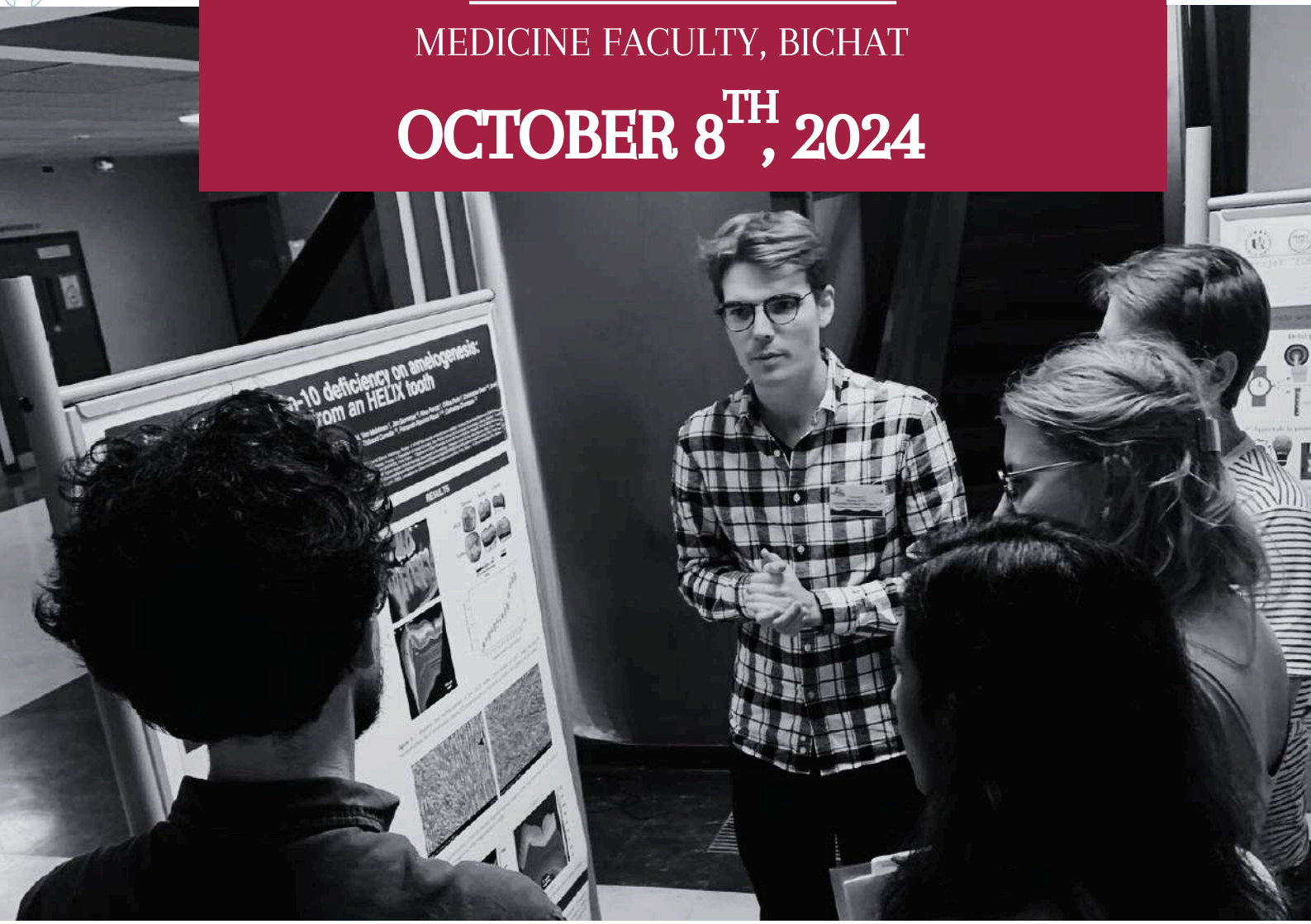
BICHAT BEAUJON YOUNG RESEARCHERS DAY

MEDICINE FACULTY, BICHAT

OCTOBER 8TH, 2024



NUMERIC VERSION

ONLINE INFOS

Program

8 H 00 **WELCOMING COFFEE**

9 H 00 **OPENING SPEECH**

9 H 15 **ORAL PRESENTATION : SESSION 1**

Rémi Gschwind - *Identification of Cefiderocol Resistance Genes in the Environment using Functional Metagenomics*

Marie Robert- *Identification of specific monocyte epigenetic signatures in Sarcoidosis and Tuberculosis patients*

Hichem Badji- *Unlocking the Potential of Omega-3 Fatty Acids: Modulation of Vascular Tone in Pulmonary Hypertension*

Marguetite Ducamp- *Towards assessing the biomechanical properties of organoids/spheroids at 35-micron resolution with Magnetic Resonance Elastography*

10 H 15 **POSTER SESSION 1**

11 H 15 **ORAL PRESENTATION : SESSION 2**

Taib Abderaouf Bourega - *Histology-based Deep Molecular Profiling using Artificial Intelligence in Pancreatic Adenocarcinoma*

Elliot Lopez - *Growth and study of tumor spheroids behavior in a biomimetic vascularized platform*

11 H 45 **PRESENTATION OF PROTEINTECH**

12 H 00 **ROUND TABLE : CARRERS AFTER PHD**

13 H 00 **LUNCH**

14 H 00 **PITCH YOUR PROJECT**

3 minutes to present your project.

15 H 00 **POSTER SESSION 2**

16 H 00 **ORAL PRESENTATION : SESSION 3**

Carlos Olivares - *Mathematical Modeling The Effects of Beta-lactam Antibiotics On Gut Microbiota Diversity*

Thibault de la Taille - *Functionalized polysaccharide nanoparticles for a targeted treatment of ischemic strokes*

Paula Gil - *Ionizable lipid nanoparticles encapsulating miR-133a: A potential RNA therapy for myocardial infarction treatment*

16 H 45 **JURY DELIBERATION - CLOSING SPEECH AND AWARD ANNOUNCEMENT**

17 H 30 **CLOSING COCKTAIL**

Posters

Lina Aguilera Munoz - Molecular plasticity of pancreatic intraductal papillary mucinous neoplasms

Audrey Beaufils - Deep learning for prediction of chemotherapy response from histopathology in pancreatic cancer

Maxime Beaulieu - Evusheld hastens viral clearance in COVID-19 hospitalized patients: a modeling analysis of the randomized DisCoVeRy trial

Asma Boumaza- Tumour mechanics and vascular fractality quantification via MR-Elastography in the context of liver metastasis from colorectal cancer

Nour Bousaidi - Characterization of 3D-Printed PEEK Inserts for Maxillofacial Tissue Engineering

Bruno Campos Silva - IgA1-Protease mRNA-LNP as a treatment for IgA nephropathy in a mouse model expressing human IgA1

Mathieu Castry - Risk factors associated with bacterial sexually transmitted infections (STIs) among men who have sex with men (MSM) during the pre-exposure prophylaxis (PrEP) era: a systematic review and meta-analysis in high-income countries (application to chemsex)

Ophélie Chapellier - New cationic polyester for miRNA delivery

Lucie Fayette - Using Fisher Information Matrix to predict covariate effects in Forest Plots and power of their relevance

Posters

Klaus Hämäläinen - A novel transcription factor regulating neuroinflammation

Niels Hendrickx - Evaluation of treatment effects in genetic ataxias using SARA score modelling:
comparison of multiple trial designs by a large trial simulation framework

Zhipeng Li- Deregulation of COX-2/PGE2 pathway and EP4 receptor of bronchi in COPD patients

Shengyi Liu - Involvement of neutrophil serine proteases in periodontitis

Gabrielle Mangin- Biomechanical phase angle as proxy to quantify the presence of microvascular invasion in hepatocellular carcinoma using MRI

Gaelle Merheb - Effects of Omega-3 on Human Coronary Vascular Tone Induced by Neurotransmitters

Assil Merlaud - To quantify the association between tumor dynamics and overall survival across cancers: a Bayesian meta-analysis

Deepak Pokhreal - Investigating the role of a novel immune receptor in regulating macrophage pro-fibrotic activity in idiopathic pulmonary fibrosis

Clarisse Schumer - Building a theoretical model of viral dynamics for SARS-CoV-2 and Influenza A co-infection

Pitch your project

Nelly Alanbari - Temocillin: risky choice for group 3 Enterobacterales infections ?

Yasmine Benhadid-Brahmi - Microbial and environmental determinants behind the evolutionary success of major bacterial clones

Louis Berthet - Dialogue miARN-microbiote en période néonatale et effets à long terme sur la santé intestinale

Guillaume Cosson - Facteurs de non réponse in vivo à l'antibiothérapie dans un modèle de prostatite aiguë murine

Anna Curioni - Study of TIGIT implication in the profibrotic activity of regulatory T lymphocytes in idiopathic pulmonary fibrosis

Nicolas Godron - Developing a metagenomics–driven framework for assessing the risk of emergence of environmental antibiotic resistance genes in pathogenic bacteria

Pierre Grès- Impact de la Protéase Nexine-1 dans l'arthropathie hémophilique, une complication majeure de l'hémophilie

Salomé Mascarell - Le tissu gingival : intérêts en médecine légale et médecine régénératrice

Killian Véron - Compréhension des mécanismes de résistance à la radiothérapie interne vectorisée dans les tumeurs neuroendocrines et carcinomes hépatocellulaires et amélioration de son efficacité

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Jury

Jury for oral presentations:

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Chloé Dujardin
PhD Student - Team Letourneur U1148 LVTS

Charles Caër
Engineer - Team Lotersztajn/Gilgenkrantz U1149 CRI

Jury for posters presentations:

Philippe Garteiser
Researcher - Team Van Beers U1149 CRI

Mathilde Varret
Researcher - Team Le Goff U1148 LVTS

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Round table

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ABSTRACTS

ORAL PRESENTATIONS

Identification of Cefiderocol Resistance Genes in the Environment using Functional Metagenomics

Remi Gschwind 1, Anna Abramova 2,3, Victor Hugo Jarquin-Diaz 4, Ulrike Loeber 4 Mehdi Bonnet 1, Faina Tskhay 5, Fozia Naheed 6, Uli Klümper 5, Thomas U Berendonk 5, Sofia K Forslund 4, Rabaab Zahra 6, Johan Bengtsson-Palme 2,3, Etienne Ruppe 1

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Antibiotic resistance is a global health concern, spanning human, animal, and environmental sectors, emphasizing the "One Health" concept. The development of new antibiotics to combat multidrug-resistant Enterobacteriaceae is critical. Cefiderocol (FDC), a novel siderophore cephalosporin recently introduced into clinical practice, is already facing resistance mechanisms. However, limited data exists on these mechanisms and the associated antibiotic resistance genes (ARGs). To identify these ARGs, we employed functional metagenomics (FMG), a technique where ARG detection is based on phenotypic resistance rather than sequence homology. This approach allows for the discovery of novel ARGs (or new activity of known ARGs) against FDC.
Environmental samples (wastewater, freshwater, soil) were collected from Europe and Pakistan. DNA was extracted, sequenced, and FMG was performed on extracts with concentrations exceeding 20 ng/µL. DNA was fragmented by tagmentation, amplified, and cloned into an expression vector used to transform Escherichia coli K12, which was plated on LB+FDC (1 µg/mL). Phenotypic characterization of resistant clones (MIC, antibiogram) and molecular characterization of their inserts (taxonomy, annotation) were performed. Alignment of sequencing reads to the insert and gene was verified.
Four samples yielded FDC-resistant clones. Genes encoding beta-lactamases (blaOXA372, blaVEB3, and ybxI) and a penicillin-binding protein (PbpC) were identified. The minimum inhibitory concentrations (MICs) observed for these clones ranged from 1 to 2 mg/L. Regarding beta-lactams, resistance was variable (up to 11 resistances out of 16 beta-lactams tested in the clone carrying blaOXA372). Alignment of sequencing reads confirmed the presence of these genes in three out of four cases. Additionally, the insert carrying blaVEB3 was identified in 32% of the sequenced samples.
In this study, we identified genes conferring resistance to FDC in environmental samples. The mobility and presence of some of these genes in pathogenic bacteria highlight the need for surveillance to prevent their dissemination.

Identification of specific monocyte epigenetic signatures in Sarcoidosis and Tuberculosis patients

Marie Robert (a,b,c), Nader Yatim (a,b), Tom Dott(d), Arthur Mageau (b,c,e), Florian Dubois (d), John Tchen (c), Etienne Villain (a), Nicolas Charles (c), Vincent Bondet (a), Tiphaine Goulenok (b), Violaine Saint-André (a,f), Darragh Duffy (a, d), Karim Sacré (b, c)

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Sarcoidosis (SARC) is a multisystemic inflammatory and granulomatous disease that most commonly affects the lungs. Mechanisms underlying granuloma formation and maintenance are still unknown, but SARC shares many similarities with tuberculosis (TB). We hypothesized that monocytes from patients with SARC and TB retain a specific epigenetic signature that drives maladaptive innate immune training and disease.

To test this, we performed genome-wide epigenetic profiling of monocytes from newly diagnosed SARC or TB patients using CUT&Tag, and assessed the acetylation of lysine 27 of histone 3 (H3K27Ac) to identify enhancers of expressed genes. From this we identified super-enhancers (SE) and predicted the autoregulatory transcription factors (TF) that are part of the core regulatory circuitries (CRC) in each disease.

Through differential analysis of genome-wide H3K27Ac profiles we identified genomic regions that specifically distinguished SARC patients from TB patients and from Healthy Controls (HC). There were 24 differentially regulated regions in SARC patients compared to HC, and one specifically H3K27Ac depleted in SARC compared with TB (shrunkenlog2FC > |0.1|, adj-p < 0.1). SE were identified in all samples and among SE-associated genes, we identified 7 auto-regulatory TF specific to SARC (i.e., TCF7, FOXJ2, PRDM1, FOXK1, FOXO3, USF1, ELF2), 3 specific to TB (i.e., ZNF219, EGR3, IRF7) and 6 shared by both diseases. Functional analysis suggested a role played by type I IFN, glucose metabolism and apoptosis pathways. This confirmed our hypothesis with evidence of specific CRCs in either disease.

Our findings provide evidence that there are distinct monocyte epigenetic signatures associated with SARC and TB, and raise new and challenging perspectives on the role played by trained immunity in inflammatory diseases. Ongoing work will incorporate transcriptomic data, additional immune phenotyping and functional assays.

Unlocking the Potential of Omega-3 Fatty Acids: Modulation of Vascular Tone in Pulmonary Hypertension

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Pulmonary hypertension (PH) is a severe disease that arises from multiple etiologies, leading to right ventricular failure and death. Pulmonary perivascular inflammation has gradually gained increased attention as an early common hallmark across different PH groups. Most of the used treatments target the pulmonary vasoconstriction (PGI2 analogus, ET-1 inhibitors and Phosphodiesterase inhibitors) that stimulate smooth muscle cell relaxation. However, pulmonary hypertension remains associated with significant morbidity.

We therefore hypothesised that inflammation plays a crucial role in the severity of abnormal vasoconstriction in PH. Based on this hypothesis, we have selected a candidate family of bioactive lipids: omega-3 fatty acid (EPA, DHA and DPA) and their metabolits with high resolving potential, called the SPM for specialised proresolving mediators (resolvins, protectins and maresins).

Human pulmonary arteries (HPA) derived from PH or non-PH patients were gathered at Bichat hospital. Using an isolated organ system, we have assessed the functional effects of EPA, DHA, and DPA alone and in combination with vasoactive compounds relevant to the pathology. Furthermore, we have examined the underlying mechanisms of the observed effects on each signalling pathway by using western blot and ELISA. We measured the endogenous SPM expressed in pulmonary vascular tissue (+/- PH) with LC/MS-MS after a stimulation with omega-3.

In summary, our findings indicate that omega-3 fatty acids, and their metabolites the SPM possess inherent vasorelaxant properties, especially in non-PH HPA. However, in the context of PH, these relaxing effects seem to diminish. Additionally, our investigations unveiled intriguing interactions between omega-3 fatty acids, notably DHA and DPA, with HPA responses to Iloprost (enhancement of vasorelaxation) and Prostaglandin E2 (reduction of vasoconstriction) for both non-PH and PH HPA.

Towards assessing the biomechanical properties of organoids/spheroids at 35-micron resolution with Magnetic Resonance Elastography

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MR-Elastography (MRE) is an imaging technique that measures tissue biomechanics, widely used for diagnosing liver fibrosis and showing promise in assessing early chemotherapy response/resistance in breast cancer patients. With the arising use of patient derived organoids to predict response to therapy, extending MRE to quantify these organoids/spheroids is important. Here, we present biomechanical results from artificial spheroids (agar) with known stiffness, embedded in collagen droplets.
Data were acquired on a 7T MRI preclinical scanner (Bruker, Ettlingen, Germany, gradient strength 660 mT/m), using a spin-echo sequence and a 20mm surface coil for signal reception. With our MRE design hardware, we generated quasi-planar waves from the bottom of a petri dish propagating upwards. The readout direction being the same as waves propagation, we can resolve objects at 35-micron resolution and reconstructing stiffness in 1D using fitting of sinus-functions. Baseline stiffness of ultrasound gel and 3% agar organoids were assessed with low-resolution MRE at 300Hz. Two setups were scanned at 35-micron resolution: 1mm agar-organoid in ultrasound gel and 400µm agar-organoid in collagen droplets surrounded by PBS.
Shear speed of 0.96m/s was found for ultrasound gel at low resolution. The 35µm resolution scan in sagittal orientation gave 0.9m/s speed with the simultaneous sinus/cosines-fit to the real/imaginary parts of the wave-component that yields a plane-wave propagation upwards. Agar gel biomechanics at low resolution indicated a shear speed of 1.23m/s. Plane-wave tracing upwards through the spheroid inside ultrasound gel showed speeds of 0.92m/s before, 1.36m/s within, and 0.9m/s behind the agar object. At 35 microns, the sinus/cosine fit of the "near reality" organoid experiment estimated the agar-spheroid speed at 1.7m/s (1.3m/s at low resolution for that agar-batch). Collagen speed was 0.3m/s, matching literature values that range of 1kPa-5kPa.
Patient-derived organoids are vital for personalized medicine, making it crucial to translate biomarkers for drug response/resistance to preclinical settings. We developed a system for MRE on organoids embedded in collagen droplets, capable of measuring stiffness of objects as small as 400µm. Next steps include using cellular organoids to track biomechanics under drug exposure, aiming to observe similar stiffness changes at the organoid level as in humans, facilitating translation of imaging signatures across scales.

Histology-based Deep Molecular Profiling using Artificial Intelligence in Pancreatic Adenocarcinoma

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Our team characterized the molecular intratumoral heterogeneity of pancreatic adenocarcinoma (PDAC) using a deep learning model to predict tile-level transcriptomic profiles from histological images. By applying the cNMF (Consensus Non-negative Matrix Factorization) technique to the predicted number of genes, we identified 13 morpho-molecular components that describe PDAC. This study combines morphological features of targeted tumor subregions (on average 2 mm²) with tailored transcriptomic data based on microdissection through deep learning, aiming to understand the complexity of PDAC and its spatial distribution.

We analyzed 100 patients with resected PDAC, selecting 2–8 morphologically distinct regions per tumor for RNA extraction and sequencing, resulting in 407 RNAseq profiles. The morphological characteristics of each tile (112 x 112 µm) were extracted using a refined deep learning model. The features were fed into a shallow neural network (3 layers, 14 million parameters) to predict 17,000 gene counts per tile. An aggregation mechanism centered on a trainable latent space provided regional predictions. cNMF applied to 70,000 tiles by 459 best predicted genes yielded 13 morpho-molecular models.

Correlations (Spearman R) greater than 0.4 were observed for 459 genes in the validation set, including markers of the classical phenotype such as TFF1 and CLDN18. Heatmaps of tile-level predictions confirmed the accuracy of the model in representing PDAC heterogeneity. cNMF revealed 13 distinct morpho-molecular patterns, with homogeneous tiles and biologically significant genes.

Combining deep learning with histological and transcriptomic data effectively characterizes the heterogeneity of PDAC. Our model's accurate gene expression predictions and identification of 13 distinct morpho-molecular patterns provide a comprehensive understanding of PDAC heterogeneity.

Growth and study of tumor spheroids behavior in a biomimetic vascularized platform

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Cancer remains a global health challenge and asks for more accurate models for drug development. Conventional monolayer cultures fail to recapitulate the complex tumor microenvironment (TME), and notably the vascular compartment, which plays a pivotal role in cancer development. Conversely, in vivo models exhibit limited versatility and present escalating ethical issues. Therefore, three-dimensional biomimetic systems emerge as promising candidates to integrate a dynamic vascularization. Yet, a compromise is to be found between straightforward but disorganized cell mixing, and precise but tedious blood vessels engineering. Models offering a precise control of the vascular network while allowing ease of manipulation are thus of major help for applications in cancer research.

Herein, we have developed a polysaccharide-based hydrogel, composed of two compartments: first, a microwells network of controllable porosity is used to produce cancer spheroids in a reproducible and standardized manner. To validate it, the effect of anticancer drugs on several cancer cell lines has been investigated. Using the same hydrogel, we have prepared a second compartment by building hollow microchannels in a porous matrix and layering them with endothelial cells to form tubular constructs. These vessels have been perfused to study the cell development, and fibroblasts have also been added to support the endothelial growth, which promoted the secretion of angiogenic factors but did not trigger angiogenesis. To go further, the combination of the two components will allow study the interactions between cancer and endothelial cells under flow.

Overall, our system provides an innovative co-culture platform integrating stromal, cancer, and endothelial cells in a biomimetic substrate to investigate interplays between spheroids and a vascularized TME. As a perspective, this system can be put into a microfluidic chip to investigate the response of the system to soluble factors or to drugs.

Mathematical Modeling The Effects of Beta-lactam Antibiotics On Gut Microbiota Diversity

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Antibiotic treatments alter gut microbiota based on their spectrum, dosage, and excretion rate, potentially causing dysbiosis and chronic diseases. We developed a model to evaluate the impact of antibiotic exposure on microbiota diversity.
Data from the DAV-132-CL1006 trial with 144 volunteers were analyzed. Participants received a 5-day IV treatment with ceftriaxone (CRO), ceftazidime/avibactam (CEF/AVI), piperacillin/tazobactam (PIP/TAZ), or were in a control group. Some also received DAV132 for 7 days. Plasma antibiotic levels were measured on days 1 and 5, and fecal samples were collected up to day 37 for antibiotic levels and Shannon diversity via 16S rRNA profiling.
Nonlinear mixed-effect modeling was used to analyze antibiotic pharmacokinetics and their effects on bacterial diversity. Parameters were estimated using the SAEM algorithm in Monolix. Model selection was based on goodness-of-fit plots and Bayesian Information Criteria.
Two-compartment models with first-order elimination were identified for plasma concentrations of all antibiotics. Fecal concentrations were modeled with transit compartments. The effect on the Shannon index was best described by an Emax model linking fecal concentration to loss rate.
The median [min; max] time for fecal antibiotic concentrations to fall below quantification after the last dose varied: 4.3 [1.3, 11.7] days for CRO, 4.6 [1.31, 20.3] for CEF, and 2.3 [0.28, 17.3] for PIP.
Our model predicted a maximal diversity loss of 0.62[0, 1.78], 1.6[0.04, 2.82], 1.5[0.002, 3.1] reached after 7.5[4.8, 27], 7.6[4, 21], 6.8[3.33, 29.3] days of beginning of treatment for CRO, CZA and PTZ respectively and the corresponding return to 95% of diversity baseline after 15.1[5.2, 71], 26.5[5.6, 76], 25.3[4.4, 83] days of beginning of treatment.
The model reveals how three beta-lactams impact gut microbiota diversity, offering insights into antibiotic effects on gut health and helping optimize treatments to preserve gut diversity.

Functionalized polysaccharide nanoparticles for a targeted treatment of ischemic strokes

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Cardiovascular diseases are held responsible for a third of all deaths worldwide, leading with heart attacks and strokes, among which the latter is responsible for over 12.2 million cases alone each year. Notably, 80 % of strokes are of ischemic nature, and the recommended care for this pathological blood clot (thrombus) is the systemic injection of a fibrinolytic drug, rtPA, which suffers from severe side effects, a short therapeutic window, and does not guarantee recanalization. It was also shown that the more complex nature of thrombi impedes their lysis, including DNA networks released from neutrophils (NETs). Our approach is therefore to design a biocompatible nanosystem targeting the thrombus, to deliver a combo of drugs for improved blood clot bursting and improved recovery.

The technology consists in nanoparticles made from a polysaccharide hydrogel, synthesized through a novel process through a water-in-oil nanoemulsion. The resulting nanogels contain a sulfated polysaccharide, fucoidan, which was demonstrated to have high affinity to P-selectin, a marker of activated platelets and endothelial cells and that can be used for thrombus targeting. They are loaded with drugs (rtPA and DNase I) by controlled adsorption and were studied for their improve thrombolysis.

These 300 nm nanoparticles were fully characterized, including composition, stability, biocompatibility, in-flow behavior, targeting to thrombi, drug loading and release, and their retained activity. Notably, they demonstrated remarkable stability in various solvents and robust batch-to-batch synthesis. Finally, their thrombolytic efficacy was demonstrated with in vitro models and with an in vivo thrombosis model in mice. Overall, these nanoparticles open new perspectives for improving therapeutical care for thrombotic diseases.

Ionizable lipid nanoparticles encapsulating miR-133a: A potential RNA therapy for myocardial infarction treatment

Paula Gil-Cabrerizo, Elisa Garbayo, Maria Blanco-Prieto

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At the forefront of global health challenges, cardiovascular diseases stand as the leading cause of death, with myocardial infarction (MI) holding particular significance. Triggered by the obstruction of coronary artery blood flow, MI leads to the death of cardiomyocytes due to insufficient oxygen and nutrients. Current treatments are unable to regenerate the heart nor reverse the inflicted damage. Importantly, microRNAs (miRNAs) emerge as pivotal gene expression regulators by modulating the translation of mRNA into proteins involved in cardiac physiopathological processes. In particular, miR-133a, highly expressed in the cardiac tissue, is known for its role in inhibiting cardiomyocyte apoptosis by targeting Caspase 9. Following MI, miR-133a levels notably decrease, suggesting a promising therapeutic potential in cardiac repair. Nonetheless, miRNAs encounter various obstacles (i.e. RNase degradation, limited cellular uptake, endosomal escape and immunogenicity) before reaching their target, making encapsulation within lipid ionizable nanoparticles (LNPs) crucial for effective therapeutic outcomes. In this study, we efficiently encapsulated miR-133a in LNPs and demonstrated the absence of cytotoxicity in H9C2 cardiomyocytes. Moreover, the bioactivity of miR-133 LNPs was verified through the reduction of Caspase 9 protein levels suggesting an anti-apoptotic effect and therapeutic potential for the treatment of MI. Firstly, miR-133a was encapsulated within LNPs by microfluidics. Briefly, miR-133a was dissolved in citrate buffer 30mM pH4 and mixed with lipid phase at an amine-to-phosphate (N/P) ratio of 10. The lipid formulations consisted of R-DODMA, DSPC, cholesterol and PEG-DMG. LNPs were 40-fold diluted in PBS (pH 7.4) and centrifuged at 5.000rpm, for 30 min thrice. LNPs were characterized by size and zeta potential and encapsulation efficiency was determined by RiboGreen. The cytotoxicity of LNPs was evaluated in H9C2 cardiomyocytes using the MTT assay. Furthermore, in vitro bioactivity was studied to evaluate Caspase 9 protein expression in H9C2 cardiomyocytes. Precisely, cellular damage was induced by exposing cells to 400uM H_2O_2 for 4 h. Subsequently, LNPs-miR-133 were added and Casp9 protein levels were quantified after 24h using the Caspase 9-Glo® Assay. Additionally, levels of reactive oxygen species (ROS) are currently being assessed by H2CDFDA. Finally, to analyze the cellular uptake, LNPs were formulated with fluorescently labelled cholesterol for subsequent flow cytometry studies. Endosomal escape is being evaluated by confocal microscopy using Cy3-labelled miRNA and LysoTracker® dye. LNPs exhibited a size of 88 nm, a zeta potential of -15.4mV and an encapsulation efficiency of 90%. Additionally, LNPs demonstrated no cytotoxicity in H9C2 cardiomyocytes. Regarding in vitro bioactivity, miR-133 LNPs showed a reduction in Caspase 9 levels after H_2O_2-induced damage suggesting a potential anti-apoptotic effect. The impact of miR-133a LNPs on ROS cellular levels and NO production is being assessed to explore their potential anti-inflammatory effects. Additionally, the cellular uptake of miR-133 LNPs is being evaluated to confirm endocytosis and endosomal escape.

ABSTRACTS

POSTER

Molecular plasticity of pancreatic intraductal papillary mucinous neoplasms

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Intraductal papillary mucinous neoplasms (IPMN) are frequent pancreatic cystic preneoplastic lesions. Three phenotypes have been described (gastric, intestinal pancreatobiliary (PB)) with different rate of progression toward invasive tumours. The aims of this study were to identify the molecular pathways involved in IPMN phenotype identity and explore the plasticity of IPMN lesions.
RNA sequencing was performed for 420 formalin-fixed paraffin-embedded (FFPE) IPMN microdissected samples derived from 136 surgical pancreatic specimens (2013-2022). DNA mutation analyses were performed on 11 IPMN specimens with a mixed phenotype.
On the 420 samples, phenotype distribution was 46% intestinal, 43% gastric and 11% PB. RNA sequencing analyses confirmed different transcriptomic profiles for intestinal phenotype compared to the gastric/PB phenotypes. Genes overexpressed in intestinal samples were enriched for proliferation pathways, whereas gastric samples were highly enriched in immune response pathways, independently of grade of dysplasia. A mixed phenotype (intestinal and gastric in the same lesion) was described in 14% of samples. In these mixed samples, only 4/11 specimens showed a common genetic background with identical GNAS and/or KRAS mutations, the remaining showing distinct ancestral precursors.
A genetic sequential clonal evolution from gastric to intestinal phenotype, supporting plasticity, seem not to be the predominant pathway to explain IPMN phenotypical heterogeneity, unlike what is seen in the gastric mucosa with intestinal metaplasia. Our results provide insights into different non genetic progression pathways depending on IPMN phenotypes.

Deep learning for prediction of chemotherapy response from histopathology in pancreatic cancer

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The PRODIGE-24/CCTG PA6 trial demonstrated that mFOLFIRINOX (FFX) significantly improves outcomes over Gemcitabine (GEM) as adjuvant treatment in resected pancreatic ductal adenocarcinoma (PDAC). We investigated whether an AI-driven approach could identify histological signatures associated with outcomes following these treatments in resected PDAC.

Anonymized hematoxylin and eosin-stained slides from two cohorts were used: a retrospective multicentric enriched series of n= 223 resected patients for model training and validations, and a subset of patients from the PRODIGE-24 trial for testing (137 GEM patients; 176 FFX patients). Slides were divided into image tiles, and features were extracted from tumoral cells. We developed and validated a deep learning-based prognostic-stratification system for prediciting disease free-survival (DFS) in PDAC patients. An additional series of tumor-centered microdissections (377 regions) with precise histology and RNAseq matching was performed for the functional analysis of predictive patterns. Transcriptomic analysis was performed using DESeq2 and Gene Set Enrichment Analysis (GSEA).

The FFX histological signature stratified patients based on DFS in the internal validation set (log-rank p = 4e-04) with a hazard ratio (HR) of 0.24 (95% CI [0.06, 0.969]). The GEM signature had a pvalue of 0.03 with a HR of 0.21([0.04, 1.14]). The statistical interaction between treatment and sensitivity was moderately significant for the FFX (p= 0.08) and GEM (p= 0.1) models. RNA analysis showed that FFX-resistant patients overexpressed extracellular matrix and stromal markers., while GEM-resistant patients showed upregulation of basal tumoral cells and fibroblasts.

Our AI-driven histologic and transcriptomic analysis identified distinct biomarkers associated with treatment response in PDAC, offering potential for personalized adjuvant therapy strategies.

Evusheld hastens viral clearance in COVID-19 hospitalized patients: a modeling analysis of the randomized DisCoVeRy trial

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The antiviral efficacy of Evusheld (AZD7442) in patients hospitalized for SARS-CoV-2 is unknown.

We analysed the evolution of both the nasopharyngeal viral load and the serum neutralization activity against the variant of infection in 199 hospitalized patients (109 treated with Evusheld, 90 treated with placebo) infected with the SARS-CoV-2 virus and included in the randomized, double-blind, trial DisCoVeRy (NCT04315948). Using a mechanistic mathematical model, we reconstructed the trajectories of viral kinetics and how they are modulated by the increase in serum neutralization activity during Evusheld treatment.

Our model identified that the neutralization activity was associated with viral kinetics. Reflecting the variant-dependent neutralization activity of Evusheld, the antiviral activity of Evusheld was larger in patients infected with pre-Omicron or Omicron BA.2 variants than in patients infected with Omicron BA.1 variant. More specifically, the model predicted that Evusheld reduced the median time to viral clearance compared with placebo-treated patients by more than 5 days in patients infected by pre-Omicron (median: 5.9; 80% PI: 2.1–13.6) or Omicron BA.2 (median: 5.4; 80% PI: 2.0–12.4), respectively. The effect was more modest in patients infected by the Omicron BA.1 variant, reducing the median time to viral clearance by 2 days (median: 2.2; 80% PI: 0.4–8.9).

Hospitalized patients treated with Evusheld had a shorter median time to SARS-CoV-2 viral clearance. As Evusheld antiviral activity is mediated by the level of neutralization activity, its impact on viral clearance varies largely according to the variant of infection

Tumour mechanics and vascular fractality quantification via MR-Elastography in the context of liver metastasis from colorectal cancer

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Colorectal cancer is a leading cause of cancer-related deaths globally, often metastasizing to the liver. Standard treatment involves chemotherapy regimens like FOLFOX and the anti-angiogenic agent BEVACIZUMAB. However, assessing therapy efficacy remains a challenge, as classical criteria such as the RECIST score are insufficient. This necessitates new imaging biomarkers to quantify both tissue integrity and vascular organization. We utilize multifrequency MR-Elastography (MRE) to analyze the vascular organization within tumors through the Hurst index derived from wave dispersion behavior. Our study employs a murine model of liver metastasis, with CT26 tumor cells injected into Balb/C mice spleens, leading to liver metastasis. Imaging is performed using a 7T preclinical MRI scanner and a custom MRE system to induce shear waves. We analyzed these waves' dispersion properties to extract the Hurst index, correlating these findings with CD31-stained histological sections using box-counting analysis.

Our results indicate a significant difference in vessel organization between liver metastasis and normal tissue. The shear modulus imaging distinctly depicts tumor stiffness, while the CD31 staining shows a dramatic difference in vessel organization, quantifiable via fractal dimension and Hurst index. The in-vivo MRE data corresponded with histological findings, although some discrepancies exist due to signal-to-noise ratio challenges.

In conclusion, we have developed a preclinical multifrequency MRE system for rodents, showing that vascular architecture quantification via the Hurst index from both histology and MRE imaging generally matches. Future work will focus on refining imaging protocols to improve SNR and investigating vascular changes during combined FOLFOX and BEVACIZUMAB therapy. These advancements could provide new criteria for assessing the efficacy of anti-tumor treatments targeting vessels.

Characterization of 3D-Printed PEEK Inserts for Maxillofacial Tissue Engineering

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Introduction: Bone regeneration is a significant challenge in regenerative medicine. While autografts remain the standard, their uses are limited (e.g., donor site morbidity, availability…) leading to the exploration of alternative solutions, as bone tissue engineering. This project is part of the development of an adequate bioactive scaffold to restore the mandible. This study aims to develop a 3D cell-seeded insert for mandibular bone defect regeneration, using polyetheretherketone (PEEK) as a scaffold. PEEK offers several advantages, such as a similar elasticity modulus to bone, biocompatibility, radiotransparency, 3D printability, and non-degradability, making it suitable for long-term patient applications. However, its bioinertness still limits its osseointegration potential.

Objectives: The aim of this project is to develop a bioactive PEEK insert 1) coated with hydroxyapatite (HA) to facilitate osseointegration and 2) biologically optimized by cellularizing it with stem cells from human exfoliated teeth (SHED).

Materials and methods: Various chemical protocols have been tested to activate the PEEK surface and produce an optimized HA coating. In parallel, the synergistic effect of fibroblast growth factor 2 (FGF-2) and bone morphogenetic protein 6 (BMP-6) was studied on SHED differentiation, in 2D environment during 14 days to determine the best conditions to obtain their osteogenic differentiation.

Results: The study demonstrates the formation of a dense hydroxyapatite layer on PEEK surface, while preliminary findings from 2D cultures suggest a promising role for combining BMP-6 and FGF-2 in directing SHED differentiation towards the osteoblastic lineage. In conclusion, this study validates the interest of combining a bioactive PEEK and SHED for craniofacial bone defect regeneration, emphasizing its potential for effective treatment. Further investigations are underway to expand on these initial results and propel the development of functionalized inserts for in vivo applications in rat bone defects.

IgA1-Protease mRNA-LNP as a treatment for IgA nephropathy in a mouse model expressing human IgA1

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IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide and one of the first causes of end-stage renal failure. IgAN pathogenesis involves circulating galactose-deficient (Gd) IgA1 complexed with anti–Gd-IgA1 autoantibodies and/or soluble IgA Fc receptor I (CD89). So far there are no specific treatment available for IgAN patients. Mouse differs from humans as they do not express IgA1. The α1KI-CD89Tg mice, which expresses human IgA1 and CD89, develops the disease after 12 weeks of age and thus represents a spontaneous mouse model of IgAN. In a previous study, we have shown that in vivo treatment with recombinant IgA1 protease (IgA1P), a bacterial protein that selectively cleaves human IgA1 in the hinge region, strongly diminishes IgA1 mesangial deposits and reduces inflammation and hematuria in α1KI-CD89Tg mice. However, considerable immunogenicity was observed against the bacterial IgA1P. The aim is to test the IgA1-P mRNA-LNP developed by Moderna in the α1KICD89Tg mice as an early preclinical candidate for IgAN treatment. 12-week-old mice (N=12 animals, 2 groups of 6 animals) received 1 mg/kg dose of LNPs encapsulating IgAP mRNA and LNPs encapsulating GFP mRNA as negative controls following a repeated dose treatment for 6 weeks. All products were IV injected at tail vein. Injections were done once a week. Serial bleeds either before injections -24 hours (h) or 24 hours post each injection were performed for IgA1 serum collections. The urine was also collected at the same time points. All the mice were sacrificed at the end of the treatment or 24h post the last injection. Serum levels of IgA1 were measured by polyclonal Abs anti-human IgA sandwich ELISA (Bethyl Laboratories). Gd-IgA1 levels were measured by KM55 kit (IBL, Japan). IgA1 fragments were analyzed by SDS-10% PAGE and Western blots in serum and urine. Immunohistochemistry for hIgA1 were performed in kidneys. Anti-IgA1P IgG antibody assay was established for immunogenicity evaluation. Western blot data revealed IgA1 Fab and Fc fragments in mouse sera treated in IgA1P mRNA-LNP at 1 week throughout 6 weeks, indicating the ability of such mRNA-LNP products to cleave serum IgA1 in vivo. No effect was seen with GFP mRNA-LNP. Moreover, Fab□1 fragments were also detected in urine as early as 3 weeks and 6 weeks of treatment. IgA1 serum levels decreased after IgA1P mRNA-LNP treatment reaching lowest levels (about 80%) after 4-5 weeks post-injection. Serum Gd-IgA1 was also decreased. Kidney hIgA1 deposits decreased after the 6 weeks treatment. The 6 weeks treatment seems to abolish immunogenicity (preliminary data). This study validated IgA1P mRNA-LNP as new strategy to target human IgA1 in vivo. These results open new avenues for mRNA drug development as a promising new therapeutic approach for IgAN.

Risk factors associated with bacterial sexually transmitted infections (STIs) among men who have sex with men (MSM) during the pre-exposure prophylaxis (PrEP) era: a systematic review and meta-analysis in high-income countries (application to chemsex)

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Introduction: The early 2000s were marked by an increase in the incidence and prevalence
of bacterial sexually transmitted infections (STIs) among men who have sex with men (MSM). Several risk factors, including chemsex, have been implicated in this rise.
Objective: This study aims to synthesize evidence and investigate the risk factors associated with three bacterial STIs (syphilis, gonorrhea, and chlamydia) among MSM in high-income countries.
Methods: In this systematic review and meta-analysis, we searched five electronic databases (PubMed, Embase, Web of Science, Cochrane, and Scopus). Data analysis using the Mantel-Haenszel (MH) methods and inverse variance with the DerSimonian-Laird estimator produced pooled Odds Ratios (ORs) (measuring the association between chemsex and one of the STIs) and tested the heterogeneity between studies.
Results: Following the selection of articles, 65 studies were deemed eligible for inclusion in the systematic review. We focused on the chemsex risk factor reported in 18 studies, 7 of which provided results in the form of ORs. The meta-analysis revealed a significant association between chemsex and STI infection, with a combined OR of 1.65 [95% CI: 1.46–1.86] in the fixed-effects model and 1.59 [95% CI: 1.18–2.15] in the random-effects model. The I^2 test = 60% indicates moderate to high heterogeneity between statistically significant studies ($p = 0.002$), highlighting the variability of chemsex practices in different MSM subgroups.
Conclusion: This study highlights the significant association between chemsex practices and STIs among MSM, underscoring the need for targeted prevention strategies focusing on chemsex in public health initiatives aimed at reducing STIs.

New cationic polyester for miRNA delivery

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Based on the central dogma, messenger RNA (mRNA) serves as the intermediary that conveys genetic information from DNA to proteins through the processes of transcription and translation. In principle, mRNA can thus regulate the function of any gene within a living organism. The function of mRNA can be modulated by microRNAs (miRNAs). The role of miRNAs in gene expression regulation has recently emerged as a significant area of interest in biomedical research, particularly in the study of carcinogenesis and infectious diseases. However, the nature of miRNA molecules makes them easily degraded in vivo, impeding their clinical application. Therefore, developing an efficient and safe delivery system for miRNA is essential for their successful translation into clinical setting. Various biomaterials have been explored for delivering nucleic acids into cells, with polymer-based systems emerging as the most promising. Polyester-based polymers, in particular, have demonstrated high biocompatibility, biodegradability, and effective encapsulation capabilities. Moreover, these materials can be customised to modulate their function by incorporating different functional groups.
Our research aims to develop a polyplex vector capable of delivering miRNA to cardiomyocyte cells following myocardial infarction to stimulate the heart muscle regeneration. The polyplex vector is made of three key components:
- Cationic polyester PDMMLA derivative
- miRNA
- Iron oxide nanoparticle

Currently, our focus lies on the development of the cationic polyester. This material exhibits the ability to bind miRNA through electrostatic interactions, safeguarding it from degradation and enhancing its delivery efficiency.

Using Fisher Information Matrix to predict covariate effects in Forest Plots and power of their relevance

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This work focuses on design of experiments for Pharmacokinetic (PK) and Pharmacodynamic (PD) studies. Non-Linear Mixed effects Models (NLMEM) modeling allows the identification and quantification of covariates that explain inter-individual variability (IIV).
The Fisher Information Matrix (FIM), computed by linearization, has already been used to predict uncertainty on covariate parameters and the power of a test to detect statistical significance. A covariate effect on a parameter is deemed statistically significant if it is different from 0 according to a Wald comparison test and clinically relevant if the 90% confidence interval (CI) of the ratio of change it causes in the parameter is outside a predetermined interval. Those ratios are represented on forest plots.

FIM calculation was extended by computing its expectation on the joint distribution of the covariates, discrete and continuous. Three methods were proposed: using a provided sample of covariate vectors, simulating covariate vectors, based on provided independent distributions or on provided copulas. Thereafter, CI of ratios, power of tests and number of subjects needed to achieve desired confidence were derived. Methods were implemented in a working version of the R package PFIM.

Methods were applied on a toy example in 4 different scenarios, including different sample sizes, sampling points, and IIV. The model was a one compartment model with IV bolus and linear elimination, with three covariates effects. Clinical trial simulations were performed using Monolix and estimations compared to predictions.

When asymptotic conditions are met and if IIV is limited, PFIM accurately predicts uncertainty on covariate effects and the power of both significance and relevance tests. The results of the three methods for FIM computation were the same in our example, but their respective impact should be further explored in complex cases.

A novel transcription factor regulating neuroinflammation

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Pax6 is an epithelial transcription factor that is essential in the development of brain neurons and eye tissue structures. Recently, we found that Pax6 is highly expressed in neonatal mouse brain microglia (MG) but it decreases upon age. Interestingly, recent human transcription studies revealed that PAX6 expression decreases with age in the brain while it is upregulated in Alzheimer's disease. However, the role of Pax6 in MG remains to be investigated. Our in vitro data suggest that Pax6 is pivotal in the regulation of neuroinflammation: PAX6 inactivation by lentiviral shRNA in the embryonic human MG cell line HMC3 shifted MG towards a pro-inflammatory phenotype and impaired their phagocytic capacity. In addition, a comparative RNA-seq analysis of HMC3, depleted or not of PAX6, highlighted the deregulation of a limited number of genes, most related to neuroinflammation and neurodegenerative diseases. To better understand the impact of Pax6 in neuroinflammation in vivo, we used the experimental autoimmune encephalomyelitis (EAE) model in inducible Pax6 knock-out mice. Intriguingly, the absence of Pax6 exacerbated EAE severity, with MG showing increased expression of activation markers by flow cytometry analysis. Collectively, our findings will contribute to identifying the mechanisms by which Pax6 could modulate MG response during neuroinflammation.

Evaluation of treatment effects in genetic ataxias using SARA score modelling: comparison of multiple trial designs by a large trial simulation framework

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Genetic cerebellar ataxias are progressive rare neurological diseases affecting the cerebellum, often with multi-systemic damage to other neurological systems, causing debilitating impairment of gait, balance, speech, and fine motor skills. More than 100 ataxia diseases are autosomal-recessive cerebellar ataxias (ARCAs). Patient's disease severity is evaluated with the Scale for the Assessment and Rating of Ataxia (SARA) score, a composite clinical score (0-40),
which can be modelled using total score (TS), or through Item Response Theory (IRT) models. There are currently no disease modifying drugs for most ARCAs, and promising treatment trials with robust designs are needed. To guide optimal trial design for disease-modifying treatments in rare neurological diseases, this work aimed to study the influence of the choice of model (TS- vs IRT-based), inclusion criteria and design on the power and type 1 error of simulated clinical treatment trials for a hypothetical disease modifying effect. To benefit from a trial, patients with neurodegenerative diseases should ideally be enrolled during the early or mid-stages of their disease. However, the rate of progression is slow and varies with the time since symptom onset (TSO) (0.1-1 point/year). Thus, TSO is also investigated as one of the inclusion criteria.We use a four-parameter logistic model (TS) fit on 173 patients with a specific genetic ataxia – Autosomal-Recessive Spastic Ataxia Charlevoix Saguenay (ARSACS) from the ARCA registry, describing the SARA score versus TSO. This model was modified to fit a drug effect slowing the disease progression rate. The second simulation model is a longitudinal IRT model fit on the 173 ARSACS patients. First, inclusion criteria based on TSO at the start of the study were investigated (early, intermediate, late, heterogeneous) with a parallel design with a TS and IRT model. Second, other designs were investigated using the TS model: a cross-over design, and a delayed start design. In each scenario, 500 trials were simulated, with 100 patients in each, with 1:1 allocation, a trial duration of 5 years with a measurement every 6 months. The simulated datasets were analysed with the simulation model (IRT or TS), a linear model and the TS model with a fixed amplitude parameter. For a parallel design, the late and heterogeneous inclusion criterion yielded the highest power. Power and type I error were highly dependent on the simulation model and the lack/presence of any misspecifications in the analysis model. Crossover and delayed start designs were shown to be less powerful than a parallel design, since the disease progression is slow and observed for a shorter duration under treatment or placebo (compared to a parallel design), so the power is more sensitive to duration than to sample size.

Deregulation of COX-2/PGE2 pathway and EP4 receptor of bronchi in COPD patients

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Chronic obstructive pulmonary disease (COPD) is characterized by airway inflammation, airflow obstruction and emphysema1,2. COX-2/PGE2 pathway is a critical inflammatory pathway in the human lung and PGE2 mediates a variety of physiologic effects through interaction with four distinct G protein-coupled E prostanoid (EP) receptors called EP1, EP2, EP3 and EP43. The four types of receptors are charactered by different actions, bronchial contractions through activation of EP1 receptors and relaxations through actions on EP2 or EP4 receptors under the stimulation of PGE2 respectively. However, there is few study showing the expression level of COX-2/PGE2 pathway and EP receptors of bronchi in COPD patients. Therefore, the aim of this study is to investigate the COX2/PGE2 and EP receptors expressions.

We analysed the expression of COX-2, mPGES1, PGE2 and its EP1-4 receptors in human bronchi homogenates using western blot, RT-PCR, ELISA and immunohistochemistry (IHC). COX-2 and mPGES1 enzymes were significantly increased in COPD patients compared with controls. PGE2 level was significantly increased in COPD patients versus control. EP4 receptor (protein and mRNA) expressions were significantly reduced in the COPD group versus controls and confirmed by IHC. No difference was found with EP1-3 receptors expressions.

Our results point to the importance of EP4 receptor expression regulation in different lung diseases. Considering all these data, we can suggest that high PGE2 synthesis with reduced expression of EP4 receptors together could contribute to inflammation deregulation and lung remodeling in the distal bronchi and contribute to COPD pathophysiology, EP4 maybe a potential target in treatment of COPD.

Involvement of neutrophil serine proteases in periodontitis

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Periodontitis is a chronic inflammatory disease characterized by the irreversible destruction of the supporting tissues of the teeth. This dysbiotic-origin disease causes severe inflammation and resorption of the alveolar bone, leading to a loss of dental attachment. Neutrophils might be involved at different stages of periodontitis progression. However, their tissue phenotypes in the microenvironment of periodontitis remain poorly understood.
Our project aims to characterize different neutrophil phenotypes depending on their locations within the periodontal tissue at various stages of periodontal inflammation and bone resorption, with a specific focus on the expression of neutrophil serine proteases.
We used a mouse model of periodontitis by applying a ligature, soaked or not soaked with Porphyromonas gingivalis, placed in the palatal sulcus of the right upper first molar, with the left side serving as a negative control. These ligatures were changed twice a week for 28 days. Micro-CT analysis allowed for longitudinal monitoring (14 days and 28 days) of periodontal bone resorption. All mice were sacrificed for histological analysis.
Micro-CT analysis showed that the mice developed alveolar bone resorption starting at 14 days, which progressed up to 28 days. After 28 days of induction, we observed an increase in the expression of each neutrophil serine protease in the periodontal tissues. However, this increase was not the same in mice treated with or without P. gingivalis. Proteinase 3 (PR3) and Neutrophil Elastase (NE) were overexpressed in connective tissue in the presence of P. gingivalis, whereas the increase in Cathepsin G (CTSG) expression was less pronounced. We noted that neutrophils expressing these serine proteases were heterogeneously distributed within the tissue: at the level of the sulcus or alveolar bone. Finally, in both conditions, we demonstrated a pool of neutrophils expressing the osteoclast activation factor RANKL, suggesting an important role for neutrophils in bone resorption during periodontitis.

Biomechanical phase angle as proxy to quantify the presence of microvascular invasion in hepatocellular carcinoma using MRI

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Hepatocellular carcinoma (HCC) is a common primary cancer with a poor prognosis due to late detection. Microvascular invasion (MVI), where tumor emboli invade nearby vessels, critically affects outcomes. Currently, MVI can only be diagnosed through histopathology of liver resections. Tumor cells in MVI alter tissue biomechanics by degrading the extracellular matrix. Magnetic resonance elastography (MRE), a non-invasive MRI-based imaging technique, measures liver biomechanics by assessing shear modulus. This study explores MRE for identifying biomarkers to evaluate HCC severity and improve patient management.

We studied 44 patients with MRE prior to HCC resection. MRE was performed using a Philips 1.5T MRI with a transducer vibrating at 40 Hz. The acquisition used a 3D motion-sensitive sequence. Three regions of interest were identified: the tumor region, the peritumoral region, and distant non-tumoral liver tissue. Biomechanical parameters, including shear stiffness (Gd), shear viscosity (Gl), and phase angle (Y) reflecting the ratio of viscosity to stiffness, were measured. Histopathology determined MVI presence, and tumor differentiation was scored by WHO standards.

The phase angle Y in tumor and peritumoral regions revealed distinct patterns. Tumors without MVI (MVI-) formed a single cluster at specific phase angles, while MVI positive tumors (MVI+) formed separate clusters in the phase space. This indicates that the phase angle of peritumoral tissue is key for distinguishing MVI presence non-invasively. In MVI+ patients, peritumoral phase angles resembled those of the tumor, reflecting biomechanical changes due to invasion. Tumor differentiation was higher in MVI- patients, aligning with biomechanical differences between tumor and peritumoral regions.

The phase angle of peritumoral tissue appears to be a promising non-invasive biomarker for detecting MVI in HCC patients. This result could help handling treatment decision for patient and avoid biopsy.

Effects of Omega-3 on Human Coronary Vascular Tone Induced by Neurotransmitters

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Coronary artery diseases are characterized by chronic inflammatory status and endothelial dysfunction. This involves an increased production of neurotransmitters such as serotonin (5-HT) and acetylcholine. On the other hand, inflammation increases levels of pro-inflammatory lipid mediators such as PGE2 and TxA2. These changes are associated with effects on the vascular function by increasing vasoconstriction. Specialized pro-resolving lipid mediators (SPM), derived from omega-3 polyunsaturated fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) play an active role in the resolution of inflammation. Recent results from our group show that DHA and metabolites (Resolvin D1, D5 and Maresin 1) reduce contractions of human coronary arteries (HCA) induced by PGE2 [1]. On the other hand, RvD5 and Mar1 production by human vagus nerve has been measured [2], their impact on the cardiac neuronal system remains unexplored. Aims: The objective of this study is to investigate the impact of omega-3 on the release and effects of neurotransmitters like acetylcholine and 5-HT in HCA. Methods: The HCA were isolated from human hearts (n=6) after transplantation at Bichat Hospital and placed in an organ bath system. They were stimulated with different voltages to release neurotransmitters, before and after 1 or 18 h of incubation with omega-3. In order to evaluate the effect of DHA/EPA on exogenous neurotransmitters, dose response curves with 5-HT and acetylcholine were realized. Vascular tone variations were analyzed using Iox software. Results: Our results show that HCA contract after electrical stimulation, with an increased effect at higher voltages. The contractions resulting from this stimulation are attributed to a direct effect on smooth muscle cells and also to the neurotransmitter release, as they are partially blocked by tetrodotoxin (10 µM). DHA (0.1 mM) demonstrates the ability to reduce the contractions induced by stimulations at 10 and 30 volts by 56% and 31%, respectively. Additionally, exogenous neurotransmitters, such as 5-HT and acetylcholine induce contractions in HCA. Acetylcholine induced vasocontractions were reduced by DHA, while the serotonin-induced contractions remain unaffected by DHA/EPA. Conclusion: Our preliminary results indicate that omega-3 may have an effect at the neuronal level in HCA, suggesting potential innovative therapeutic strategies.

To quantify the association between tumor dynamics and overall survival across cancers: a Bayesian meta-analysis

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In oncology clinical trials, the primary clinical endpoint is overall survival (OS). Tumor size measurements, summarized as the Sum of Longest Diameters (SLD) of target lesions1, are collected over time as a marker of disease progression and treatment response. The on-treatment growth constant (kg) of the SLD in the model by Stein et al2 has been shown to be a good explanatory variable of OS3,4. Thus, we propose to assess whether the strength of the association between kg and OS is similar across cancer types using a joint model approach5, in a desire to bridge predictive capabilities among clinical trials.

This study aims to develop a meta-analysis of nonlinear joint models6,7 of SLD trajectories and survival in the atezolizumab (ATZ) based treatment arm of 10 clinical trials investigating five cancer types.

For each clinical trials separately, a Stein model2 was fitted to describe the SLD dynamics and we assumed an impact of the logarithm of the kg on the survival accelerated failure time8 OS sub-model, in a Bayesian framework9. The inter-study variability was estimated using a random-effect meta-analysis on the estimates of the joint model parameters focusing on the kg-OS association parameters.

As expected, kg varied considerably across studies. For RCC patients treated by ATZ and bevacizumab, the tumor volume doubling time was estimated at 6.5 years. In contrast, for SCLC treated with ATZ, carboplatin, and etoposide, the estimate it was about a year.

For each individual study, an increase of kg was found to significantly reduce the OS time. However, non-negligible between-study variability was identified. Indeed a large 95% prediction interval of this association parameter was obtained: for a new study one would predict an increase of survival times between 6% and 132% for a kg divided by two.

This work reinforces the idea that kg can help describe OS, regardless of the study, cancer and treatment type. However, the magnitude of the kg-OS association varied across studies and cancer types. Modelling the dynamics of each lesion within a patient instead of the SLD should enable to capture the kg-OS association at the organ level10,11, which we expect to show a reduced heterogeneity across cancer types

Investigating the role of a novel immune receptor in regulating macrophage pro-fibrotic activity in idiopathic pulmonary fibrosis

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Idiopathic pulmonary fibrosis (IPF) is a fatal interstitial lung disease with an unknown etiology. It is characterized by the progressive and irreversible accumulation of fibrous tissue in the pulmonary interstitium and alveolar spaces, drastically affecting breathing. The anti-fibrotic drugs nintedanib and pirfenidone can reduce the rate of disease progression but do not prevent the inevitable progression toward fatal respiratory failure. Recent developments in fundamental and translational studies demonstrate that immune cells play a significant regulatory role in IPF. Lung macrophages constitute a major immune population in the lung and are known to generate multiple growth factors and mediators, such as TGF-β1, CCL18, and MMPs, which greatly affect the initiation and progression of IPF. Given their plasticity, it is essential to develop therapies that shift macrophage polarization away from fibrotic activity. Our preliminary results revealed a novel immune receptor that may regulate lung macrophages in IPF. Transcriptomic datasets showed that the identified receptor is predominantly expressed in macrophage populations. Flow cytometry results from our human cohort confirmed dysregulated expression of the receptor in IPF patients' alveolar macrophages. Interestingly, several clinical parameters, such as total lung capacity, correlate with receptor expression. We further developed a human monoclonal antibody to investigate the impact of a disrupted expression of the receptor on macrophages' fibrotic pathways. Our transcriptomic results revealed that receptor inhibition in alveolar macrophages potentiates their pro-fibrotic phenotype. The mechanisms of action are now being investigated to better understand the receptor's role in programming macrophage activity in IPF and to assess the therapeutic potential of a specific agonist. Overall, this study has the potential to uncover a new immune target in a fatal pulmonary disease.

Building a theoretical model of viral dynamics for SARS-CoV-2 and Influenza A co-infection

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Millions of people are infected annually by various respiratory viruses, leading to illness that can range from benign to severe ([1],[2].) Recent advancements in techniques for simultaneous detection of multiple viruses have revealed the frequent occurrence of co-infections, which may lead to more severe disease [3]. However, the interactions between these viruses within a host and their impact on virulence on disease progression is still poorly understood, specifically the role of the immune response. The objective of this work is to investigate the viral dynamics and interactions between influenza A virus (IAV) and SARS-CoV-2 in the upper respiratory tract (URT) by using mathematical modelling.

We have first described viral kinetics in mono-infection by fitting viral load in humans for each virus. We have compared different models for innate and adaptive immune response. Model selection relied on Bayesian Information Criteria (BIC) and Visual Predictive Check (VPC.)

The model that best describes the kinetics of both mono-infection incorporates the action of interferons (IFNs) by reducing viral production and inducing cells to become refractory, as well as the adaptive immune response by increasing infected cell death rate. We found important differences between IAV and SARS-CoV-2 in term of time to viral peak and time until virus elimination.

Next, we applied this framework to co-infection to simulate kinetics by varying the order of infection, the delay between infection and the susceptibility of cells of the URT to different viruses. With an equivalent delay, IAV seems to have higher impact on SARS-CoV-2 kinetic than vice versa, likely due to its specific tropism. When the delay between infections is small, the protection induced by IFN prevents the second infection from reaching the levels observed in mono-infection.

ABSTRACTS

PITCH YOUR PROJECT

Temocillin: risky choice for group 3 Enterobacterales infections ?

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Temocillin (TEM) is a narrow-spectrum β-lactam derived from ticarcillin, active against class A and C β-lactamases, including ESBLs (extended-spectrum β-lactamases) and certain carbapenemases. Its impact on the intestinal microbiota is limited, making it an interesting alternative to carbapenems. The mechanisms of resistance to TEM are not well known. A new mechanism of resistance to TEM described in Enterobacter cloacae complex (ECC), involving a mutation in the baeS gene, responsible for an increased efflux of TEM, which does not impact its efficacy in vivo in a murine peritonitis model when E. coli carries it. We evaluated the impact of this mutation on the effectiveness of TEM in a murine peritonitis model involving ECC. An isogenic pair of clinical E. asburiae strains, resistant (E. asburiae temo-R, carrying a single Thr175Pro mutation in baeS, responsible for increased efflux via the AcrD pump) or not (E. asburiae temo-S) to TEM were studied. The in vitro activity of TEM and in vivo in a murine model of peritonitis with high inoculum was studied, using cefepime (FEP) as a reference. Resistant strains emerging under treatment were sequenced. In vitro, TEM MICs were 4 mg/L and 64 mg/L for E. asburiae temo-S and E. asburiae temo-R, respectively. In vivo, TEM was ineffective on both E. asburiae temo-R and temo-S strains: survival rates were 23% and 42% for TEM-treated temo-R and S strains versus 100% for FEP-treated mice, regardless of the strain. This TEM failure was explained by the rapid emergence of resistant mutants carrying the same Thr175Pro mutation in the baeS gene. TEM is ineffective in a high-inoculum model against both temo-S and temo-R ECC strains, despite favorable PK/PD conditions. The rapid emergence of resistant mutants in sensitive strains through mutation in the baeS gene suggests that TEM is not a suitable treatment for high-inoculum infections caused by ECC. Further studies are needed to confirm these results with other clinical ECC strains.

Microbial and environmental determinants behind the evolutionary success of major bacterial clones

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The intestinal microbiota is composed of 30 phyla, with bacterial counts reaching up to 10^14 bacteria per gram of feces. It evolves throughout life, influenced by various environmental and anthropological factors, yet retains a unique phylogenetic identity. One major factor influencing microbiota composition is antibiotic use, which can induce dysbiosis, creating a favorable environment for antibiotic-resistant strains and facilitating horizontal gene transfer. The World Health Organization (WHO) estimates that antibiotic resistance could lead to 10 million deaths by 2050. The Dynamics of REsistance to Antibiotics within the human gut Microbiota (DREAM) project, funded by the French National Research Agency (ANR) for six years, investigates how gut microbiota composition influences the establishment and modulation of antibiotic resistance genes. This project collaborates with NutriNet-Santé, which collects dietary and demographic data from 170,000 volunteers. Fecal samples from 100 volunteers were collected and analyzed to select 16 representative microbiotas for testing the impact of antibiotics on gut microbiota. Initial results from in vitro studies using the Mini Bio Reactor Array (MBRA) model show differential responses to antibiotics depending on baseline microbiota composition. The MBRA is a continuous-flow culture system that maintains stable microbiota cultures under anaerobic conditions. Using this system, the project has demonstrated that baseline microbiota composition influences the response to antibiotics like amoxicillin and ceftriaxone, suggesting that it may also affect the colonization of resistant strains. The primary aim of this PhD project is to extend these findings by studying the impact of commonly used antibiotics (trimethoprim-sulfamethoxazole and cefixime) on the microbiota of 16 donors using the MBRA model. Further, the project will assess factors favoring the establishment of resistant strains. The analysis will include metagenomic sequencing and selective culturing of fecal samples before, during, and after antibiotic treatment. The project is divided into two axes: 1. Constructing a collection of E. coli strains with resistance genes and genetic barcodes using CRISPR/Cas9, including various beta-lactamase variants (blaCTX-M, blaTEM-1) and other resistance determinants (sulA, tetA, Cat, quinolone resistance). 2. Evaluating the colonization of these strains in MBRA cultures of the selected microbiotas, tracking barcode frequencies over time through next-generation sequencing (NGS). This project aims to answer a key unresolved question: what are the determinants of the evolutionary success of certain resistant clones? By exploring genetic, plasmid, resistance gene, and microbiota ecosystem factors, this research will provide insights into the selective pressures driving resistance

Dialogue miARN-microbiote en période néonatale et effets à long terme sur la santé intestinale

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Les conditions de colonisation initiale de l'intestin du nouveau-né par les bactéries commensales jouent un rôle crucial dans le développement de l'enfant. Des altérations précoces du microbiote semblent avoir un impact majeur sur la santé intestinale à l'âge adulte, comme l'ont montré plusieurs études. Par exemple, l'exposition précoce aux antibiotiques est liée à une susceptibilité accrue à des maladies chroniques telles que les Maladies Inflammatoires Chroniques de l'Intestin (MICI). Cependant, les mécanismes par lesquels le microbiote influence l'homéostasie intestinale de l'hôte dès la naissance restent mal compris. À l'interface hôte-microbiote, les microARN (miARN), de petits ARN non codants régulant environ 60% du transcriptome humain, semblent jouer un rôle clé. Notre équipe a montré que la surexpression ou sous-expression de miARN fécaux est associée à l'inflammation dans les MICI, impactant des fonctions digestives critiques telles que la barrière intestinale et la dysbiose. Leur rôle durant les premières étapes de la vie reste cependant inexploré. Cette étude cherche à comprendre si et comment les interactions miARN-microbiote au cours de la période néonatale influencent la santé intestinale à long terme. Nous avons donc mené une expérience en administrant par gavage des miARN identifiés comme pro-inflammatoires à des souriceaux C57BL/6J, une fois par jour de 7 à 10 jours. Les souris ont été surveillées jusqu'à 51 jours. La supplémentation en miR-B durant la deuxième semaine de vie a induit une augmentation de marqueurs inflammatoires à l'âge adulte, notamment la myéloperoxydase et l'interleukine 6 dans le côlon. Des analyses sont en cours pour évaluer l'étendue des changements microbiotiques induits. Nos résultats sont les premiers à suggérer un rôle modulatoire des miARN sur le développement de l'interface hôte-microbiote.

Facteurs de non réponse in vivo à l'antibiothérapie dans un modèle de prostatite aiguë murine

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Male urinary tract infections (MUTI) account for 20% of all urinary tract infections, with a relapse rate of 20%. However, the microbiological factors favoring these relapses are poorly understood, and the hypothesis of the existence of quiescent bacterial reservoirs remains to be explored. We set up a mouse model of MUTI, infecting mice with an Escherichia coli UTI-89 strain, previously modified to contain a genetic reporter system for bacterial division, resulting in the expression or non-expression of a lacZ gene. Mice were treated or not with antibiotics to study their impact on bacterial counts and bacterial division. An ex vivo experiment was also conducted to examine a potential barrier effect, exposing organs to antibiotics in the presence or absence of Triton X-100. In our antibiotic-free model, spontaneous bacterial clearance was observed, associated with a rapid cessation of bacterial division by D2. Later, a resumption of division is possible, associated with a re-increase in bacterial counts. Antibiotics failed to reduce bacterial counts compared with control groups, with a quiescent, non-antibiotic-resistant surviving population. These results contrast with in vitro data showing a significant bactericidal effect of antibiotics on the strain, even in the stationary phase. The addition of Triton ex vivo enhances the effect of ciprofloxacin ($p=0.0097$) and fosfomycin ($p=0.0215$) in the prostate. For the other antibiotics, as well as in the bladder, efficacy also appears to be increased, although not significantly. These results suggest the existence of quiescent bacterial reservoirs that may promote MUTI recurrence. Antibiotic ineffectiveness in our model is probably multi-factorial, combining bacterial tolerance to antibiotics, a probable barrier effect, and an optimizable antibiotic therapy protocol. The characteristics of the reservoirs remain to be clarified, as do the potential existence of biofilms and bacterial-microenvironment interactions.

Study of TIGIT implication in the profibrotic activity of regulatory T lymphocytes in idiopathic pulmonary fibrosis

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Idiopathic pulmonary fibrosis (IPF) is the most frequent and severe type of lung fibrosis, with a median survival of 3 to 5 years following diagnosis. IPF is characterized by breathing difficulties associated with progressive and irreversible accumulation of fibrous tissue in the lungs, mainly due to aberrant activation of fibroblasts. In this context, immune cells can polarize towards a pro-fibrotic phenotype and secrete pro-fibrotic mediators, including the transforming growth factor beta (TGF-β). Nintedanib and pirfenidone are the only anti-fibrotic drugs that were approved for the treatment of IPF and progressive pulmonary fibrosis. Besides a high-cost burden for patients and healthcare systems, both drugs can slightly reduce rates of disease progression but do not prevent an inevitable evolution toward fatal respiratory failure. Thus, new therapeutic strategies are urgently required against IPF. Regulatory T cells (Tregs) are crucial for immune regulation and their functions seem to be altered in IPF, with increased numbers linked to disease severity. Tregs secrete pro-fibrotic factors like TGF-β and interleukin (IL)-10, which contribute to fibrosis worsening. The T cell immunoreceptor with Ig and ITIM domains (TIGIT) is a novel immune checkpoint that is widely studied in the field of anticancer immunotherapy. TIGIT is known to shape the immune response in different pathological contexts through the enhancement of the suppressive functions of Tregs. Moreover, high TIGIT expression/ligation suppresses T helper (Th)1/Th17 cells and marks increased Th2 response associated with fibrinogen-like protein 2 and IL-10 production. It is worth mentioning here that much evidence shows the predominance and the profibrotic effect of type-2 responses in IPF. The research hypothesis underlying this project is that TIGIT inhibition would reprogram Tregs in IPF and limit their fibrotic activity, suggesting therefore a potential therapeutic target against a fatal disease.

Developing a metagenomics–driven framework for assessing the risk of emergence of environmental antibiotic resistance genes in pathogenic bacteria

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Antimicrobial Resistance (AMR) is a global and developing threat, causing more than a million deaths each year around the world. This is mainly due to the acquisition and successful spread of antibiotic resistance genes (ARG) by pathogenic bacteria such as Enterobacterales. Strikingly, very little is known about the origin of the ARG acquired by pathogenic bacteria, in terms of the source and the drivers of such emergence. Nonetheless, ARG harbored by Enterobacterales and whose origins could be traced back originated from environmental bacteria. Hence, there is a need to assess the risk of emergence of environmental ARG to bacterial pathogens. While ARG seem to be shared among phylogenetically-close bacteria, we and others showed that some of them could be shared by distantly related ones. Therefore, there is a need to better quantify the phylogenetic drivers of ARG sharing among bacteria to better understand the likelihood of their potential emergence to pathogenic bacteria. Besides, there is a major lack of knowledge about the phenotype conferred by ARG. While it is already challenging to identify ARG in understudied environments, it is even more difficult to predict which antibiotics they actually are active on. To address this limitation, functional metagenomics can be used as it enables the identification of ARG based on the resistance they confer. In this work, we aim at assessing the risk of ARG emergence in pathogens by (1) quantifying the phylogenetic distances between bacteria sharing ARG using a large database of culturable bacteria, (2) expand this work to a large repertoire of metagenome-assembled genomes (MAGs), (3) apply mathematical models and machine learning methods to assess the risk of transfer between two taxa and (4) apply these models on functional metagenomics data obtained in the lab.

Impact de la Protéase Nexine-1 dans l'arthropathie hémophilique, une complication majeure de l'hémophilie

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L'hémophilie est une maladie hémorragique héréditaire due au déficit d'un facteur de la coagulation, le facteur VIII (FVIII) pour l'hémophilie A (HA) ou le facteur IX (FIX) pour l'hémophilie B (HB). Ces déficits entrainent un défaut de génération de thrombine responsable des hémorragies. L'hémophilie se caractérise aussi par la dégradation du cartilage articulaire. La survenue de micro-saignements indétectables par le patient est un facteur important du développement de l'arthropathie hémophilique. Le tissu synovial et le cartilage présents au niveau des articulations sont les cibles d'enzymes protéolytiques (activateurs du plasminogène, metalloprotéases...) connues pour être impliquées dans l'évolution de l'arthropathie hémophilique. Les articulations doivent pouvoir se protéger des lésions protéolytiques en produisant des antiprotéases. Ainsi, la balance entre les protéases et leurs inhibiteurs est essentielle pour l'homéostasie des articulations. Les serpines forment une famille de protéines structurellement apparentées, dont la majorité sont des inhibiteurs de sérine protéase. Parmi elles, la serpine E2 ou protéase nexine-1 (PN-1) est une serpine produite par divers types cellulaires. La PN-1 inhibe de nombreuses sérine protéases dont la thrombine, les activateurs du plasminogène (uPA, tPA) et la plasmine. La PN-1 est ainsi apparue comme un acteur important dans la régulation de la dégradation protéolytique au niveau tissulaire. L'objectif est d'Etudier l'impact de la PN-1 présente dans le tissu articulaire dans le développement de l'arthropathie hémophilique. Pour cela nous allons réaliser des études in vivo sur des chondrocytes et in vitro sur un model murin d'hémarthrose.

Le tissu gingival : intérêts en médecine légale et médecine régénératrice

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Le délai post-mortem (DPM) correspond au temps écoulé entre le décès d'un individu et son examen médico-légal. C'est une donnée cruciale pour les autorités judiciaires mais les techniques actuelles ne permettent d'établir qu'une fenêtre de temps sans valeur précise. Afin d'apporter une approche complémentaire, nous étudions la cinétique d'expression et les produits de dégradations des protéines de la voie de l'hypoxie médiée par HIF1-α, dans la gencive. Récemment, le tissu gingival est apparu comme un tissu bien adapté à l'analyse médico-légale, notamment grâce à la protection offerte par les lèvres limitant l'influence des facteurs environnementaux. De plus, il est facilement accessible et son échantillonnage est peu invasif, même en présence de rigidité cadavérique. Dans la littérature, une expression différentielle de HIF-1α, le médiateur maître de l'environnement hypoxique prenant place après la mort a été mise en évidence par une analyse immunohistochimique dans des échantillons gingivaux à différents délais post-mortem. Notre première hypothèse est donc que cette expression variable de HIF-1α ou d'autres composants en aval des voies hypoxiques pourrait servir d'indice pour identifier des biomarqueurs susceptibles d'aider à élucider le DPM. Par ailleurs, le tissu gingival est riche en cellules diverses, dont des cellules au potentiel souche (GSC) ayant une appétence pour les conditions hypoxiques. Notre deuxième hypothèse est que la population de GSC possèderait une capacité de survie après la mort, constituant dès lors une nouvelle source de cellules souches pouvant être utilisée en médecine régénératrice. Afin d'évaluer nos hypothèses, nous avons d'abord travaillé sur le modèle souris et étudié l'expression de HIF-1α à différents temps post-mortem (qPCR, Western Blot et histo- et immuno-marquages). La nature des cellules responsables de l'expression de HIF-1α a été recherchée via des cultures cellulaires et cytométrie en flux. Notre analyse s'est étendue de l'heure exacte du décès jusqu'à 100 heures PM correspondant à un état de putréfaction avancée de l'animal. Nos résultats montrent une bonne stabilité post-mortem du tissu gingival une augmentation rapide de l'expression de l'ARNm de HIF-1α dans les temps post-mortem courts (jusqu'à 4h PM) puis une décroissance lente de l'expression des transcrits avec un signal détectable jusqu'au moins 100h PM (3) l'expression de la protéine HIF-1α au niveau cellulaire jusqu'au moins 100h post-mortem sous sa forme dimérisée active la présence de la protéine HIF-1α dans les strates épithéliale et conjonctive du tissu avec une accumulation du signal dans les deux étages gingivaux jusqu'au moins 32h après la mort. Par ailleurs, la mise en culture du tissu gingival post mortem a montré la présence au sein du tissu gingival post-mortem d'une population de cellules « GSC-like », d'origine crête neurale, capables de multi-différenciations, exprimant les marqueurs de surface caractéristiques des cellules souches mésenchymateuses ainsi que HIF-1α. Cette étude pré-clinique a permis de démontrer l'utilité du tissu gingival et du modèle murin pour les analyses post-mortem et l'intérêt de l'analyse de protéines comme HIF-1α pour l'estimation du DPM. Nous avons dès lors développé une collaboration avec l'Institut médico-légal de Paris et commencé nos analyses sur tissu gingival cadavérique humain.

Compréhension des mécanismes de résistance à la radiothérapie interne vectorisée dans les tumeurs neuroendocrines et carcinomes hépatocellulaires et amélioration de son efficacité

Killian Véron

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Deux cohortes de patients atteints d'un CHC ou d'une TNE et ayant reçu un traitement de TARE (Transarterial Radioembolization) ou de PRRT (Peptide Receptor Radionuclide Therapy) ont été constituées. Seuls les échantillons prélevés avant la date du traitement du patient seront utilisés. L'ADN et l'ARN de ces tumeurs seront extraits pour profilage moléculaire. Les profils génomiques et transcriptomiques des répondeurs et des non répondeurs seront comparés pour définir une signature moléculaire de résistance à la TRT (targeted radionuclide therapy). 2. Compréhension des effets et des mécanismes de résistance à la TRT et test de nouvelles combinaisons thérapeutiques associant des potentiateurs Deux lignées cellulaires de CHC et de TNE du pancréas ont été sélectionnées. Elles seront exposées à des doses croissantes de TRT pour déterminer leur sensibilité et des transcriptomes seront réalisés afin de déterminer les pathways activés et leur cinétique. Nous exposerons également des tranches de tumeurs fraiches à la TRT durant leur culture qui présentent pour avantage de permettre le maintien de l'architecture et de la composition cellulaire de la tumeur. Après une exposition à la TRT, ces tranches seront dissociées et profilées par single cell RNAseq pour évaluer l'effet sur tous les types cellulaires. Une fois les acteurs clés dans la résistance/réponse à la TRT définis, nous tenterons de potentialiser la TRT en y associant des inhibiteurs spécifiques. 3. Recherche de nouvelles cibles thérapeutiques pour la PRRT Une quinzaine de molécules membranaires ont été identifiées comme des cibles potentielles de la PRRT. Nous évaluerons l'expression de ces marqueurs sur ces types tumoraux par immunohistochimie. Les plus prometteurs pourront être testés sur des lignées ou des tranches après couplage de leur ligand à des émetteurs alpha ou beta.

Acknowledgments

The organization comittee thanks all participants for coming again to this annual meeting, many thanks to all the young researchers that presented a poster or an oral communication for discussing your research project with us.

Many thanks to the speakers during the round table for sharing their wonderful career path. We hope it will inspire students and young researchers.

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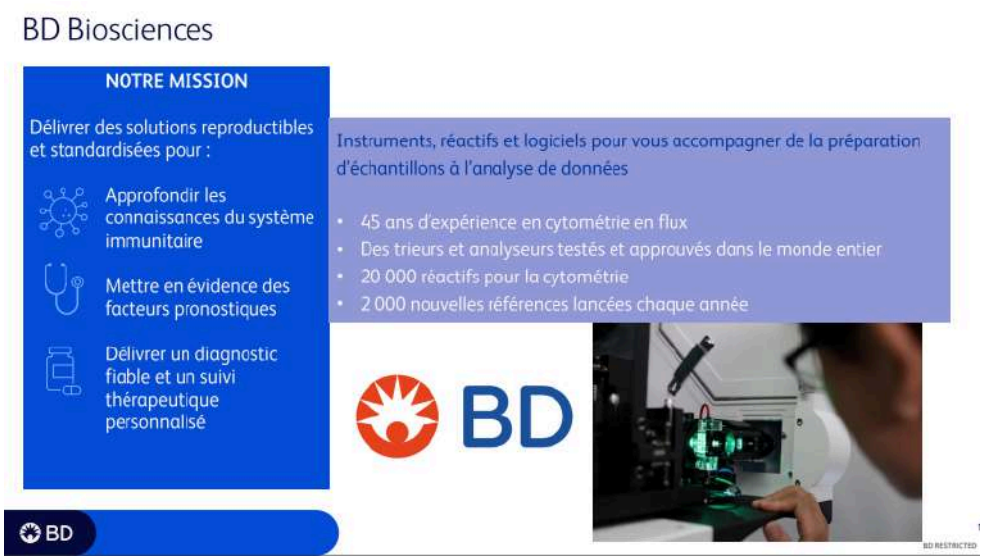
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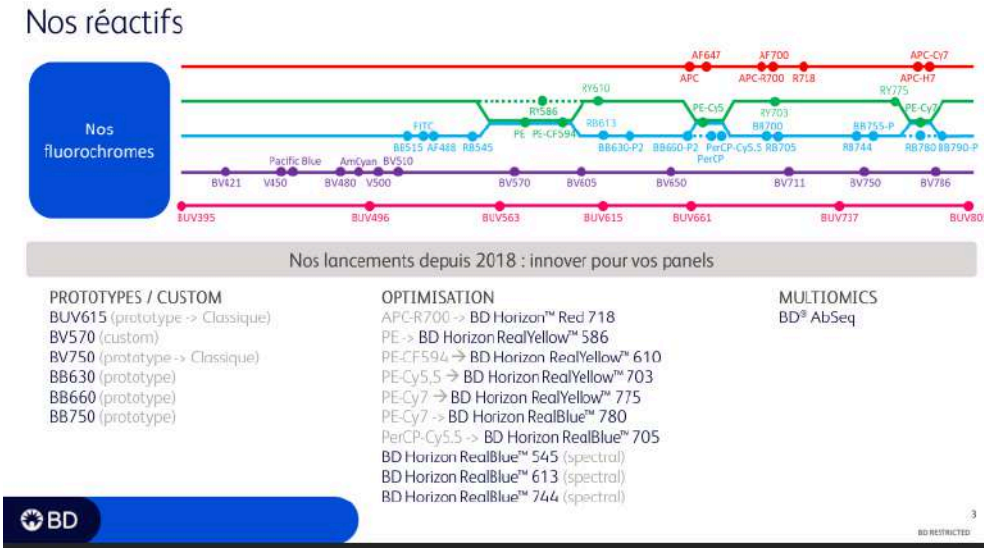
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