprolactone-co-lactide) (PCLA), was synthesized with various molar percentages of lactide (10, 20, and 30 %) and structures (copolymer or blend). These polymers were electrospun into sheets of aligned nanofibers. Then, a multi-lamellar 3D implant was assembled by stacking the PCLA sheets and incorporating an anchoring system (wings that are glued on the adjacent vertebrae). The thermal, mechanical, and structural properties of the novel polymers were analyzed, including the impact of gamma-irradiation sterilization and their in vitro degradation over 6 months. Next, the cytocompatibility of the implant was assessed in vitro with ovine AF cells and ex vivo using a bovine tail disc model. Finally, the implant's regenerative potential was evaluated in a sheep model of simulated herniation (n=4).

PCLA sheets had a Young's Modulus ranging from 20 to 37 MPa, close to that of AF tissue. Moreover, gamma irradiation (25 kGy) caused a Young's Modulus increase by 21-31 MPa when lactide > 20%. The 6-month in vitro degradation study of PCLA showed a molar mass loss of 70 ± 0.4% for the copolymer and 53 ± 17% for blends. Furthermore, scanning electron microscopy revealed fiber breakage in the copolymer. Furthermore, PCLA sheets guided the in vitro alignment and proliferation of ovine AF cells and maintained the expression of AF markers for up to 2 weeks (collagen type I and type II). Ex vivo, the multi-lamellar implant was maintained within a full-thickness annular defect (4mm biopsy punch) of bovine tail discs during 4 weeks of culture, and initial cell infiltration into the implant was observed. In vivo, despite instances of implant dislocation, disc hydration was preserved at one month. Interestingly, substantial cellular infiltration and AF-like tissue ingrowth were evidenced within the implant layers. The long-term repair efficacy and implant degradation at 1 month and 6 months were then evaluated in a sheep model of AF defect. We demonstrated that the copolymer implants degraded faster than the PCL or Blend ones.

Poster 2

Bioconjugation of the capsid of adeno-associated viruses for osteoarthritis treatment by gene therapy

Héloïse Delépée

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This project focuses on chemically engineering adeno-associated viruses (AAV) through bioconjugation to enhance specificity toward cartilage tissue to treat osteoarthritis.

Cartilage is a non-vascularized tissue in which chondrocytes, the sole extracellular matrix (ECM) producing cells, generate a highly negatively charged matrix due to its major component, glycosaminoglycans. In osteoarthritis, chondrocyte dysfunction leads to cartilage degradation, affecting over 500 million people worldwide. Despite its prevalence, osteoarthritis remains incurable, due to the challenges of delivering therapeutic agents to chondrocytes embedded in the dense ECM.1

AAV are promising gene therapy vectors, as demonstrated by four ongoing clinical trials targeting cartilage. However, their broad tropism and limited ability to reach targeted cells reduce their efficiency. To address these limitations, our team developed a chemical modification strategy to enhance AAV specificity and efficacy for targeted cells or tissues.2

The AAV capsid is chemically modified in two steps: biotin ligands are bioconjugated to capsid lysines, followed by non-covalent binding of avidin, a positively charged protein. This modification exploits the strong biotin-avidin interaction and imparts an overall positive charge to the vector. This charges facilitates electrostatic interactions with the negatively charged ECM, enhancing vector retention, adhesion, and penetration into deeper cartilage layers.3

Preliminary results demonstrate that these engineered AAVs efficiently transduce healthy primary chondrocytes from mini-pigs and beagles, as well as human osteoarthritic chondrocytes. In cartilage explants, where cells remain within their native matrix, modified vectors achieved up to twofold higher transduction efficiency compared to unmodified AAVs. Ongoing in vivo studies in mice are assessing biodistribution and cartilage targeting.

This approach represents a breakthrough for cartilage-targeted gene therapy, providing a promising pathway toward clinically viable treatments for OA.

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Poster 3

Use of a plant-based biomaterial for cartilage engineering

Cécile Demey

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Cartilage repair remains a major clinical challenge, as this tissue has very limited self-regeneration capacity. Degenerative joint diseases, trauma, and congenital malformations result in irreversible cartilage loss, often leading to pain, impaired mobility and reduced quality of life. Current surgical solutions such as autologous grafts are limited by donor site morbidity, poor integration, and suboptimal long-term outcomes. Innovative strategies in tissue engineering are therefore urgently needed to address musculoskeletal disorders.
In this project, we investigate the potential of a decellularized plant-based biomaterial, derived from celery, as a scaffold for cartilage regeneration. This natural matrix is biocompatible, abundant, and inexpensive, while its intrinsic microarchitecture offers promising cues for tissue remodeling due to its high Young's modulus after decellularization. Several cell types are being evaluated for their chondrogenic potential on this scaffold, including human mesenchymal stem cells and auricular perichondrium progenitor cells.
Preliminary results indicate that perichondrium progenitor cells outperform mesenchymal stem cells in terms of cartilage matrix deposition when seeded onto the decellularized celery scaffold. In parallel, protocols for biomaterial decellularization and culture handling are being optimized to improve reproducibility and facilitate manipulations. Efforts are also underway to refine the seeding technique in order to achieve a uniform cell distribution within the celery microarchitecture, expected to enhance tissue homogeneity and mechanical performance.
Molecular analyses further support these findings: RT-qPCR results show a tendency toward increased expression of chondrogenic markers (SOX9, COL2, and ACAN) compared to control culture conditions. Ongoing validation of engineered constructs includes in vivo implantation in a small animal model monitored by MRI, as well as histological and immunohistological staining (collagen type II, aggrecan, elastin), and biomechanical testing to assess stiffness and elasticity relative to native cartilage.
This work represents the first attempt in France to use a decellularized plant scaffold for cartilage engineering. By providing an alternative to synthetic or animal-derived biomaterials, this approach could open new avenues for sustainable, cost-effective, and patient-specific regenerative strategies. Ultimately, this project contributes to the ROAD to 2030 vision of transforming musculoskeletal care through innovative tissue engineering solutions that may reduce the burden of rheumatic and degenerative diseases.

Keywords: cartilage regeneration, tissue engineering, decellularized plant biomaterials, perichondrium progenitor cells, chondrogenic markers, regenerative medicine

Poster 4

Intestinal microbiota: a factor in chronic pain in rheumatoid arthritis?

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Introduction:
Recent studies highlight the central role of the vagus nerve (VN) in rheumatoid arthritis (RA), with reduced vagal activity in patients and vagotomy identified as a risk factor for RA. This phenomenon, linked to the immunomodulatory properties of the VN, could also be explained by its role in the gut-brain axis. Dysbiosis is present in RA. Thirty percent of RA patients suffer from persistent pain even after inflammation has been controlled. The autonomic nervous system (ANS) dysfunction observed in these patients has been associated with pain. Preclinical and clinical studies suggest that stimulation of this nerve could relieve chronic pain. Our hypothesis is that dysbiosis, particularly through its effect on the ANS, contributes to chronic pain in RA.

Materials and Methods:
Fecal microbiota transfer (FMT) was performed using intestinal microbiota (IM) from patients with active RA (aRA-FMT), patients in remission with persistent pain (cpRA-FMT), patients in remission without pain (rRA-FMT), or healthy controls (HC-FMT) in male C57/Bl6 mice. The impact of FMT was assessed on ANS function using telemetry-based heart rate variability (HRV) analysis, as well as on mechanical sensitivity (Von Frey test) and anxiety-depressive behaviors (Sucrose Splash Test (SST)). Statistical analyses were performed using Mann-Whitney tests.

Results:
HRV analysis showed that aRA-FMT altered cardiac parasympathetic activity in mice compared to HC-FMT ($p < 0.0001$, $n = 34$/condition), mimicking the VN dysfunction observed in RA. In addition, the same alteration in parasympathetic activity was present in cpRA-FMT but absent in rRA-FMT. An increase in mechanical sensitivity was also observed for aRA-FMT ($n = 10$ RA-FMT mice; 10 HC-FMT). For SST, a reduction in grooming time was observed ($p = 0.0146$, $n = 16$ aRA-FMT mice; 13 HC-FMT), reflecting depressive behavior in RA-FMT mice.

Conclusion:
Our results suggest that the gut microbiota (GM) of RA patients may contribute to ANS dysfunction. In addition, the GM of patients in remission but with chronic pain exerts a comparable modulation, which is not found in patients in remission without pain. This influence appears to contribute to altered tactile sensitivity and the onset of depressive behaviors observed in vivo. Thus, targeting the GM-VN axis represents a promising therapeutic avenue for the management of chronic pain in RA.

Poster 5

Evaluation of cannabidiol toxicity on osteoarthritic human joint cells

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Introduction
Osteoarthritis (OA) is the most common joint disease, characterized by progressive cartilage degeneration and moderate inflammation of the synovial membrane, causing chronic pain and functional disability. The endocannabinoid system, expressed in joint tissues, could play a role in modulating pain and inflammation, making its ligands potential therapeutic target. Because of these potential effects, cannabidiol (CBD), a non-psychoactive cannabinoid, is very popular among patients with OA, despite a lack of preclinical and clinical data. Moreover, no data about its safety on joint tissues is available. The aim of this study was to evaluate in vitro the toxicity of CBD on human joint cells.

Materials and methods
Chondrocytes and synoviocytes were isolated from cartilage and synovial membrane obtained during total knee replacements from different patients (n= 3). Primary monolayer cells were seeded in 96-well plates and then exposed or not to increasing concentrations of CBD (100 nM to 1000 µM) for 6 hours or 24 hours. Mitochondrial activity (MTT assay) and cell viability (LDH activity) were then measured at the end of treatment and every 24 hours until 72 or 96 hours. Results were compared to the control without CBD with two-way ANOVA and Tukey's post hoc tests.

Results
Low concentrations (≤30 µM) did not induce significant cytotoxicity on chondrocytes or synoviocytes compared to the control (vehicle only) with a near survival rate greater than 80% at 72 or 96 hours. In contrast, CBD concentrations of 100 µM, 300 µM, and 1000 µM caused a significant increase in cell death and a decrease in mitochondrial activity, with a dose- and time-dependent effect reaching approximately more than 90% cell death at the highest dose (1000 µM) for both cell types after only a 6-hour treatment and were completely cytotoxic after 24 hours of treatment for both cell types.

Discussion and conclusion
Our results highlight the significant toxicity of CBD at concentrations above 100 µM on human joint cells, whereas concentrations below or equal to 30 µM appear to be well tolerated. This study is an essential first step in defining a potential therapeutic margin for CBD in osteoarthritis. It suggests caution regarding high-dose intra-articular use and highlights the need to investigate its anti-inflammatory and analgesic effects at low doses. Further studies are essential to assess the benefit/risk balance and clarify the conditions for safe use of CBD in OA.
« avec le soutien financier de la Société Française de Rhumatologie ».

Poster 6

Degradation processes of carbonate and silicate-doped hydroxyapatites: an in vivo study.

Morgane Margottin

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Calcium phosphate-based bioceramics, such as hydroxyapatite (HA) and β-tricalcium phosphate (β-TCP), are widely used as bone substitutes due to their chemical similarity to bone mineral. Doping HA with bioactive ions is a promising strategy to modulate the properties of the HA-based bioceramics and, thus improve their performance. More specifically, carbonate ions, the most abundant ion substitute in bone mineral, promote HA resorption when incorporated into the ceramic lattice. The silicate ion is also of interest because its bioavailable form, $Si(OH)_4$ has been shown to stimulate osteogenic differentiation and bone mineralization. Silicate-doped hydroxyapatites (SiHAs) have been extensively studied but remain as poorly soluble as HA. Co-doping HA with both silicate and carbonate ions could combine the advantages of both by allowing optimal degradation of the material while enhancing bone regeneration. This combined doping strategy remains largely unexplored and the degradation potential of monophasic carbonate and silicate-doped HA (CSiHA) has never been evaluated. Therefore, the aim of this study was to evaluate the degradability of CSiHA bioceramics and to identify the primary mechanisms involved, such as dissolution or osteoclast-mediated resorption.
Granules of five ceramic compositions (HA, Si0.4HA, C0.8HA, C0.8Si0.4HA, and β-TCP; 200-500µm) were implanted subcutaneously in mice to assess degradation in a non-osteogenesis environment. µCT scans over 6 months showed stable ceramic volumes, indicating minimal dissolution. To evaluate ceramic degradation by immune cells and OCs, ceramics were implanted with MSCs subcutaneoulsly in mice as this model induces bone formation and OC recruitment. After 8 weeks, the resorption rates were negligible for HA and SiHA, 8% for CHA, 23% for CSiHA, and 30% for β-TCP. Gene expression analysis of macrophages at 7 and 14 days post-implantation further revealed that apatites regulated inflammation as M1 markers decreased (Tnf, Il1b) and M2 increased (Il10); whereas bTCP increased M1 markers (Tnf, Il1b). Besides, osteoclastic genes (Ctsk, Car2, Rank) were downregulated for CSiHA, besides strong resorption observed in SEM images of explanted granules for this specific group. In summary, our study showed that co-doping HA with carbonate and silicate enhances apatite degradation by osteoclasts, to a greater extent than carbonate doping. Lastly, β-TCP was found to promote M1 pro-inflammatory macrophages, which may further enhance osteoclastic activity.

Poster 7

The murine MIA model: a sex-inclusive and predictive model of osteoarthritis?

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Osteoarthritis (OA) is the most common musculoskeletal disease, affecting more than 528 million people worldwide according to the World Health Organization. Patients experience joint pain that severely reduces their quality of life. Female sex is a major risk factor: after the age of 55, almost 75% of patients with OA are women. Yet, most animal models fail to reflect this sex bias. For instance, in murine models of post-traumatic OA, male mice generally develop more severe joint damage, such as cartilage degradation or bone remodeling, which has led to the predominant use of males in preclinical studies. In other models, male and female responses have rarely been compared. The monosodium iodoacetate (MIA) model, known for its inflammatory component inducing both pain and joint damage, has been widely used in rodents of both sexes for over 30 years. However, to our knowledge, no direct comparison between males and females has been reported. The aim of our study is therefore to characterize sex-specific responses in mice in order to better understand the relevance of this model. Tactile sensitivity was assessed using the Von Frey test in sham and MIA-treated male and female mice. Safranin O staining was performed to determine the OARSI score of the joints. In addition, joints were analyzed by micro-CT to identify potential bone remodeling. After 8 weeks of OA, female mice seem to display greater hypersensitivity than males. Similarly, OARSI scores revealed more severe cartilage degradation in females than in males. Bone remodeling were more important in male than in female. In conclusion, the MIA model induces both pain and joint damage in both sexes, with different tissue remodeling according to gender. Despite its artificial nature, the MIA model induces an inflammatory form of osteoarthritis that closely mirrors key features of the human disease, making it potentially more representative than surgical models, particularly in capturing sex differences.

Poster 8

Catechol-O-Methyltransferase Modulates NF-κB-Mediated Inflammation and Catabolism in Osteoarthritis Chondrocytes

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Background:
Osteoarthritis (OA) is a serious, disabling, and painful disease for which therapeutic options remain insufficient. Unpublished data from our laboratory suggest that Catechol-O-Methyltransferase (COMT) may be involved in joint pain and OA. The aim of this study was to elucidate the role of this enzyme in chondrocytes.

Methods:
Human chondrocytes were isolated from femoral head cartilage of OA patients undergoing prosthesis surgery. The impact of IL-1β stimulation on COMT expression and localization was studied by Western-Blot of total or subcellular protein fractions, as well as by immunocytochemistry. In parallel, a COMT-deficient human C28/I2 chondrocyte cell line was generated using CRISPR-Cas9. This model was used to analyze the expression of inflammatory and catabolic markers by RT-qPCR and to study the NF-κB pathway by Western-Blot and immunocytochemistry.

Results:
Human chondrocytes expressed COMT in two isoforms: a 30 kDa membrane-associated form and a 25 kDa soluble form. The membrane form was predominantly detected in nuclear and plasma membrane, whereas the soluble form was nuclear and cytoplasmic. In OA chondrocytes, IL-1β stimulation did not significant alter COMT expression or localization. Interestingly, COMT invalidation in the chondrocyte cell line reduced the expression of inflammatory (IL-6) and catabolic (MMP1, MMP13) markers. This effect correlated with decreased nuclear accumulation of p65-NF-κB in IL-1β stimulated cells, without changes in IκBα phosphorylation.

Conclusion:
This study demonstrated for the first time a direct role of COMT in chondrocytes, though the modulation of the NF-κB pathway reducing inflammatory and catabolic gene expression. These findings suggest that COMT is a key mediator in OA development and a potential therapeutic target, warranting further investigation on its mechanisms in joint tissues.

Key words: COMT, chondrocytes, IL1β, NF-κB

Poster 9

Reconstruction of the cartilage/bone junction area to promote graft integration in osteochondral lesions.

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Background.
Tissue engineering approaches for the treatment of focal osteochondral joint lesions focus primarily on cartilage reconstruction and do little to integrate the bone anchorage zone. One of the difficulties is producing an implant that takes into account the composition and layered architecture of this anisotropic tissue, which gives each zone specific biomechanical properties. The absence of this transition zone could compromise the integrity of the osteochondral structure (alteration of the bio-functionality of the upper layers by bone stimuli), limiting bio-integration at the lesion site. The objectives are (1) to develop bio-inks suitable for reconstructing this pivotal cartilage/bone zone and (2) to reproduce an artificial tidemark to limit the diffusion of mediators between the cartilage layers (deep and calcified) and the subchondral bone plate.

Results.
We worked on a bio-ink dedicated to cartilage reconstruction (sodium alginate based), adapting its composition to obtain our cartilage/bone transition zone. To this purpose, we used micrometric sized hydroxyapatite particles to modify the micro-environment of resident cells (MSCs) to orientate their ECM biosynthesis. This functionalization of the bio-ink induced a noticed modification of the biosynthesis capacities of matrix constituents (decrease of collagen type II and proteoglycans, increase of osteogenic markers expression), which were assessed by histological and immunohistochemical staining.
Our strategy aimed also to incorporate a biosynthetic PCL membrane with controlled porosity, replicating the separation zone (tidemark) between the deep layer and the calcified cartilage. Initial histological analyses indicate that this membrane remains embedded between the different layers of alginate (no delamination).

Conclusions.
Bio-extrusion 3D printing is suitable for producing osteochondral structures with different layers of distinct matrix components by modifying the composition of the bio-ink used. This technology also makes it possible to integrate a temporary physical boundary within the continuously produced structure, thanks to the use of a common base bio-ink that (1) is locally enriched to reproduce cartilage tissue anisotropy and (2) will limit the delamination phenomena observed when different biomaterials are combined.

Poster 10

Osteoporosis: computerized screening and coordinated monitoring to improve patient adherence and limit the number of fractures

Didier Poivret

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Osteoporosis and the fractures it causes in the elderly cost €7 billion annually. Falls alone cost €2 billion. Yet we have screening and effective treatments for osteoporosis and fall prevention. We know the risk factors for falls and how to address them. We also know the risk factors for osteoporosis: early menopause, corticosteroid therapy above 7.5 mg/day, underweight, hormonal treatment for breast or prostate cancer, rheumatoid arthritis, and IBD.

Yet barely 10% of people who suffer a fracture from a fall due to osteoporosis receive a fall risk assessment and a prescription for osteoporosis treatment, not to mention that 50% of them discontinue it after a year. Fall risk assessment is easily performed using the Appchute application, available free of charge, which allows the patient to determine their personal risk of falling by answering a few standardized questions and to give them an attitude to adopt proportionate to their risk. The medical assessment for fall prevention requires medication reconciliation to limit the prescrition of treatments that promote falls, often through self-medication (analgesics, sleeping pills, anxiolytics), an evaluation of antihypertensive treatments, a source of hypotension and therefore falls, an assessment of vision, hearing, and balance on the ground using simple tests such as single-leg support on the ground.

We have, with the Cpts de Briey, implemented an osteoporosis screening program based on risk factors, carried out by pharmacists or midwives. A bone density scan is performed if one or more risk factors are detected and sent to the attending physician for treatment initiation according to the recommendations of learned societies. Once treatment is initiated, we use Pulsy to create a computerized, multi-professional monitoring program for 3 years, the minimum timeframe for achieving an improvement in bone mineral density and limiting the risk of fractures. The attending physician monitors the treatment, the pharmacist is responsible for contacting patients who have discontinued treatment, and the advanced practice nurse contacts the patient every 6 months to assess their experience and treatment follow-up. All members of the care circle are invited to issue an alert, which is distributed to everyone in the event of treatment discontinuation or a fall.

We included 80 patients in one year; all started treatment, all are continuing it at one year, and are satisfied with the follow-up. Only one fell.

We hope to increase the number of patients screened and treated and limit the number of subsequent fractures by max 50%.

Poster 11

Therapeutic potential of FGF19 against osteosarcopenia: effects on muscle strength and bone health in aged male mice

Maura Strigini

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Osteosarcopenia, characterised by the coexistence of osteopenia/osteoporosis and sarcopenia, represents a significant health concern in geriatrics, with an increased risk of falls and fractures. Fibroblast Growth Factor 19 (FGF19), a hormone produced in the intestine (ileum) post-prandially, was recently shown to prevent muscle weakness in several preclinical models. We have now investigated the therapeutic potential of FGF19 in mitigating bone and muscle deterioration in aged male mice. Twenty-one-month-old C57BL/6 male mice received daily injections of human recombinant FGF19 (0.1mg/kg) for 21 days. Histological and functional analyses revealed a shift towards larger muscle fibers in FGF19-treated mice as well as an increased muscle strength, without affecting muscle mass. In parallel, X-ray microtomography (microCT) showed that FGF19 had no overt negative impact on bone, with a range of modest, site-specific, and opposing effects. In the distal femur metaphysis FGF19 it reduced cortical thickness, but significantly increased bone cross-sectional area, with an overall increased polar moment of inertia, a geometrical parameter linked to favourable mechanical properties. It also elevated cortical bone porosity in the same region. There were no significant effects on trabecular bone or cortical bone parameters in the proximal femur side at the lesser trochanter level, nor at the femoral diaphysis or in the tibia. In the L2 vertebra, cortical porosity decreased. Histomorphometry of trabecular bone and analysis of transcriptional output of selected genes in femurs revealed only minor changes in bone cellular activities and gene expression after three weeks of treatment. In conclusion, FGF19 treatment increased muscle strength in aged male mice, without negatively impacting aging bone.

Poster 12

Effects of a ketogenic diet on the progression of osteoarthritis in obesity - articular, metabolic and epigenetic characterisation in in vio and in vitro models

Maura Strigini

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The metabolic inflammation and excessive mechanical loading on joints of obesity exacerbates the progression of osteoarthritis (OA). A low carb/high fat ketogenic diet (KD) can promote weight loss, reduce metabolic inflammation and elevate circulating levels of the ketone body betahydroxybutyrate (BHB). BHB is a putative histone deacetylase (HDAC) inhibitor, molecules with the ability to slow OA progression in both in vitro and in vivo models, possibly through epigenetic mechanisms.

Could KD mitigate obesity compounded OA by modulating joint metabolism and slowing cartilage degradation, through metabolic rewiring and epigenetic mechanisms?

We fed mice a highfat diet (HFD), and induced knee OA by medial meniscus destabilization at 16 weeks of age and then fed them one of three diets ad libitum: HFD, KD or standard diet (STD) for 8 weeks. We assessed disease progression by OARSI score, microCT analysis of periarticular bone and OA marker expression/metabolic state of articular chondrocytes by RT-PCR and Western blot.
We analyzed histone modifications by Western blot in (i) peripheral tissues and (ii) in cultured mouse and human chondrocytes treated with BHB and HDACi.
BHB levels increased tenfold in KD group only. Glycemia decreased in STD and even more in KD ($p< 0,001$). HFD mice kept gaining weight, while STD and KD lost weight comparably. OA progression was moderately limited by KD: Severe OA cases (OARSI score>2.5) were less frequent (HFD>STD>KD, $p=0.037$); osteophytes were smaller ($p< 0.001$). For OA marker genes in cartilage, MMP13 mRNA was 2-fold lower in KD compared to HFD ($p=0.005$) and to STD ($p=0.02$); OPN was lower in KD than in HFD ($p<0.05$). COL 10 was reduced in KD compared to STD ($p<0.05$). Leptin expression was lower in KD than in both HFD and STD ($p<0.05$), whereas p16 expression was lower in KD compared to HFD ($p<0.05$). Western blot analysis supported these findings.
Diets were associated with specific metabolic signatures in serum and with distinct ketogenesis and ketolysis gene expression profiles in joint tissue. BHB significantly increased histone betahydroxybutyrylation in cultured chondrocytes, without effects on histone acetylation.
KD demonstrates a moderate beneficial effect on disease progression in a post-traumatic model compounded by obesity. This effect is accompanied by the downregulation and modulation of key OA markers. KD promotes a metabolic shift in chondrocytes, suggesting its potential in maintaining a healthy chondrocyte phenotype. The modulation of the novel histone modification betahydroxybutyrylation, and not histone acetylation, may also contribute to the observed beneficial effects.

Poster 13

Iron excess alters in vitro deposition of collagen and hydroxyapatite by osteogenic cells.

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Introduction.
Osteoporosis, characterized by a decrease in bone strength, is a public health problem. Bone remodeling and homeostasis are driven by three cell types: osteoblasts and osteocytes -synthesis and deposition of bone extracellular matrix (ECM)- and osteoclasts -ECM resorption-. Iron overload is reported to favor bone fragility. Our study aims to investigate the impact of iron excess on bone matrix mineralization and deposition by osteoblasts and osteocytes.

Materials and methods.
Murine cell lines -MC3T3 pre-osteoblasts and MLO-A5 osteocyte-like cells- were independently exposed or not to ferric ammonium citrate (FAC). ECM mineralization process and organization was analyzed by transmission electron microscopy (TEM) and Alizarin Red staining. Raman spectroscopy was used to characterize the deposition of the inorganic (hydroxyapatite) and organic (collagen) components of ECM.

Results.
TEM showed distinct matrix organization regarding the cell line: MLO-A5 exhibited direct mineral nucleation foci, while MC3T3 mainly deposited collagen fibrils. In both cell lines exposure to 5 µM FAC reduced ECM deposits evaluated by Alizarin red staining, while 10 µM completely suppressed the mineralization process. Raman spectroscopy analysis allowed identification of a strong phosphate peak (960 cm^{-1}), characteristic of hydroxyapatite, in MLO-A5, whereas in MC3T3 it appeared later and with lower intensity, reflecting their preferential collagen-first strategy. Peaks at 853 and 875 cm^{-1}, corresponding to proline and hydroxyproline, confirmed a major collagen deposition in MC3T3. Importantly, treatment with 10 µM FAC resulted in the disappearance of the 960 cm^{-1} peak in both cell lines, indicating impaired mineralization.

Conclusion.
Our results show that: (i) osteoblasts and osteocytes contribute differentially to bone ECM deposits, (ii) MC3T3 and MLO-A5 exhibit distinct ECM deposition strategies; (ii) iron excess significantly alters mineralization in both osteogenic cell models They provide new insights into the impact of iron overload on bone cells and contribute to a better understanding of iron-related bone fragility.

Poster 14

Mitochondrial transfer: a promising strategy to improve cellular metabolism in intervertebral disc degeneration

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Mitochondria, the cell's powerhouse, are critical for energy production and play key roles in cellular metabolism, apoptosis, and homeostasis. Recently, mitochondrial dysfunction has been implicated in intervertebral disc degeneration, which is also characterized by cellular metabolism changes. Advances in mitochondrial transfer and cell therapy offer promising treatments for mitochondrial diseases, including disc degeneration.
Research has demonstrated that mesenchymal stromal cells (MSCs) can transfer mitochondria via nanotubules to nucleus pulposus cells (NPCs, native disc cells) and that this mitochondrial transfer enhances the metabolic function of NPCs. These results, however, were obtained in standard culture conditions and may be challenged in the harsh, highly specific degenerative disc environment (e.g., inflammation, low pH).
We therefore developed a degenerative microenvironment model that closely mimics the degenerative disc niche to study the MSC effects on NPC metabolism in this specific environment.
Preliminary results (n = 1, with technical triplicate) showed that after seven days of culture in a degenerative environment, co-cultured cells exhibited enhanced aerobic respiration, increased ATP production, and greater mitochondrial dependence. qPCR analysis revealed that in NP cells, the expression of glycolytic enzymes HK2 and LDHA was downregulated, while the expression of FH, a key enzyme in the tricarboxylic acid cycle, was upregulated. Assessment of mitochondrial content and function demonstrated a significant increase in mitochondrial abundance in cells exposed to the degenerative environment, with the co-culture group displaying the lowest overall mitochondrial content. Moreover, mitochondrial membrane potential in NPCs was markedly reduced under the degenerate condition, whereas co-culture with MSCs exerted a notable rescue effect. Collectively, these findings suggest that MSCs promote metabolic reprogramming in NPCs by enhancing mitochondrial health and supporting aerobic respiration.