27^{ème} Journée Scientifique de l'EDISS ADAPTATIONS PHYSIOLOGIQUES A LA MICROGRAVITE

ABSTRACT BOOK & PROGRAM

Program





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If you are presenting a poster, please stand next to your poster during the whole session. The jury members will come see you.

AMPHITHEATRE MERIEUX Program

08:00	Welcome meeting. Sylvie Ricard-Blum
08:35	D1 representative elections
08:45	Sponsor presentation
08:50	Association presentation
09:00	Break
09:30	Plenary session. <i>Alain Guignandon</i> (Saint-Etienne)
10:20	Lung inflammatory and tissue injury mechanisms in response to pollution-derived fines particles in a mouse model. <i>Tanguy Déméautis</i>
10:35	Effectiveness of medical management in the field of rare diseases. The exemple of fibrous dysplasia in bone. <i>Mélanie Legrand</i>
10:50	Off-label use of cinacalcet in pediatric primary hyperparathyroidism : a French multicenter experience. <i>Julie Bernardor</i>
11:20	Break
11:30	Allometric relationships between body mass and mitochondrial efficiency of birds. Jessica Barbe
11:45	Characterization of an antimicrobial peptide resistance system involved in virulence in Streptococcus pneumoniae. <i>Agathe Faure</i>
12:00	Triple negative breast cancer and active-targeted nanomedicine : the use of monoclonal antibodies. Silvia Breusa
12:30	Lunch break
14:00	Development of an in-vitro platform for dynamic maturation of full-thickness skin model. Zaidi Hamza Raza
14:15	Impact des horaires de travail des soignants sur l'identification de la douleur en réanimation. <i>Laura Schmidt</i>
14:30	Investigating the role of CozE in S. pneumoniae ; from peptidoglycan syntesis to membrane homeostasis. <i>Linus Wilhelm</i>
14:45	3D printable alginate-gelatin hydrogels with variable viscoelastic properties as sole differentiation factor of induced pluripotent stem cells for tissue engineering. <i>Lucas Lemarié</i>
15:00	Films Antimicrobiens Biodégradables à base de Nanocapsules pour la Biopréservation des Aliments. <i>Fatemeh Baghi</i>
15:30	Break
16:00	Increased mitochondria retention in mature sickle red blood cells. Sofia Esperti
16:15	Impact of phenylacetic acid, a microbiota-derived metabolite, on hepatic endoplasmic reticulum- mitochondria interactions and steatosis. <i>Rémy Lefebvre</i>
16:30	A journey from Vibrio vulnificus to priority pathogens transketolase. Georges Rainier-Numa
16:45	Round table – professional perspectives after a PhD
17:45	Awards and closing ceremony
18:00	Afterwork – Les Salons d'Anthouard (5 minutes walk from the venue)

SALLE DE PRESSE Program

10:20	Estimation of the dose delivered by Cone-Beam CT patient positioning system for prostate VMAT treatments using an innovative plastic scintillating dosimeter. <i>Christian Popotte</i>
10:35	Unravelling motor neuron identity and new cell – extracellular matrix interplay in zebrafish motor axon development and regeneration. <i>Laurie Nemoz-Billet</i>
10:50	Association of hospital bed turnover with patient outcomes in digestive surgery. Arnaud Pasquer
11:20	Break
11:30	The HIV-1 Integrase C-Terminal domain induces TAR RNA structural changes promoting Tat binding. <i>Camille Louvat</i>
11:45	Assessment of skeletal muscle energy metabolism by 31P MRS in long-term fasting. Antoine Naegel
12:00	Development of an innovative lipid vector with a poly(lactic) acid core for the delivery of mRNA. <i>Camille Ayad</i>
12:30	Lunch break
14:00	Identification and distribution of circulating Leptospira strains in humans, dogs, and comparison with circulating Leptospira strains in urban small mammals in France, between 2019-2021. <i>Marta Garcia Lopez</i>
14:15	Influence of marker weights on scapular kinematics in a multibody kinematic optimization. <i>Félix Lefebvre</i>
14:30	An innovative phyllosilicate-based hydrogel for skin decontamination against chemical warfare agents. <i>Kardelen Durmaz</i>
14:45	NUAK1-dependant metabolic underpinnings of adult muscle stem cells. <i>Ha My Ly</i>
15:00	Are subjects suffering from orthorexia nervosa characterized by specific food categorization strategies and cognitive flexibility impairments? <i>Clara Lakritz</i>
15:30	Break
16:00	Sex differences in skeletal muscle regeneration in a mouse model of lengthening contraction- induced injury. <i>Charline Jomard</i>
16:15	Overepression, kinetic characterization, and molecular modeling of a new (phospho)lipase from Fusarium annulatum Bugnicourt strain CBS. <i>Ahlem Dab</i>
16:30	Impact of the hyper-radiosensitivity to low-dose phenomenon on hyperfractionated radiation therapy. <i>Eymeric Le Reun</i>

SALLE DES DAMIERS Program

10:20	Impact of the contrast of CT images and FLAIR MRI for stroke lesion segmentation with deep neural networks. <i>Juliette Moreau</i>
10:35	Micro-elastography on spheroid tumor models and the impact of ultrasonic cavitation. Gabrielle Laloy-Borgna
10:50	Preclinical study of immunomodulating nanoparticles in a Hepatitis B Virus infected mice model. <i>Fanny Charriaud</i>
11:20	Break
11:30	Selective agonist PET radioligand (18F)F13640 for functional 5-HT1A receptor imaging in humans. <i>Pierre Courault</i>
11:45	Methods of radiotherapy planning for head and neck tumors with multiparametric MRI. <i>Laura</i> <i>Sayaque</i>
12:00	Curvilinear shear wave elastography for crystalline lens elasticity measurement in the context of presbyopia treatment by ultrasonic cavitation. <i>Alice Ganeau</i>
12:30	Lunch break
14:00	A new role of endoplasmic reticulum-mitochondria calcium coupling in nutrient-induced Glucagon- Like Peptide 1 (GLP-1) secretion by L cells. <i>Alexandre Humbert</i>
14:15	Purification, biochemical and kinetic characterization of a novel alkaline sn-1,3-regioselective triacylglycerol lipase from Penicillium crustosum thom P22 with biotechnological interest. <i>Ismail Hasnaoui</i>
14:30	Identification of pathogenic <i>Leptospira kirschneri</i> serogroup Grippotyphosa in water voles of Auvergne, France. <i>Elena Harran</i>
14:45	Influence of anesthesia during the establishment of a porcine model of acute kidney injury induced by ischemia-reperfusion. <i>Axel Guilpin</i>
15:00	The Blood Proteome of Imminent Lung Cancer diagnosis. Hana Zahed
15:30	Break
16:00	Dental prevention in children: what factors influence its implementation in healthcare settings? <i>Guillemette Lienhart</i>
16:15	Design of small molecule ligands for the study of the VDAC1 protein. <i>Hubert Gorny</i>
16:30	Parental experience of parent-mediated intervention for children with ASD. A systematic review and qualitative evidence synthesis. <i>Lucie Jurek</i>

HALL – POSTERS Program and poster number

40.00	
10:20	Identication and characterization of F9 deep intronic variations in haemophilia B patients. Amy Dericquebourg (poster #1)
	Eect of hip and knee joint angles on resting hamstring muscles rigidity in men and women. <i>Jérémie Bouvier</i> <u>(poster #2)</u>
	The cold receptor TRPM8, a new target against the aggravating eects of metabolic syndrome in heart failure with preserved ejection fraction <i>Mariam Wehbi</i> (poster #3)
	Meta-analysis of Wilson disease in Morocco. Nadia Abbassi (poster #4)
11:20	Break
11:30	Determination of inammatory and Ca2+ prole by flow cytometry in PBMC of non-STEMI versus STEMI patients. <i>Camille Brun</i> (poster #5)
	Antibiotic therapy for infectious hemodialyzed patients in Bamako: Pharmacokinetic analyses and first improvement suggestions. Balla Coulibaly (poster #6)
	Occupational risk factors for testicular cancer: A case-control study in France. <i>Margot Guth</i> (poster #7)
	Improvement of nifedipine dissolution rate by particle size reduction and its impact on transdermal delivery. <i>Thibault Massias</i> (poster #8)
12:30	Lunch break
14:00	The effect of acute physical and cognitive exercise on sequential motor learning. <i>Guillaume Digonet</i> (poster #13)
	Measuring the commuter exposure to air pollution in Lyon. Marie Ramel-Delobel (poster #14)
	Additive manufacturing of silicone in a powder matrix for medical devices. Arthur Colly (poster #15)
	Prehabilitation program for peritoneal carcinomatosis patients having cytoreductive surgery: a complex intervention developpement. <i>Guillaume Economos</i> (poster #16)
	Can COS preserve cell from low temperature effects : A preliminary cytotoxicity study Catia Silvia Dias (poster #17)
	In silico genotoxicity prediction by similarity search and machine learning algorithm: optimization and validation of the method for High Energetic Materials. <i>Mailys Fournier</i> (poster #18)
	Post-infarction inflammation influences diastolic function avec STEMI. Simon Leboube (poster #9)
	Multiple sclerosis clinical forms classication based on brain morphological connectivity through graph convolutional network. <i>Enyi Chen</i> (poster #10)
	Hemodynamic Changes Before and After Endovascular Treatment of Type B Aortic Dissection by 4D Flow MRI. <i>Benoit Cosset</i> (poster #11)
	Characterisation of new intracellular replicative clinical isolates of Acinetobacter baumannii. Charline Debruyne (poster #12)
	<i>Dias</i> (poster #17) In silico genotoxicity prediction by similarity search and machine learning algorithm: optimization and validation of the method for High Energetic Materials. <i>Mailys Fournier</i> (poster #18) Post-infarction inflammation influences diastolic function avec STEML <i>Simon Leboube</i> (poster #58)

HALL – POSTERS Program and poster number

15:30 Break

16:00 Covid-19 health crisis in cancer patients followed in the ONCORAL program: what do patients think about telehealth? *Virginie Larbre* (poster #23)

Influence of administration route on mRNA vaccine immunogenicity: role of ionizable lipids. *Altan Yavuz* (poster #24)

Pain and emotions during a visit to the emergency department: First results of the SOFTER IV-POSTER study. *Claire Pilet* (poster #25)

3D bioprinted cellular structures for universal production of therapeutics. *Laura Chastagnier* (poster #26)

Time-Resolved structural transitions of the Multidrug Transporter BmrA under turnover conditions. *Loïck Moissonnier* (poster #19)

The morphogenic protein TseB controls the spatio-temporal dynamics of PBP1a and PBP2b in Streptococcus pneumoniae. *Cassandra Lenoir* (poster #20)

Microuidization: an eco-friendly process to improve oral bioavailability of poorly soluble API. **Oksana Lemasson** (poster #21)

Oxygen metabolism with MRI : Towards a better prediction of the ischemic penumbra in stroke. *Lucie Chalet* (poster #22)

Biologie moléculaire et structurale, biochimie



The HIV-1 Integrase C-Terminal domain induces TAR RNA structural changes promoting Tat binding.

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Résumé

As for all retroviruses, Human Immunodeficiency Virus type 1 (HIV-1) integrase (IN) catalyzes the integration of viral cDNA into the host genome. This step is essential for HIV-1 productive infection (Maertens et al, 2021). Retroviral IN are modular proteins that contain three structured domains: the N-terminal domain, the catalytic core domain and the C-terminal domain (CTD), connected by unstructured regions. All three domains show protein-protein and protein-DNA interaction properties and are essential for enzymatic activity (Maertens et al, 2021). The CTD is involved in DNA interaction, multimerization, and possesses a SH3-like fold followed by a flexible 18-residues tail (CT) (Rocchi et al, 2022). The mutational study of flexible CT revealed a moderate implication in IN enzymatic activity, but significant effect on the incorporation of IN into virions and on HIV-1 infectivity (Rocchi et al, 2022). However, the exact function of CT region remains largely unknown. Recently, the interaction of HIV-1 IN with the TAR RNA, the 5' extremity of genomic RNA, have been identified in cellulo and in virio (Kessl et al, 2016; Liu et al, 2021). This observation, together with the recent finding of HIV-1 IN involvement in proviral transcription (Winans et al, 2020), prompted us to study the interaction of IN with TAR RNA and its interplay with the viral transcriptional trans-activator Tat protein. Our results revealed that despite the apparent lack of structural specificity of IN in vitro, the CT flexible tail discriminates for proper TAR apical stem-loop. Moreover, the binding of IN-CTD on TAR modifies its structure consistently with the modifications observed in virio (Liu et al, 2021). We describe the subsequent Tat-TAR interaction and propose a working model which foresees a possible involvement of IN in proviral transcription elongation before the arrival of Tat.

Mots-Clés: Integrase, HIV, 1, CTD, RNA interaction, integrase molecular partners, proviral tran-scription.

^{*}Intervenant

Characterization of an antimicrobial peptide resistance system involved in virulence in Streptococcus pneumoniae

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Résumé

Antibiotic resistance is an increasing global public health threat. Antimicrobial peptides are considered as promising alternative therapeutics to fight pathogens. In bacteria, one of the resistance mechanisms against antimicrobial peptides involves ATP-binding cassette (ABC) transporters coupled to two-component regulatory systems (TCS). *Streptococcus pneumoniae* is a major human pathogen causing diseases such as otitis or more severe ones as pneumonia and meningitis. We demonstrated that in *S. pneumoniae*, a BceAB-type ABC transporter cooperates with TCS01 to sense and induce resistance against a variety of bacterial antimicrobial peptides. However, these antimicrobial peptides all target undecaprenylpyrophosphate or lipid II, which are essential precursors of cell wall biosynthesis. In the same operon encoding the BceAB transporter, an ORF encoding a 36-mer peptide has been identified. Preliminary results show that this peptide is induced by some antimicrobial peptides and during cell infection. Using a synthetic peptide, we showed that it displays a cytotoxic effect against human cells and may thus have a role in virulence.

Mots-Clés: S. pneumoniae, AMP resistance, virulence, ABC transporter

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Identification and characterization of F9 deep intronic variations in haemophilia B patients

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Résumé

With current molecular diagnosis, about 1% of haemophilia B patients remains genetically unresolved. In these cases, deep intronic variation could be causal.

To identify the causal variation in 6 unrelated mild-to-moderate HB patients in whom no genetic variation was found using conventional genetic exon-focused approaches.

The whole F9 was sequenced using Next Generation Sequencing capture method. All candidate variations were confirmed using Sanger sequencing. The putative splicing impact of these deep intronic variations was studied using both *in silico* analysis (Splicing Sequences Finder and MaxEntScan) and minigene assay.

Next generation sequencing data revealed 3 candidate variants in F9 introns. The c.278-1806A> C was found in three patients with a mild phenotype, while the c.724-2385G> T and the c.723+4297T> A were found in a mild and a moderate haemophilia B patient, re-spectively. Additionally, a *de novo* 6-kb LINE retrotransposition in F9 intron 4 was found in the remaining patient with mild phenotype. In silico analysis strongly predicted that both c.724-2385G> T and c.723+4297T> A impacted the splicing. Conversely, no impact was predicted for the c.278-1806A> C. For all substitutions, an abnormal mRNA pattern was found using the minigene assay. The c.724-2385G> T led to the insertion of a 84 bp pseudo-exon due to the creation of a *de novo* donor splice site. The c.723+4297T> A led to the exonisation insertion of a 180 bp sequence by enhancing the strength of a pre-existing cryptic donor splice site. The c.278-1806A> C led to the retention of a 199 bp pseudo-exon.

With this comprehensive work combining next generation sequencing and functional assays, we report for the first time deep intronic variants that caused haemophilia B through splicing alteration. This study highlights the usefulness of whole F9 sequencing for the progressive reduction of genetically unexplained haemophilia B.

Mots-Clés: Hémophilie B, F9, génétique, variants introniques profonds

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Films Antimicrobiens Biodégradables à base de Nanocapsules pour la Biopréservation des Aliments

Fatemeh Baghi^{*†1}, Emilie Dumas^{‡1}, Sami Ghnimi^{§2}, and Adem Gharsallaoui^{¶1}

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Résumé

L'emballage actif biodegradable multicouche est une nouvelle classe d'emballages alimentaires innovants contenant des composes bioactifs qui sont capables de maintenir la qualite des aliments et de prolonger leur duree de conservation en liberant un agent actif pendant le stockage. Cet agent actif peut etre incorpore directement dans la matrice du film ou encapsule puis incorpore. Ce système pourrait permettre d'obtenir une vitesse de liberation controlee du compose actif pour une activite prolongee ainsi que de meilleures proprietes physicochimiques telles que les proprietes barrière, la resistance mecanique ou la thermoscellabilite. Dans ce contexte, cette thèse vise à developper et à caracteriser des films actifs biodegradables tricouches : 2 couches exterieures d'ethylcellulose et une couche interne de pectine contenant des nanocapsules de trans-cinnamaldehyde comme agent antimicrobien. La pectine est un biopolymère hydrophile qui sera protege par les deux couches d'EC hydrophobes qui possèdent de bonnes proprietes filmogènes et barrière à l'oxygène. Les resultats de caracterisation de ces films multicouches ont montre qu'ils possèdent une activite antimicrobienne contre 4 bacteries pathogènes comprenant des souches Gram positif et Gram negatif. De plus, la technique multicouche a amélioré les propriétés mécaniques du film monocouche avec une plus grande résistance à la rupture et une plus grande extensibilité.Neanmoins, d'autres analyses qui permettraient la comprehension des mecanismes de liberation de la molecule active à partir des films sont envisages.Les resultats ont montre que le film multicouche d'ethylcellulose et de pectine, contenant des nanocapsules de transcinnamaldehyde a un grand potentiel pour des applications de biopreservation de certains produits alimentaires.

Mots-Clés: emballage, biodégradable, agents bioactifs, bioconservation

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Impact of the hyper-radiosensitivity to low-dose phenomenon on hyperfractionated radiation therapy.

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Résumé

Introduction: stereotactic body radiation therapy (SBRT) permits to deliver high doses in few sessions. Hypofractionation of the dose has been evoked to explain the SBRT efficiency, although considering additive effect of some Gy separated from few days fails to provide a relevant and actual specificity. By contrast, each SBRT session is divided into several hundred microbeams of low dose converging to the tumour with a sub-millimetric precision. Hence, this hyperfractionation of the dose (lower than one Gy) delivered by each microbeam invokes the phenomenon of hyper-sensitivity to low dose (HRS) repeated several times. Furthermore, the radiation-induced ATM protein nucleoshuttling (RIANS) model gives a relevant explanation to the HRS phenomenon. Aim: to characterize the specific radiobiological effects of SBRT in human HRS-postive and HRS-negative tumour cell lines, in the frame of the RIANS model. Methods: human tumor cell lines were cultured to confluence, and then irradiated by CyberKnife(R) according to several different fractionation schemes. After irradiation, ATM, H2AX, and MRE11 proteins were tracked by immunofluorescence technique. Results: one SBRT session of 2 Gy produced much more unrepaired DNA double-strand breaks than a single dose of 2 Gy, a single dose of 0.2 Gy, or else a repetition of 10 doses of 0.2 Gy in 5 HRS-positive vs 2 HRS-negative human tumour cell lines. Besides, some highly damaged cells specifically appeared in Cyberknife conditions while they are absent with the single-dose conditions. **Conclusion:** the RIANS model may provide a relevant biological explanation of the SBRT efficiency. The hyperfractionation of one SBRT session is more deleterious on cells expressing the HRS phenomenon. In each submillimetric region of an HRS+ tumor, the effect of low doses hyperfractionation may be much higher than the cumulated physical dose per session. These results may lead to refine the prescription dose according to the HRS status.

Mots-Clés: Radiation therapy. ATM protein. Radiosensitivity. Low dose. SBRT.

*Intervenant

Overexpression, kinetic characterization, and molecular modeling of a new (phospho)lipase from Fusarium annulatum Bugnicourt strain CBS

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Résumé

Aim: Lipases are among the most traded enzymes in the global enzyme market, which is expected to reach \$14,507.6 million by 2027, owing to their usefulness in numerous biotechnological fields. The aim of this study is to identify and produce new catalytically active lipases/phospholipases from a new fungal strain.

Methods: Among twenty fungal strains screened for their lipolytic activity, a strain designated as CBS with lipase and phospholipase A (PLA) activity was selected and identified by classical taxonomic and molecular approaches as *Fusarium annulatum* Bugnicourt. The gene encoding for a new lipase named rFAL, was subcloned into the pPICZ α A vector containing the *Saccharomyces cerevisiae* α -factor secretion signal. The heterologous expression was determined by electroporating the plasmid into *Pichia pastoris* X33 competent strains. The rFAL was successfully purified by affinity chromatography using Ni-IDA column

Results : rFAL was purified X-fold with a final yield of 47%. The SDS-PAGE analysis of the purified rFAL showed two forms with a molecular mass of approximately 34 and 36 kDa. Both protein bands were shown to be active by zymography analysis. Upon digestion using endoglycosidase H (Endo H), only one protein band at 34 k Da was observed, indicating that the protein might be glycosylated. The rFAL has a specific activity of 6000 and 6500 U/mg on trioctanoin and egg-yolk phosphatidylcholine, respectively. The optimum activity of the

purified recombinant enzyme was measured at pH 9.0–10.0 and 45 to 50°C. rFAL is remarkably stable at alkaline pH values up to 12 and at temperatures above 55°C. rFAL exhibited a clear regio-preference towards the *sn*-1 position of the surface-coated triglycerides (TG) and phospholipids. A 3D model of rFAL was built with alpha-fold server and then used to confirm the *sn*-1 streo-preference by the docking *in silico* of TGs and phospholipids in its active site.

Mots-Clés: Overexpression, lipases, phospholipases, purification, modeling, molecular docking

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NUAK1-dependent metabolic underpinnings of adult muscle stem cells

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Résumé

Skeletal muscle regeneration relies on activation, proliferation, and differentiation of muscle satellite cells (MuSCs). A subset of MuSCs also undergo a process known as self-renewal to replenish stem cell pool. These processes are so-called MuSC fate, which depends of the metabolism of the cells. The metabolic cellular functions of our candidate NUAK1, a kinase related to the regulator AMPK, whose primary functions in MuSCs is unexplored. To investigate impact of Nuak1 loss on MuSC fate, we generated a conditional and inducible mouse model by crossing Pax7-CreERT2 driver with Nuak1LoxP conditional mutant mice. The conditional KO NUAK1 mice allow for tamoxifen inducible specifically deletion of Nuak1 in MuSCs and undertook the analysis of NUAK1 for regulating MuSC function. Using a model of muscle regeneration in mouse by cardiotoxin injection, we observed a significant alteration of *Tibialis Anterior* muscle's mass as well associated with an impairment of skeletal muscle tissue remodeling at 28-day post-injury. By histological analyses, we observed a depletion of MuSCs in KO animals following regeneration. Furthermore, cross-sectional-area of muscle fiber was reduced, suggesting a defect in myogenesis. This defect was recapitulated in vitro, as magnetic-activated-cell-sorting from mice lacking NUAK1 had a lower fusion index of MuSCs. In parallel, we assessed sequential steps of myogenesis on MuSC ex vivo through myofiber isolation and showed that MuSCs were impaired in their ability to enter the cell cycle. Based on these results, we hypothesized that NUAK1 is a key regulator of adult MuSC fate choice. Furthermore, to identify how NUAK1 contributes to the metabolic remodeling involved in myogenesis, we take advantage of in-depth proteomic analysis in MitoTag mice, which will be bred with Pax7-CreERT2-NUAK1 mice to label mitochondria originate from MuSCs. Altogether, the outcome of this research will provide significant advances in the link between metabolic regulation and stem cell fate.

Mots-Clés: Skeletal muscle regeneration, muscle stem cells, NUAK1, Pax7, myogenesis

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Investigating the role of CozE in S. pneumoniae ; from peptidoglycan syntesis to membrane homeostasis

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Résumé

Streptococcus pneumoniae is a bacterial pathogen that divides by binary fission. To achieve its ovoid shape and to pass it to its progeny, different processes, including cell constriction, cell wall assembly, chromosome replication and segregation and synthesis of its protective polysaccharidic capsule should be finely regulated and tightly coordinated in the course of the cell cycle. Recently, two conserved proteins in Gram-positive bacteria, named CozEa and CozeB, have been shown to be crucial for cell wall assembly and cell division. However, their precise function remains elusive even if they are proposed to regulate some PBPs, the enzymes involved in the biosynthesis and maturation of the peptidoglycan, the main component of the cell wall. However, our experiments have shown that the role of CozEa and CozEb is far more complex than expected and that the impact of CozEa and CozEb on the activity of PBPs is likely indirect. In my presentation, I will present my most recent observations that allow to revisit the role of the two CozEs proteins in *S. pneumoniae*, redefining their role from peptidoglycan synthesis towards membrane homeostasis and highlighting that the proper physiochemical properties of the membrane are crucial for the cell wall assembly.

Mots-Clés: Streptococcus pneumoniae, Cell wall, Cell division, Cell morphology, Cell membrane

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The morphogenic protein TseB controls the spatio-temporal dynamics of PBP1a and PBP2b in Streptococcus pneumoniae

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Résumé

Penicillin-binding proteins (PBPs) are key for the assembly of the peptidoglycan mesh, the main component of the bacterial cell wall. However, the control and coordination of these enzymes' activity over the course of the cell cycle remains poorly understood. Recently, we reported that the protein TseB interacts with PBP2A and is required for the elongation of Bacillus subtilis cells. In this study, we investigated the role of the TseB homolog in Streptococcus pneumoniae using a range of techniques involving bacterial genetics, protein biochemistry and live cell imaging. First, we find that the pneumococcal TseB arrives relatively late at the cell division septum. In addition, the deletion of tseB leads to wider cells. Using co-immunoprecipitation and bacterial two hybrid (B2H), we observe that TseB interacts with two PBPs, the class A PBP PBP1a and the class B PBP PBP2b, that are both required for cell elongation. Microscale thermophoresis combined with B2H further reveal that these interactions occur through their transmembrane domains. We also demonstrate that TseB co-localises with PBP1a and PBP2b throughout the duration of the cell cycle. Strikingly, the deletion of tseB alters the dynamics of PBP1a and PBP2b. Indeed, the two PBPs remain present at the division site for longer and localise later at the division site of daughter cells. All together, these data show that the pneumococcal TseB is a spatiotemporal regulator of PBP1a and PBP2b required for the morphogenesis of pneumococcal cells.

Mots-Clés: peptidoglycan, cell wall, penicillin, binding, protein, Streptococcus pneumoniae

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Design of small molecule ligands for the study of the VDAC1 protein

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Résumé

The VDAC channel is the major protein of the outer mitochondrial membrane. It allows the passage of all compounds of mass lower than 5 kDa. This protein is therefore the starting point of many metabolic processes within the mitochondria. Its oligomerization and interactions with different protein partners like hexokinase make it a trigger of the mitochondria-mediated apoptosis. Modifications of its activity and expression are found in numerous pathologies (cancers, neurodegenerative diseases, cardiac diseases, lupus, type 2 diabetes ...). VDAC then appears as a potential therapeutic target. However, it has not been yet exploited. There is indeed a lack of data on the impact of a pharmacological modulation of the channel. To address this issue, we plan to design new VDAC ligands with high affinity and specificity. A virtual screening was performed using the ZINC database and multiple 3D structures of VDAC. The 50 molecules with the best scores were tested by NanoDSF and microscale thermophoresis on recombinant human VDAC. Two chemical series were identified as VDAC ligands and confirmed by NMR chemical shift studies. Analogues from these 2 series were synthesized to perform preliminary structure-activity relationship studies.

Mots-Clés: VDAC, microscale thermophoresis, NanoDSF

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Sex differences in skeletal muscle regeneration in a mouse model of lengthening contraction-induced injury

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Résumé

After injury, skeletal muscle regenerates thanks to a dynamic interplay between satellite cells (SCs) and their microenvironment. Among mechanisms involved in muscle repair, a sexual dimorphism has been suggested. More particularly, a higher estrogen production may contribute to the regulation of SC fate or inflammatory response. This hypothesis is still controversial due to a lack of ovarian cycle control and non-standardized muscle damage in previous studies.

We assessed the impact of sex on skeletal muscle regeneration in adult male and female C57Bl6/J mice using a standardized model of injury and controlling the ovarian cycle of females. Muscle damage was induced by 30 electrically-evoked lengthening contractions with females being in estrus. Isometric force measurements were performed before, immediately after, and up to 14 days post-injury. The *Gastrocnemius* muscle was harvested at different time points to perform histological analyses by immunostaining.

Isometric force loss was lower and recovery was faster in females than in males. The proportion of injured/regenerating myofibers and the number of SCs were higher in females than in males. There was also less macrophages in females and the number of endothelial cells and fibro/adipogenic progenitors was not significantly different between sexes. *In-vitro*analyses showed that SCs extracted from females had a greater ability to proliferate as compared with males while no difference was observed for both differentiation and fusion.

We demonstrated sex differences in muscle regeneration which could be related to specific regulation of SC fate. Further analyses are required to investigate the role of estrogens in this process.

Mots-Clés: Skeletal muscle, force, regeneration, estrogen

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Increased mitochondria retention in mature sickle red blood cells

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Résumé

La drépanocytose (SCD) est une maladie héréditaire du sang caractérisée par une falciformation des globules rouges (globules rouges), qui sont plus sensibles à l'hémolyse et peuvent contribuer à physiopathologie de la maladie. très recemment il a été reporté la presence abnormale des mitochondries dans les globules rouges drépanocytaires, qui pourraient contribuer à une augmentation du stress oxidatif et de l'hémolyse. Nous avons evalué la présence des mitochondries dans les globules rouges d'un group de 61 patients drépanocytaires et nous avons investigué si cette présence est associée à des changements des proprietées rheologiques, à une expression des marqueurs de senescence et d'hémolyse. nous avons aussi evalué si ces mitochondries sont encore actif. Les résultats montrent une corrélation avec des marqueurs d'hémolyse et avec certains marqueurs de sénescence. Les résultats de réspiration mitochondriale montrent une consommation d'oxygen par les globules rouges drépanocytaire, qui indique que ces mitochondires sont fonctionnels.

Mots-Clés: Drépanocytose, globules rouges, mitochondries, hémolyse

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Characterisation of new intracellular replicative clinical isolates of Acinetobacter baumannii

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Résumé

Acinetobacter baumannii is a nosocomial pathogen that is becoming a major health threat worldwide, notably due to the acquisition of extensive antibiotic resistance. Patients in intensive care with assisted ventilation, indwelling catheters or severe burns are particularly at risk. Of increasing concern is the recent appearance of hypervirulent strains associated with higher mortality rates and hospital persistence.

Previous work from the laboratory discovered that a subset of clinical strains, including some considered hypervirulent, have acquired the ability to invade and multiply inside cells for prolonged periods. The objectives of this study are to further characterize this intracellular compartment, its prevalence and the bacterial factors involved.

We have screened over 50 clinical isolates and identified several that present this intracellular phenotype, including an isolate from a recent outbreak in La Reunion. Hyper-invasiveness and ability to replicate intracellularly correlated with enhanced virulence in model organisms such as *Galleria mellonella*. In addition, we have shown that intracellular replication occurs without induction of cell death. Finally, we have found that *A. baumannii* invasion and subsequent intracellular replication are dependent on the bacterial growth stage. The identified bacterial genes potentially contributing to these phenotypes will be discussed. Understanding the mechanisms that could be contributing to enhanced virulence and per-

Understanding the mechanisms that could be contributing to enhanced virulence and persistence of *A. baumannii* will hopefully contribute to the development of diagnostic tools and therapeutic approaches specifically directed at these types of strains to help combat this pathogen in clinics.

Mots-Clés: Acinetobacter baumannii, clinical isolates, intracellular trafficking

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Lung inflammatory and tissue injury mechanisms in response to pollution-derived fines particles in a mouse model.

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Résumé

A large body of evidence have not only documented the deleterious impact of air pollutants on health, but also pinpointed to particulate matter (PM), namely fine particulates as a major culprit in disease development especially in the lungs. Secondary organic aerosols (SOA) have emerged in recent years as major component of PM. SOA are formed in the air through a series of complex tropospheric multiphase chemical reactions transforming volatile organic compounds (VOCs), from both biogenic or anthropogenic origin, into low volatility compounds that ultimately condense to form organic particles. Cell culture studies revealed a role for SOA in cell oxidative stress, toxicity and inflammation and only few studies investigated short-term SOA exposure in animal models. Here, mice were chronically exposed to SOA for one and two months. Weight monitoring indicated a marked mass loss, especially in females, upon chronic exposure to SOA. Significantly, cytokine antibody microarray approach and RT-qPCR analysis revealed a SOA-induced abnormal lung inflammation. Histological analyzes of lung tissues found airspace enlargement and alveolar wall destruction. Altogether, these findings are reminiscent of cigarette smoke-induced COPD. Our present study adds a new insight that is the considerable contribution of SOA to the development of atmospheric pollution-mediated chronic lung inflammation, which seems to resemble COPD, an important lung disease with a major impact on human health and economic burden, worldwide. It must be emphasized that in recent years atmospheric pollution became a serious health concern, which surpassed that of cigarette smoke. We hope that our data generated from this study will pave the way for new studies to enhance our understanding

of the underlying pathogenic mechanisms of SOA.

Mots-Clés: Pollution / Secondary Organic Aerosol / Lungs / Inflammation / mouse

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A journey from Vibrio vulnificus to priority pathogens transketolase

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Résumé

In the beginning of the XXth century, antibiotic discovery had a real impact in human and animal medicine. Because of misuses during the last century, numerous multi-drug resistant bacterials. Due to the decline of antibiotics efficacity, 1.29 million of people died in 2019 across the world. This will increase to 10 million people in 2050 following predictions. Global warming also increases due to the prevalence of deadly bacteria like V. vulnificus discovered in the 80's and already multi-drug resistant. In this context, it's necessary to identity targets and to discover new lead molecules.

Transketolase (TK) is a hub enzyme of the non-oxidative branch of the pentose phosphate pathway, implied in the stress limitation and nucleic acid bases synthesis *via* NADPH and ribose-5-phosphate (R5P) synthesis. TK transfers a two-carbon unit from a ketone donor like fructose-6-phosphate (F6P) and graft it transiently to its cofactor (thiamine pyrophosphate, TPP). Finally, this two-carbon unit is transferred to an aldehyde acceptor like R5P.

In the 80's, a kinetic assay was developed in order to follow the TK reaction using only a ketone donor and ferricyanide as oxidant of the grafted TPP. The decrease of absorbance of ferricyanide at 420 nm is due to its reduction into ferrocyanide. The two-carbon unit is then released as a glyoxylate. Although the kinetic mechanism still not clearly understood. TK of V. vulnificus (TKvv) is well over-expressed. Its structure is now solved by X-ray crystallography. Docking experiments of ferricyanide on TKvv structure indicates that it can bind the active site through three histidyl residues. According to this, kinetics with various concentrations of F6P and ferricyanide demonstrate a Michaelian behavior. Early kinetic models tend to show a competitive inhibition between F6P and ferricyanide but it is now clear that ferricyanide is an enzymatic substrate of TKvv.

Mots-Clés: Antibiotics, Multi drug resistant bacterials, Transketolase, Kinetic mechanism, Structure

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Purification, biochemical and kinetic characterization of a novel alkaline sn-1,3-regioselective triacylglycerol lipase from Penicillium crustosum thom P22 with biotechnological interest

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Résumé

The aim of this work is the production, purification, and characterization of novel lipase from *Penicillium crustosum* Thom strain P22, isolated from Moroccan olive mill wastes.

*Intervenant

The isolation of *Penicillium crustosum* Thom was carried out by using two tests: a first qualitative test on agar culture media supplemented with 1% (v/v) of olive oil and 0.01% of rhodamine B (w/v), lipolytic activity is indicated by the appearance of orange fluorescent halos around the colonies. A second quantitative test based on the titration of fatty acids (FA) released during lipolysis by the pH-Stat technique and using trioctanoin (TC8) as the substrate. This isolate was identified by phenotypical and molecular characterization. The *Penicillium crustosum* lipase (PCrL) was purified using ammonium sulphate (70%) precipitation followed by anion exchange chromatography using a HiTrap Q-Sepharose column. The purified PCrL was analyzed by SDS-PAGE.

The Penicillium crustosum Thom P22 demonstrated the ability to produce an extracellular lipase at 60 U.mL-1 achieved after 6 days of cultivation on an optimized liquid medium. PCrL was purified 63-fold to homogeneity with a total yield of 34% and a specific activity of 5,000 and 10,000 U.mg-1 on olive oil and TC8 emulsions, respectively. PCrL has a molecular mass of 28 kDa, estimated by SDS-PAGE. PCrL exhibited a clear regioselectivity towards the sn-1 position of the surface-coated triglycerides which were esterified with α -eleostearic acid at the sn-1/3 position. PCrL showed high activity and stability in the presence of water-immiscible organic solvents, surfactant and oxidizing agents, and showed considerable compatibility with commercial laundry detergents. Washing performance analysis revealed that it could effectively remove oil-stains. Hence, PCrL has several attractive properties that make it a promising potential candidate for detergent formulations.

Mots-Clés: lipase, orlistat, olive oil, olive mill wastewater, Penicillium, regioselectivity

Impact of phenylacetic acid, a microbiota-derived metabolite, on hepatic endoplasmic reticulum-mitochondria interactions and steatosis

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Résumé

Background and Aims: The gut-liver is as an important factor in the development of non-alcoholic fatty liver diseases (NAFLD). Microbiota-derived metabolites such as phenylacetic acid (PAA) can trigger hepatic steatosis in human primary hepatocytes but the molecular mechanism involved is not elucidated. Moreover, mitochondrial dysfunction is also a key component of NAFLD and oxidative capacities of mitochondria are regulated by its communication with endoplasmic reticulum at contact points named mitochondria-associated membranes (MAMs). Hence, MAMs are controlling mitochondrial oxidative metabolism and ER-mitochondria miscommunication was associated with hepatic steatosis. We hypothesized that PAA may induce hepatic steatosis through a disruption of MAMs integrity. Method: We investigated the impact of PAA on MAMs integrity and steatosis in Huh7 cell line and primary mouse hepatocytes (PMH) incubated for 16 hours in normal (BSA) and lipotoxic (palmitate) conditions. Co-treatments with diazoxide or EGTA allowed to investigate the involvement of electrogenic effects of PAA in Huh7 cells. ER-mitochondria interactions were measured by in situ proximity ligation assay (PLA) targeting VDAC1 (mitochondrial protein) and IP3R1 (reticular protein) proximity and BODIPY labelling was used to evaluate hepatocyte lipid accumulation. Fixed cells were analyzed by fluorescent microscopy and images analyses were performed to quantify mitochondria-endoplasmic reticulum contacts and lipid droplets size.

Results: Treatment with PAA reduced MAMs in Huh7, it also induced lipid accumulation in Huh7 and PMH. The effect of PAA on MAM integrity is observed as soon as one hour of treatment in Huh7, it is fully prevented by diazoxide which inhibits membrane depolarization and partially by EGTA treatment, a Ca2+ chelation agent. Altogether, these results suggest an electrogenic mechanism of PAA action on MAMs.

Conclusion: PAA, a gut-microbiome derived metabolite, induces MAM disruption and hepatocyte lipid accumulation. The effect of PAA on MAMs is mediated through an electrogenic mechanism.

Mots-Clés: MAMs microbiota hepatic steatosis

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Time-Resolved structural transitions of the Multidrug Transporter BmrA under turnover conditions

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Résumé

According to the World Health Organization (WHO), antibiotic resistance is a predominant and worrying health problem for humanity due to the emergence of multi-resistant bacteria. Several resistance mechanisms in bacteria are involved including the overexpression of efflux pumps which can expulse the drug out of the cell below its cytotoxicity threshold. Some ABC (ATP-Binding Cassette) transporters drug efflux pumps conferring to the cell the resistance phenotype. BmrA is an ABC transporter conferring resistance to Bacillus subtilis against cervinycin C, an antibiotic secreted by a competitor Streptomyces tendae from the same biotope. BmrA has a broad ligand specificity that can bind and transport a variety of structurally and chemically unrelated molecules. BmrA is therefore a multidrug transporter. To better understand the details of this mechanism, the team solved its 3D structure by X-ray crystallography and cryo-EM and shedded light on how BmrA manipulates its ligands and expels them. The team recently showed that BmrA structurally deforms in specific regions to accommodate rhodamine 6G (ligand) and proposed a new mechanism of structural plasticity. My thesis follows this work by studying the biomechanics of this transporter and temporally characterizing the conformational transition that occurs during ligand transport. I developed measurement conditions to track this transition using the fluorescence of BmrA tryptophan residues. The conformational population modulation is possible by playing on the temperature or the ATP concentration. Following these experiments, the first tests in time-resolved cryoEM tested between 12 and 40 seconds. The interest is to visualize the population variation and compare it with the previously obtained structures by looking at the differences in the transmembrane helices.

Mots-Clés: Time, resolved cryo, EM, ABC transporter, fluorescence, conformational change of membrane protein

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Physiologie cardiovasculaire, métabolisme, endocrinologie, nutrition

Off-label use of cinacalcet in pediatric primary hyperparathyroidism: a French multicenter experience

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Résumé

Background: Cinacalcet is a calcimimetic approved in adults with primary hyperparathyroidism (PHPT). Few cases reports described its use in pediatric HPT, with challenges related to the risk of hypocalcemia, increased QT interval and drug interactions. In this study, we report the French experience in this setting.

Methods: We retrospectively analyzed data from 18 pediatric patients from 7 tertiary centers who received cinacalcet for PHPT. The results are presented as median (interquartile

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range).

Results: At a median age of 10.8(2.0-14.4) years, 18 patients received cinacalcet for primary HPT (N=13 inactive CASR mutation, N=1 CDC73 mutation, N=1 multiple endocrine neoplasia type 1, N=3 unknown etiology). Cinacalcet was introduced at an estimated glomerular filtration rate (eGFR) of 120(111-130) mL/min/1.73 m2, plasma calcium of 3.04(2.96-3.14) mmol/L, plasma phosphate of 1.1(1.0-1.3) mmol/L, age-standardized (z score) phosphate of -3.0(-3.5;-1.9), total ALP of 212(164-245)UI/L, 25-OHD of 37(20-46) ng/L, age-standardized (z score) ALP of -2.4(-3.7;-1.4), PTH of 75(59–123) ng/L corresponding to 1.2 (1.0-2.3)-time the upper limit for normal (ULN). The starting daily dose of cinacalcet was 0.7(0.6-1.0)mg/kg, with a maximum dose of 1.0(0.9-1.4) mg/kg per day. With a follow-up of 2.2(1.3-1.4)4.3) years on cinacalcet therapy, PTH and calcium significantly decreased to 37(34-54) ng/L, corresponding to 0.8 (0.5-0.8) ULN (p=0.01), and 2.66(2.55-2.90) mmol/L (p=0.002), respectively. In contrast, eGFR, 25-OHD, ALP and phosphate and urinary calcium levels remained stable. Nephrocalcinosis was not reported but one patient displayed nephrolithiasis. Cinacalcet was progressively withdrawn in three patients; no side effects were reported. **Conclusions:** Cinacalcet in pediatric HPT can control hypercalcemia and PTH without significant side effects.

Mots-Clés: Children, primary hyperparathyroidism, Cinacalcet, hypercalcemia

Unravelling motor neuron identity and new cell-extracellular matrix interplay in zebrafish motor axon development and regeneration

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Résumé

During development and nerve regeneration, axons of motoneurons (MN) follow stereotypical trajectories to their muscle targets, guided by various molecular cues including extracellu-lar matrix (ECM) proteins. In zebrafish, every trunk hemisegment is innervated by three different MN. Motor axons first extend through a common path, pause at the choice point and then diverge to arborize in a specific territory of the myotome. The common path is made of ECM proteins known to provide guidance to developing axons. Their absence often arrests axon growing beyond the choice point. Among them is the myotomal matrix pro-tein collagen XV-B (COLXV-B)1. The mechanisms underlying motor axon navigation and MN-specific divergence are poorly documented. We thus aim at characterizing (1) the motor axon identity using single cell transcriptomic analysis (scRNA-seq) and (2) the key ECM proteins that orchestrate this process.

We used MN-specific transgenic line mnx1:gfp to isolate MN by FACS and perform scRNA-seq and to carry out real-time monitoring of nerve regeneration as a tunable model of axonogenesis.

Clustering analysis revealed a pMN-specific gene expression signature that distinguishes the three pMNs indicative of a pMNs subtype identity. We then developed a laser abla-tion method to injure the ventral nerve of mnx1:gfp and col15a1b-/-;mnx1:gfp larvae. Using video-microscopy and lysotracker dyes, we showed that COLXV-B, which is enriched in the common path, may have additional roles to those shown in development1 by acting more specifically on Wallerian degeneration, clearing-cells recruitment and the formation of the regenerated nerve.

We are now investigating the behavior of Schwann cells, macrophages and neutrophils by using diverse transgenic lines in control and mutant larvae.

This study opens new leads on the interplay between nerve-derived actors, ECM cues and inflammatory cells in motor axon growth in development and regeneration.

Mots-Clés: Motoneuron, extracellular matrix, development, regeneration, zebrafish

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Allometric relationships between body mass and mitochondrial efficiency of birds

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Résumé

While allometric studies on mitochondrial oxygen consumption have been performed, the coupling between energy synthesized (ATP) and oxygen consumption to synthesize this energy is seldom measured. Consequently, we are leaving out an essential part of the metabolism, at the root of all individual performances (i.e., growth, locomotor activity) and the question of the mitochondrial efficiency arises as well as the advantage/disadvantage of being a big or small organism. This question first emerged in mammals for which recent studies showed that mitochondrial oxygen consumption and ATP synthesis evolve with body mass following a scaling exponent ranging from -0.124 to -0.137. In contrast, mitochondrial efficiency (ATP/O) did correlate or correlated positively with body mass, depending on the metabolic intensity. Hence with the greater the body mass, the better the mitochondrial energy efficiency at low metabolic intensity. In a comparative perspective, we propose to extend the exploration to the second clade of endotherms: birds. To date, we have investigated mitochondria isolated from two muscle tissues (skeletal muscle and heart) from 11 species of birds, with body mass ranging from 18 g to 160 kg. Our results suggest that avian mitochondria of skeletal muscle follow the allometric trends of mammals but with a lower allometric exponent. Compared to mammals, we observed a high variability around our allometric relationship which suggests a different approach is needed. Statistical models incorporating intraspecies variability in birds and a reconsideration of body mass into size/wingspan will give us a new and more robust view of the allometric relationship of mitochondrial bioenergetic fluxes in birds.

Mots-Clés: Bird, Allometry, Mitochondria, Efficiency

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Determination of inflammatory and Ca2+ profile by flow cytometry in PBMC of non-STEMI versus STEMI patients

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Résumé

Myocardial infarction affects more than 120000 people every year in France. Despite the increasing effectiveness of patient management, the morbi-mortality remains high. Peripheral blood mononuclear cells (PBMC) have been recently shown to present a phenotype characteristic of a pathology, which could provide prognostic and/or diagnostic information. Objective: We aim to characterize the inflammatory and Ca2+ profile of PBMC from non-STEMI versus STEMI patients. Regarding cell phenotyping, lymphocytes were distinguished from monocytes according to their morphological criteria. Using the CD14, CD16, CCR2, and CX3CR1 markers, pro-inflammatory monocytes were further differentiated from antiinflammatory monocytes. To analyze Ca2+ fluxes, different cell compartments were marked with chemical probes: FuraRed-AM (cytosol), Rhod2-AM (mitochondria), and MagFluo4-AM (reticulum). Using a pharmacological approach, the optimal conditions for measuring Ca2+ exchange between the different cell compartments were applied to a cohort of STEMI and non-STEMI patients. Decreased lymphocyte proportion towards an increase in the monocyte proportion, specifically classical monocytes, was measured in STEMI patients. Caffeine stimulation led to a non-significant decrease in Ca2+ transfer to the cytosol and to mitochondria and in the reticular Ca2+ release, in the STEMI PBMC. A significant reduced IP3Rinduced Ca2+ re-sponse in the cytosol and in the mitochondrial compartment was also reported in the STEMI PBMC. Our study led to the setup of a multiparametric analysis by flow cytometry of Ca2+ and inflammation in PBMC. We demonstrated an altered Ca2+ homeostasis in STEMI PBMC. A higher heterogeneity in the inflammatory profile and calcium response in STEMI patients suggests a potential molecular signature of PBMC according to the clinical outcome. Therefore, we now plan to analyze PBMC from an existing and still ongoing co-hort (HIBISCUS) of postmyocardial infarction patients with a 3-year clinical follow-up to identify new circulating prognosis biomarkers.

Mots-Clés: Myocardial Infarction, Ca2+, Cytometry

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A new role of endoplasmic reticulum-mitochondria calcium coupling in nutrient-induced Glucagon-Like Peptide 1 (GLP-1) secretion by L cells.

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Résumé

Postprandial GLP-1 secretion by enteroendocrine L cells plays an impor-tant role in the control of glucose homoeostasis, making it a very important target for thera-peutics against Type 2 Diabetes. This study evaluated the implication of contact sites linking endoplasmic reticulum (ER) and mitochondria, termed MAMs (*Mitochondria-Associated ER Membranes*), in nutrient-induced GLP-1 secretion. MAMs indeed are dynamically regulated by nutrients and act as crucial regulators of both calcium and energy homoeostasis, both crucial for hormone secretion.

Nutrient (glucose, bile acids (BA), fatty acids and amino acids) action on MAMs and GLP-1 secretion were assessed in STC-1 cells during 1-hour treat-ments using *in situ* Proximity Ligation Assay (PLA)/transmission electronic microscopy and ELISA, respectively. A pharmacological approach enabled the characterisation of the signalling pathways implicated in nutrient-induced MAMs regulation. Their causal role in GLP-1 secretion was challenged by adenoviral-mediated expression of the organelle spacer, FATE1.

All nutrients previously described as GLP-1 secretagogues simultaneously induced both GLP-1 secretion and MAMs after 1 hour of treatment in STC-1 cells. FATE1-induced MAM disruption prevented GLP-1 secretion in response to glucose and BA, validating the causal role of MAMs in nutrient-induced GLP-1 secretion. This was further confirmed by the pharmacological inhibition of the ER calcium channel IP3R1 (Inositol 3-Phosphate Re-ceptor 1) involved in organelle calcium exchange at MAMs. While glucose sensing relies on an electrogenic mechanism through SGLT1 and action potential-mediated calcium entry, BA sensing is rather mediated through a TGR5-cAMP-PKA pathway. **Discussion/Conclusion:** Altogether, these results demonstrate a new role of ER-mitochondria contact sites in nutrient-induced GLP-1 secretion in L cells. MAMs are induced through dif-ferent signalling pathways, often appearing downstream of signalling cascades. MAMs might then act as an integrative platform of nutrient sensing, regulating GLP-1 secretion. Confir-mation of these data in more physiological models is currently underway.

Mots-Clés: Diabète, Signalisation, Communication, Mitochondrie, Calcium

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Influence of anesthesia during the establishment of a porcine model of acute kidney injury induced by ischemia-reperfusion

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Résumé

Acute kidney injury (AKI) is one on the main complication of surgery. To investigate AKI physiopathology, we purpose a new swine model of AKI induced by ischemia-reperfusion. Ten pigs (30-50kg) were used. Pigs were premedicated (tiletamide-zolazepam 6mg/kg IM) and induced (propofol, administration at effect). For 5 pigs, anes-thesia was realized by inhalation of sevoflurane (group "sevoflurane"). For 5 others pigs, anesthesia was realized by perfusions of ketamine (20mg/kg/h IV), diazepam (0.3mg/kg/h IV) and medetomidine $(2.5\mu g/kg/h IV)$ (group " ketamine "). For all of them, analgesia was assured by morphin (0.3mg/kg/h). After surgical opening of the retroperitoneal space, vascular pedicles of each kidney were clamped for 90min and physiological and biochemical measures were followed during next 8h. Linear mixed models were used to estimate evolution of the parameters over time. 3 pigs in the sevoflurane group developed malignant hyperthermia (hyperthermia, myoclonia, respiratory acidosis, hemodynamic instabilities). In both groups, we ob-served a significant increase of kaliemia (sevoflurane : 0.34mmol/L/h, 95%IC = (0.29-0.37)), P< 0.0001, ketamine group : 0.25mmol/L/h, 95%IC = (0.21-0.29), P< 0.0001), of cre-atinemia (sevoflurane : 18.6µmol/L/h, 95%IC = (16.9-20.2)), P< 0.0001, ketamine group : 16.34µmol/L/h, 95%IC = (14.8-17.9), P< 0.0001), of uremia (sevoflurane : 0.91mmol/L/h, 95%IC = (0.87-0.95)), P< 0.0001, ketamine group : 0.47mmol/L/h, 95%IC = (0.43-0.5), P< 0.0001). In ketamine group, we observed a significant decrease of glycemia (ketamine group : 95%IC P< 0.59mmol/L/h, (0.48-0.7),0.0001). Azotemia and hyperkaliemia observed proved the establishment of AKI. Majorated hyperkaliemia in sevoflurane group may be caused by rhabdomyolysis ob-served during malignant hyperthermia. Ketamine group was associated with hypoglycemia. These results were promising for a future validation of this porcine model of AKI. In the future, anesthesia should be performed with the ketamine protocol. In addition, glycemia will need to be monitored carefully.

Mots-Clés: acute kidney injury, ischemia reperfusion, anesthesia, malignant hyperthermia, glycemia

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The cold receptor TRPM8, a new target against the aggravating effects of metabolic syndrome in heart failure with preserved ejection fraction

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Résumé

Heart failure with preserved ejection fraction (HFpEF) is major public health issue. It's usually associated with metabolic syndrome (MS). Desaturase SCD1, interesting target in MS, converts saturated fatty acids into monounsaturated fatty acids. We found that the cold receptor, TRPM8, controls SCD1 expression in epithelial cells and we would like to investigate whether TRPM8 knockout (KO) could protect from both MS and HFpEF by downregulating SCD1 expression. Wild type and TRPM8 KO mice are put under chow or high fat high sucrose diet (HFHSD) for 24 weeks. During this, body weight is monitored and metabolic tolerance tests are done. HFHSD establishes MS in mice. Endurance test, strength test, blood chemistry, echocar-diography will be done to assess development of HFpEF. Lipidomic analysis will determine changes in lipid profile between mice groups and inflammation will be assessed by ELISA and flow cytometry. SCD1 expression between the wild type and KO will be studied by western blot and Q-PCR.

For first round of mice (22 mice out of 88). We found a 50% decrease in SCD1 expression in the liver of TRPM8 KO mice associated with a decreased monounsaturated/saturated fatty acid ratio as measured by Lipidomics.

Insulin tolerance test reported increased insulin sensitivity in the KO mice under HFHSD compared to the wild type. KO mice under HFHSD has shown tendency towards decreased endurance compared with the chow diet KO mice however there is no significant difference in strength between the 2 groups.

At level of cardiac function, echocardiography showed a tendency towards the development of HFpEF in both wild type and KO mice under HFHSD although the actual number of animals included does not enable a firm conclusion yet. We believe that TRPM8 would be an interesting target to alter lipogenic and metabolic profiles in the favor of fighting MS progression.

Mots-Clés: TRPM8, SCD1, metabolic syndrome, HFpEF

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Santé publique, recherche clinique, innovation thérapeutique et diagnostique

The Blood Proteome of Imminent Lung Cancer diagnosis

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Résumé

Introduction: Lung screening with low-dose CT reduces lung cancer mortality, as demonstrated by several large, randomized trials. However, imprecise selection criteria for CT can lead to overdiagnosis, as well as many false positive results. Identification of novel risk protein biomarkers may enhance early detection of smoking-related lung cancer as previously shown by our team. In this project we sought to identify novel circulating proteins indicative of imminent lung cancer.

Methods: We measured 1,162 proteins in blood samples drawn at most three years before diagnosis in 731 smoking-matched case-control sets nested within six prospective cohorts from the US, Europe, Singapore, and Australia. Odds ratios for incident lung cancer were estimated per standard deviation increment in relative protein concentrations (ORstd) using conditional logistic regression.

Results: We found 67 proteins associated with lung cancer risk after accounting for multiple comparisons. We then implemented a resampling algorithm to select proteins with consistent associations across random splits of the data and identified 36 robust markers. The 36 proteins included several growth factors (e.g. HGF, IGFBP-1, IGFP-2), tumor necrosis factor-receptors (e.g. TNFRSF6B, TNFRSF13B), and chemokines and cytokines (e.g. CXL17, GDF-15, SCF). The odds ratio per standard deviation ranged from 1.31 for IGFBP-1 (95% CI: 1.17-1.47) to 2.43 for CEACAM5 (95% CI: 2.04-2.89). We mapped the 36 proteins to the hallmarks of cancer and found that proliferative signaling, tumor-promoting inflammation, and activation of invasion and metastasis were most frequently implicated.

Conclusions: After assessing 1,162 circulating proteins prior to lung cancer diagnosis, we identified 36 markers of imminent lung cancer with a wide range of functions in carcinogenesis. This study provides a first expansive view of the blood proteome in the years leading up to lung cancer diagnosis and can serve as a reference for investigations seeking to identify early protein markers of lung cancer.

Mots-Clés: lung cancer, biomarkers, molecular epidemiology, early diagnosis

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Identification of pathogenic *Leptospira* kirschneri serogroup Grippotyphosa in water voles of Auvergne, France

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Résumé

Mots-Clés: Leptospiroses, zoonoses, bovine, PCR, MAT, L. kirschneri, Grippotyphosa

^{*}Intervenant

Are subjects suffering from orthorexia nervosa characterized by specific food categorization strategies and cognitive flexibility impairments?

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Résumé

Mots-Clés: eating disorders, cognition, food perception, healthiness, nondeclarative methods

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Measuring the commuter exposure to air pollution in Lyon

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Résumé

Daily travel can represent a significant part of personal exposure to air pollution, up to 30% of the daily inhaled dose, despite very short exposure times (3-6% of circadian time). This exposure varies considerably depending on the mode of transport. This study aims to quantify the difference in exposure during daily mobility by carrying out a microsensor mea-surement campaign. The data collected will be used in epidemiological studies evaluating the link between chronic exposure to air pollution and the risk of breast cancer.

We have undertaken a six-week measurement campaign (from November to December 2021) on three different routes in the metropolitan city of Lyon (France). These routes were chosen to be representative of different urban areas (e.g. city centre, periphery, vegetated areas). The measurements were taken twice a day (during the morning and evening peak hours) using simultaneously four different modes (walk, bike, car and public transport). Two different portable air quality sensors were used: the MONICA sensors (developed by ENEA) measuring PM1, PM2.5, PM10, NO2, CO and O3 and the AirBeam 2 sensors (provided by ATMO AURA) measuring the particulate matters.

In total, 242 measurements were made. Concerning PM10, PM2.5 and PM0.1, the highest concentrations were observed in the underground microenvironment. Cycling and walking were the most exposed mode in terms of NO2. Except for CO, the lowest concentrations were measured by car. Concerning the exposure ratios between modes, the highest variation was observed for PM, the lowest for ozone.

Preliminary results show that private car users are generally affected by lower levels of pollu-tants compared to the other modes, except for CO. Nevertheless, the concentrations by car can be strongly influenced by the type of ventilation used (internal/external air recirculation, windows open/closed).

Mots-Clés: exposure assessment, air pollution, mobile monitoring, traffic, commuting

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Improvement of nifedipine dissolution rate by particle size reduction and its impact on transdermal delivery

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Résumé

Many poorly water-soluble drugs are commonly administered orally and associated with poor bioavailability. This outcome may occur due to physicochemical properties and physiological factors related to these drugs. Among them, nifedipine (NIF), which is widely applied for oral treatment of hypertension and angina pectoris is a BCS Class II drug (low solubility/high permeability). NIF undergoes variable first-pass effect between patients. To limit this variation, the transdermal route may be considered. In order to increase the diffusion through the skin layers, the physicochemical properties of the solid state should be improved. Particle-engineering technologies belonging to green chemistry, such as processes assisted by supercritical CO2 (ScCO2) are an interesting approach to enhance bioavailability of poorly water-soluble drugs. Rapid Expansion of Supercritical Solution (RESS) and Supercritical AntiSolvent (SAS) processes, in which CO2 is used as a solvent and an antisolvent of the drug respectively, are able to reduce particle size and change the solid state. The objective of this study was to evaluate the impact of reduced crystal sizes on the improvement of NIF flux through skin. Physicochemical characterization and dissolution kinetics were performed at 32 oC and permeation studies were carried out using Franz cell chambers. The use of RESS and SAS processes leads to smaller NIF particles (NIF-RESS and NIF SAS) with a volumeweighted mean diameter of 5.6 μ m and 9.6 μ m respectively compared to raw NIF (36 μ m) particles. Dissolution studies, performed in sink conditions, provided great improvement of dissolution rate for NIF-RESS and NIF-SAS samples. Permeation experiments conducted on skin explants showed a higher permeation rate compared to raw NIF, as this one was stacked in epidermis and dermis layers. The reduction in size of NIF particles using ScCO2 process was correlated to a dissolution rate improvement that finally promotes a higher flux of NIF through skin.

Mots-Clés: Transdermal delivery, Nifedipine, Dissolution, Supercritical carbon dioxide, Crystallization

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Association of hospital bed turnover with patient outcomes in digestive surgery

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Résumé

Introduction: The volume-outcome relationship in surgery has been extensively investigated over the past decades. Volume is a proxy that does not accurately measure hospital productivity. We wanted to determine the influence of patient turnover per hospital bed (TO) on the occurrence of major adverse events after digestive surgery.

Methods: From the national MCO PMSI, we included all stays for patients who underwent minor surgery (hernia repair, cholecystectomy, appendectomy, bariatric procedure) or major surgery (colorectal, hepatopancreatic, esophageal, and gastric procedures) between January 1, 2013, and December 31, 2018. TO was defined annually for each hospital, allowing comparison of outcomes among patients admitted to facilities classified into low, medium, and high TO tertiles. The primary endpoint was a composite of serious adverse events within 30 days of surgery according to Dindo-Clavien (death, ICU admission, or reoperation). GEE modeling was used to estimate the association between TO and the primary outcome.

Results: Patients from 631 French hospitals were considered, representing 2,087,894 stays for minor surgery and 489,178 stays for major surgery. Patients with minor surgery had a lower risk in high-TO hospitals than in low-TO hospitals of major adverse event occurrence (odds ratio 0.89; CI95% 0.81-0.97), death (0.87; 0.78-0.98), ICU admission (0.83; 0.70-0.99), and reoperation (0.91; 0.85-0.97). Among patients with major surgery, there was no difference between high and low TO hospitals, except for reoperation (0.93; 0.88-0.99).

Conclusion: The centralization of surgical activities and the increase in productivity of hospitals is an evolution that has already largely started. We show that a very high rotation of patients in beds seems beneficial for minor procedures but remains of questionable interest for major surgeries.

Mots-Clés: Turn over, post operative morbidity

Covid-19 health crisis in cancer patients followed in the ONCORAL program: what do patients think about telehealth?

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Résumé

The Covid-19 pandemic has disrupted our health care system due to massive influx of patients into hospital, containment and social distancing measures. In Oncology, hospital medical consultations have been widely replaced by telemonitoring to limit patients' exposure to COVID-19. The aim of this study is to describe patients 'perception about telemonitoring. Study population was ambulatory patients under oral anticancer treatment included in Oncoral, a Hospices Civils de Lyon city-hospital multidisciplinary program, who had telemonitoring for drugs, adherence or adverse events follow up, during the first containment from mars to may 2020. A questionnaire was set and data were collected during individual phone interviews.

178 patients have benefited from telemonitoring during the study period, among which 67.4%(n=120) had answer the questionnaire. Population was composed of 50.8% (n=61) of men, with a mean age of 70 years old (34-93). Pathologies were haematological (66.4%, n=80) and solid tumours (33.6%, n=40). According to connected tools, 78% (n=93) of patients had a smartphone, tablet or computer. Screen time was more than 1 hour per day for 66%. 21.6% (n=26) of patients have already done tele monitoring. 2 main disadvantages for telemonitoring were pointed out: loss of human contact (61%) and difficulties to interact (37%). main advantages: lack of displacement (59%) and time saving (43%). Factors which may telemonitoring feeling screen time...) has to be confirmed. influence (age, Totally 83% of patients were satisfied of telemonitoring. 71% were invested in the dia-logue and 69% would be favourable experienced telemonitoring to at new. Data of this study highlight patients' feelings about telehealth and patients' available re-sources to improve system set up during this period. This will allow the deployment of teleconsultation with new tools adapted to the needs of patients to ensure optimal care.

Mots-Clés: telehealth, telemonitoring, self, management, Covid, 19, oral anticancer drugs

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Occupational risk factors for testicular cancer: A case-control study in France

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Résumé

Objectives: Testicular germ cell tumors (TGCT) are the most frequently diagnosed cancer in men of working age and their incidence rate has increased dramatically in recent decades. Occupational factors may play a role in testicular cancer etiology. The aim of this study was to further explore the association between occupation, industry, and the risk of TGCT in adulthood in France.

Methods : The TESTIS study included 454 histologically confirmed TGCT cases, aged 18-45 years. Controls (N=670) were frequency-matched to cases on 5-year age group and region. Full occupational histories were ascertained through telephone interviews. Occupations were coded according to ISCO68, and industrial sectors according to NAF99. A manual backward stepwise selection procedure was performed to select the covariates to be included in our analyses. For each job held, odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for potential confounders, were estimated using conditional logistic regression.

Results: In most of the occupations and industrial sectors studied, no increase in the risk of TGCT was observed. Nevertheless, an increased risk of TGCT was observed for two subgroups of "production and transportation" workers (ISCO: 7/8/9): "machine fitters/assemblers" and "electrical fitters, electrical and electronic workers" (ISCO: 8-41; adjusted OR = 2.46; 95% CI (1.08-5.62) / ISCO: 8-5; adjusted OR = 1.80; 95% CI (1.11-2.91), respectively). Analyses by industry confirmed these results. In addition, an increased TGCT risk (adjusted OR = 1.71; 95% CI (1.02-2.82)) was identified for " agricultural and animal husbandry workers" (ISCO: 6-2).

Conclusion: Our results suggest that occupational exposures may be associated with an increased TGCT risk in agricultural, machinery, and electrical/electronic workers, which is consistent with previously published studies. Because these occupations may result exposure to a variety of potential carcinogens/endocrine disruptors, further studies with job-exposure matrices application are needed to identify the agents or chemicals in these high-risk occu-pations involved in the TGCT development.

Mots-Clés: Occupational health, testicular cancer, men's health, case-control study, agriculture

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Dental prevention in children: what factors influence its implementation in healthcare settings?

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Résumé

Dental caries is one of the most prevalent chronic diseases in childhood, affecting almost 8% of the general child population in 2017. For this reason, bad oral health in children is considered to be a common issue for dentists as well as for family physicians and paediatricians who provide regular well-child visits during the first years of the child's life. In addition to surgical treatment, prevention measures and counselling are widely considered to be an essential part of caries management in international guidelines. Yet, health professionals report spending little time on it in their everyday practice. The gap existing between the theoretical importance of dental prevention and the actual lack of its clinical implementation requires further investigations. In this regard, we conducted a systematic review aiming to identify and classify factors perceived by health professionals to be barriers or facilitators to caries prevention in children. This study reveals multiple systemic barriers affecting all organizational levels of the health system. Among all factors discussed in this systematic review, health professionals commonly mention parents as a barrier to effective oral health prevention in children. Parents of children with dental caries are described as lacking oral health knowledge, parental skills, motivation, and authority. In the field of obesity, it has been demonstrated that the health professionals' negative perceptions of their patients could affect disease management quality with shorter consultations, less respectful communication, and a less patient-centered approach. In light of this, our research team is conducting a qualitative study to further investigate health professionals' perceptions of children with dental caries and their parents and how their opinions can influence attitudes and quality of care

Mots-Clés: Child, Dental Caries, Prevention, Health professionals

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Multiple sclerosis clinical forms classification based on brain morphological connectivity through graph convolutional network

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Résumé

Multiple sclerosis is a inflammatory, demyelinating and neurodegenerative disease that affects over 2 million people worldwide. The study of brain connectivity reveals how diseases alter relationships between brain regions. In particular, morphological connectivity which measures characteristic features of the gray matter(GM) constitutes a potential clinical tool as it requires only T1 weighted MR images. In this work, we implement graph convolutional network(GCN) methods for the classification of MS clinical forms.

We processed 660 T1w images and segmented the cortical surface. Using three distinct atlases-Desikan, Destrieux, Glasser- GM is divided into small regions. Then, we extract morphological properties like thickness of each region. To provide a thorough picture of the distribution of the measurements, we extract for each region and feature four statistical moments per region and compute their dissimilarity by Mahalanobis distance. Thus, we describe with a graph the brain gray matter network where each cortical region is a node with the four statistical moments, and edges are the Mahalanobis distance between all regions. Thresholds were used to only keep the substantial differences between regions. All graphs were then fed into the GCN for the clinical forms classification.

Five classification tasks related to clinical needs were implemented: CIS vs. RR vs. SP vs. PP; CIS + RR vs. SP vs. PP; CIS + RR vs. SP; CIS + RR vs. PP; SP vs. PP. For the 3 first tasks, best results were observed in 80% threshold on the Glasser atlas. Best accuracy can be attained in the CIS + RR vs. PP task utilizing 80% threshold on the Desikan atlas. 60% rejection on the Desikan atlas is suggested as the optimal SP/PP splitting outcome. Our works suggest that GCN can provide better overall classification results than classical machine learning approach (SVM by Barile 2022) if threshold and atlas are carefully chosen.

Mots-Clés: multiple sclerosis, gray matter, graph convolutional network, morphological connectivity

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Prehabilitation program for peritoneal carcinomatosis patients having cytoreductive surgery: a complex intervention developpement.

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Résumé

Peritoneal carcinomatosis is a poor prognosis metastatic dissemination shape of most intraperitoneal cancers. Cytoreductive surgeries with or without hyperthermic intraperitoneal chemotherapy (HIPEC) re a recent therapeutic opportunity for these patients. Psychiatric conditions are potential comorbidities that might be increased by the surgery, but also have an influence on the surgery outcomes. Unfortunately, very few data are available for psychi-atric comorbidities.

Our project aims to assess psychiatric condition epidemiology following the cytoreductive surgeries in peritoneal carcinomatosis and to develop a complex intervention to prevent and follow-up these comorbidities.

We will develop a complex intervention based on the medical research Council guidelines. First, we will conduct two epidemiologic assessments (one retrospective on a database and one prospective based on an ePatient Reported Outcome tool) for a better understanding of the epidemiology of psychiatric comorbidities following cytoreductive surgeries. Then, we will develop a theoretical framework based on a systematic review, realist synthesis, semistructured interview study, and focus group study to finally define the potential items that must be included in the intervention. These items will be finally validated by a Delphi method involving all stakeholders of peritoneal carcinomatosis care.

The first analysis confirmed the increased epidemiology of psychiatric comorbidities with a statistically significant increase in the depression screening scale six months after the surgical procedure (p=0.04). Then, the upcoming results of our literature reviews will provide information relatives to psychiatric prehabilitation interventions in cancer surgery and which implementation settings promote their effectiveness. The data provided from qualitative studies will enable to refine the theoretical framework. Finally, the Delphi method will enable to define the intervention in the most appropriate way for all stakeholders.

Our project will enable the rigorous development on a complex intervention to provide a psychiatric prehabilitation to peritoneal carcinomatosis patients having a cytoreductive surgery.

Mots-Clés: Peritoneal Carcinomatosis, Depression, Anxiety, Cytoreductive surgery, Complex Intervention

Effectiveness of medical management in the field of rare diseases. The example of fibrous dysplasia of bone.

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Résumé

Introduction. Reference Centers and Rare Disease Health Networks aim to improve management of patients with rare diseases. The French reference center for Fibrous Dysplasia (FD) was certified in 2006. The objective of our study was to assess the effectiveness of our reference center since its constitution.

Methods. In a retrospective cohort study, we compared the activity of our center, including the time elapsed between diagnosis and access to the center and the diagnostic delay (defined as the time to diagnosis > 6 months) of patients with FD between two periods, 1996-2006 (before certification) and 2007-2019 (after certification). Data were extracted from patients' records (Easily® software). Wilcoxon and Fisher tests were performed, using R (v4.0.2).

Results. Our cohort included 528 patients. The activity of the FD center has increased significantly by 2.8fold since the certification. Mean time elapsed to diagnosis of FD was 1.5 years before 2007 and 1.9 years after 2007 (p=0.14). There was a non-significant decrease in the number of patients with delayed diagnosis (44% in the first period had a diagnostic delay vs 33% in the 2nd period, p=0.07). Patients were referred to our center on average 6.8 years (before 2007) and 7.9 years (after 2007) after their FD diagnosis (p=0.86).

Conclusion. Healthcare organization with reference centers did significantly impact the management of FD/MAS patients, with a significant increase in the activity of our center, that roughly tripled since certification. This healthcare organization was also associated with a trend toward decreasing diagnostic delay. However, the time to access to the center remained long and patients were referred to our center on average 7 to 8 years after their diagnosis of FD. The current challenge lies in informing primary care providers and patients about the existence of reference centers for earlier and more effective specialized management of rare diseases.

Mots-Clés: Fibrous dysplasia of bone, Mc Cune Albright syndrome, fracture, rare bone disease, healthcare organization

Identification and distribution of circulating Leptospira strains in humans, dogs, and comparison with circulating Leptospira strains in urban small mammals in France, between 2019-2021

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Résumé

Leptospirosis is a worldwide bacterial zoonotic disease, caused by pathogenic leptospires. It is a public health problem with more than one million cases in humans and 60,000 deaths/year. The main reservoirs of leptospires are rodents, which excrete bacteria in their urine and contaminate the environment. Humans and animals become contaminated by direct contact indirectly with urine of infected or animals. A study was conducted to identify and describe the distribution of circulating Leptospira strains in humans and dogs in mainland France between 2019-2021. The inclusion crite-ria were compatible leptospirosis clinical signs and a positive biological diagnosis by PCR (patients' samples from the CNR of Leptospirosis, and dog's samples from the LAV of VetA-gro Sup). Sequencing of the lfB1 gene amplification product was performed on 176 samples, including 116 humans and 60 dogs. In humans, the genotypic analysis showed that L. interro-gans serogroup (sg) Icterohaemorrhagiae (57%)/Australis (5%)/Canicola/Pomona (5%); L. kirschneri sg Grippothyphosa (28%) and L. borgpetersenii (5%) were detected. In dogs, L. interrogans sg Icterohaemorrhagiae (67%)/Australis (28%)/Canicola (3%) and L. kirschneri sg Grippothyphosa (2%) were identified. These results showed a diversity of circulating strains, and the principal infectious agent was L. interrogans Icterohaemorrhagiae in both species.

A second study was carried out to determine the carriage and identification of *Leptospira* strains in urban small mammals, especially rodents, and thus compare them to the strains found in humans and dogs. 656 animals were captured in Lyon between 2020-2022 and 6 different species were identified (rats, mice, field mice, shrews and voles). The animals detected positive by PCR were 69 rodents. Genotypic analysis showed that *L. interrogans* (Icterohaemorrhagiae/Australis) and L. kirschneri (Grippothyphosa) were present in these reservoirs' species. These studies will serve us as a basis to better characterize exposure to reservoirs in mainland France and develop preventive strategies for the disease.

Mots-Clés: leptospirosis, humans, dogs, rodents, France

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Impact des horaires de travail des soignants sur l'identification de la douleur en réanimation

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Résumé

L'empathie à la douleur est importante pour la qualité de soin. Elle permet une compréhension de la douleur basée sur 1/ la détection et 2/ l'évaluation de l'intensité douloureuse nécessaire à sa prise en charge. L'objectif de cette étude était d'évaluer l'impact des horaires décalés, caractéristiques des soignants, sur les processus de détection et d'évaluation de l'intensité douloureuse.

L'étude a été réalisée auprès d'une équipe de 21 infirmiers de réanimation cardiaque pédiatrique de Lyon (31 ± 7 ans, 20 femmes). Les tests ont été effectués le matin et le soir, en début et fin de garde de 12h de jour ou de nuit. Dans le premier test, les soignants devaient indiquer si les visages présentés de manière subliminale exprimant de la douleur ou non. Dans le second test, ils devaient estimer l'intensité douloureuse de visages sur une échelle numérique.

Les performances ne variaient pas en fonction des horaires (matin ou soir), ni en fonction des heures travaillées (début ou fin de poste). Le score de somnolence (KSS) était négativement corrélé à la capacité de détection de la douleur suite à une garde de nuit (r = -,51, p = .018), mais n'influençait pas la capacité à juger l'intensité de la douleur.

La capacité de la compréhension de la douleur à travers des visages n'a pas été impactée par les horaires de travail des soignants et semble être stable dans le temps. Par contre la performance étaient influencées par le niveau de somnolence. Des facteurs plus individuels doivent être analysés en détail pour expliquer des altérations comportementales dans la gestion de la douleur.

Mots-Clés: Horaires décalés, empathie, douleur, détection subliminal, visages douloureux

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Pain and emotions during a visit to the emergency department: First results of the SOFTER IV-POSTER study

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Résumé

In 2019, emergency departments in France recorded approximately 22 million visits, providing opportunities for strong feelings, pain and emotions. However, if they are useful, they can also become pathological and/or influence the development of health problems such as chronic pain or depression. Until now, clinical studies have focused mainly on pain and rarely on emotions and their interactions.

The study was based on 1192 patients included in 7 adult emergency departments in France as part of the SOFTER/POSTER study. They completed a questionnaire at entry and at discharge, and in particular evaluated their pain on a numerical scale from 0 to 10, and their emotions on a scale from 0 to 5.

The proportion of patients with no or low pain increased from 40% to 56% between entry and discharge from the emergency department. Severe pain decreased by half, from 28% to 14%. Negative emotions were felt less at discharge, but with differences depending on the emotion, with a 13-point decrease for fear and a 2-point decrease for anger. Conversely, positive emotions are more often felt on discharge, also with differences according to emotion, notably an increase of 15 points for contentment, and 3 points for interest.

At entry, negative emotions are of higher intensity for those with strong pain. On the other hand, people with little or no pain felt relief more strongly. On the other hand, at discharge, only negative emotions are felt differently according to the level of pain declared, with differences for all levels of pain.

This study is the first part of an investigation into the determinants of chronic pain after trauma.

 ${\bf Mots\text{-}Cl\acute{es:}} \ {\rm pain,\ emotions,\ emergency\ department,\ interaction}$

Antibiotic therapy for infectious hemodialysed patients in Bamako: Pharmacokinetic analyses and first improvement suggestions

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Résumé

Infection which occurs in renal kidney failure patient have to be therapeutically managed immediately and the treatment must be aggressive to be quickly efficient. In Bamako (Mali). Posology adaptation cause a problem in nephrology, especially for the most common used antibiotics to care these infections. Drug dosage is not routinely performed in Bamako. The main objective of this work is to compare anthropometric, clinical and pharmacokinetic profiles and the clinical future between infected hemodialysis patients following an antibiotic therapy in Bamako and Lyon (hospital used as a reference). To reach these objectives, a preliminary punctual study of clinical pharmacokinetic of vancomycin were set up at Bamako, following the personalization therapeutics model from Lyon. Bamako patients' samples were imported to France and dosage analysis were performed at Lyon. BestDose software was used to view and compare complete pharmacokinetic profile. It includes for the first time, in routine, the 50 ml/mn of the renal function during dialyses for 58 patients: 31 for Bamako and 27 for Lyon. The residual concentration at the beginning of the dialysis session was com-pared. In Bamako, patients are younger, the renal failure is more severe and arteriovenous fistula are never set up, treatments are limited in dose and in duration; the residual concen-tration before the dialyses are too low; as a consequence, infections are rarely quickly reduced and more especially the death linked to these infections are more important (9 in Bamako versus 1 in Lyon). Urgent corrective measures have to be proposed: propose a conciliation between therapeutic requirements formulated within Lyon protocols and the financial ability of the patient, to promote arteriovenous fistula creation as soon as possible, and develop first dose strategy (unfortunately there is often only one dose): a more aggressive dose estimated from simulation profile performed in this study.

Mots-Clés: Adaptation, Africa, Hemodialysis, Infection, Pharmacokinetics.

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Triple negative breast cancer and active-targeted nanomedicine: the use of monoclonal antibodies

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Résumé

Treatment of triple negative breast cancer represents an important challenge for researchers. Its aggressiveness is mainly due to bad response to conventional treatments and a high metastasis rate. Ongoing phase I/II clinical trials have been set up to evaluate the antitumoral efficacy of chemotherapy combined with immunotherapy, in particular to immune checkpoint inhibitors, obtaining very promising results. In parallel, the overexpression of a particular protein in the tumor microenvironment has been related to unfavorable prognos-tic, as its interaction with the receptor made the cancer cells escaping apoptosis. In order to block the activity of this protein at the tumor site, a monoclonal antibody was developed. Preclinical studies are ongoing and aimed at evaluating its efficacy combined with immune checkpoint inhibitors.

In this context, the objective is to combine the targeting properties of the antibody with immunotherapy and chemotherapy. To do that, a novel active-targeted drug-loaded nanomedicine has been developed. Nanoparticles were prepared through microfluidic technique, and their size and surface charge were 90 nm and -35 mV respectively, showing good stability over a month. Then, their surface was modified by adding the antibody through a click-chemistry reac-tion. Once the conjugation has been verified, the binding affinity of the antibody to its ligand was evaluated.

Preliminary *in vitro* cytotoxicity studies were carried out on EMT6 murine breast cancer cell line, showing the safety of the nanosystem and its compatibility with intravenous administration (IC50= 13 mg/ml). In vivo biodistribution studies on EMT6 tumor bearing mice are ongoing and aimed at determine the optimal dose and administration schedule for further efficacy study. Once these experiments are validated, the in vivo immune response to this nanomedicine will be evaluated.

Mots-Clés: Nanoparticles, monoclonal antibody (mAb), click, chemistry, triple negative breast cancer, drug delivery

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Meta-analysis of Wilson disease in Morocco

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Résumé

Background: Wilson's disease (WD) is an autosomal recessive genetic disorder characterized by a toxic accumulation of copper in the body, primarily in the liver, central nervous system and cornea. The worldwide prevalence of WD is variable, with an average of 1/30,000. In Morocco is most higher.

Objective: To study the epidemiological profile, the clinical characteristics, the diagnostic, and therapeutic means of WD in Morocco.

Methods: We performed a Meta-analysis of 82 cases of WD record from different series of study in CHU of Morocco during the period 2000 to 2016.

Results: Our study collected 82 cases over a period of 16 years from January 2000 to June 2016. The average age of discovery of WD in our study is 10 years, with extremes of 5 and 18 years. Among all patients, there was a male predominance, with 48 boys (58.5%) versus 34 girls (41.5%), a sex ratio of 1.4. Consanguinity was found in 51 patients, or 62.2% of cases. The average time between the appearance of the first signs clinical trials and the diagnosis was 17 months. The clinical examination revealed 57 patients have a hepatic form (69.5%), 39 patients have a neurological form (47.6%). The Kayser-Fleischer ring is found in 38 cases (46.3%). 6 patients were asymptomatic diagnosed during screening (7.3%). The diagnosis is made by the clinical and biological confrontation (MRI, Abdominal ultrasound, NFS...) and cupric balance (cupremia, cupruria and ceruloplasmin). The treatment was based on D-penicillamine in 73 cases (89%), zinc acetate in 22 patients (26.8%) and zinc sulphate in 8 patients (9.8%), no patient is benefiting from liver transplantation. The evolution was favorable just for 39 patients. 31 patients died, whose 9 with cirrhosis decompensated, and 5 with hepatic encephalopathy. 6 patients are lost to view.

Mots-Clés: Wilson's disease, copper, Meta, analysis, Morocco.

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Ingénierie biomédicale, biotechnologie



3D BIOPRINTED CELLULAR STRUCTURES FOR UNIVERSAL PRODUCTION OF THERAPEUTICS

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Résumé

Cell-based biopharmaceutical market is constantly expanding and particularly the demand for monoclonal antibodies. To meet this demand, bioproduction intensification requires the access to large, expensive infrastructures and equipment. In another field, bioprinting have been developed to produce 3D tissues for regenerative medicine. Such technique allows to entrap living cells into 3D hydrogel structures. Its transfer to bioproduction applications is a clear breakthrough and gives access to cellularized structures of highly controlled shapes with homogenous seeding. It will later allow the development of small-scale local bioproduction units for biologic's manufacturing.

Our work proposes a novel strategy for the manufacturing of biologics. The strategy combines bioprinting with bioproduction technologies. Bioprinted structures cellularized with production cell lines (CHO, Vero, MDCK, HEK293, SF-9) were used to evaluate the potential of our approach to produce very high cell density constructs. This aims to enable a reduction of production volumes by increasing volumic productivity and facilitating product separation and recovery. Bioprinting parameters, including bioink formulation and consolidation or the 3D shape and porosity, were optimized to favor cell proliferation, in-situ cell transformation and bioproduction. Additionally, a bioreactor set-up was developed for the culture of bioprinted structures.

We successfully cultivated bioprinted structures of 10 cm3 seeded with several production cell lines over 15 days while tightly controlling their environment (pH, temperature, oxygen) thanks to our bioreactor set-ups. Optimization of the bioprinting parameters lead to the selection of the optimal condition with increased cell growth. We also produced mAbs from bioprinted CHO structures and achieved in-situ cell engineering and GFP transgene expres-sion. To our knowledge, it is the first time that therapeutic biomolecules are produced from bioprinted living structures. The project is supported by the funding of Sartorius thanks to the joint laboratory 3D InnovationLab.

Mots-Clés: Bioproduction, Bioprinting, Monoclonal antibodies, In situ transfection, In situ transduction, Bioprocesses, 3D cell culture

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Development of an in-vitro platform for dynamic maturation of full-thickness skin model

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Résumé

Skin is the largest organ of the human body. Natural human skin growth occurs simultaneously as the human body is exposed to multiple stresses and environmental conditions. So far, current skin models have not been able to achieve mimicking these stresses during the development of skin in vitro. There has yet not been a dedicated bioreactor available in the market for dynamic maturation of skin tissues.

A new bioreactor platform has been developed and validated based on the principles of fluid dynamics. This bioreactor is simple to use, has a defined air / liquid interface mechanism, avoids degradation & contraction of skin structure, provides mechanical forces in a controlled manner and delivers continuous maturation to cells embedded in the skin hydrogel. The bio-ink consisting of fibroblasts and keratinocytes cells used on this bioreactor was developed in the group previously for scaffold free skin bioprinting1. This whole bioreactor setup is designed to fit on standard 6 and 12 well plates and the whole setup can be placed on any laboratory shaking system. In addition, the bioreactor is open at the bottom to expose the hydrogel for microscopy. At this orientation, the skin maturation can be visualized in real-time during its development.

Initial results using this bioreactor device validate the design principle and are matching the expected hypothesis. Computational fluid dynamics simulation studies indicate the fluid velocity and shear stress around the skin hydrogel can be controlled using various shaking parameters. Preliminary results using this bioreactor demonstrates higher collagen production, higher cellular viability, reduced hydrogel degradation and faster skin maturation. This bioreactor could be used for in-vitro skin model production.

Mots-Clés: Skin, Bioreactor, Maturation, Tissue model

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3D printable alginate-gelatin hydrogels with variable viscoelastic properties as sole differentiation factor of induced pluripotent stem cells for tissue engineering

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Résumé

As cell source, stem cells are of great interest due to their pluripotency, and human induced pluripotent stem cells (hiPSC) present similar advantages but can be more easily obtained. However, their mechanosensitivity and the resulting potential to control their dif-ferentiation through the viscoelastic properties has not yet been investigated. Here, the aimed to (i) evaluate the ability of hiPS to auto-organize in 3D environment and (ii) characterize the impact of the viscoelastic properties on the hiPS differentiation of in the absence of biochemical factors. Hydrogels Preparation Alginate-gelatin (AG) hydrogels were prepared with factorial incrementation of their concen-trations (1X) being composed of 1 wt% alginic acid and 2 wt% bovine gelatin in ultrapure water maintained under stirring at 80°C for 2h.

hiPS Culture and Inclusion The "AG08C5" human induced pluripotent cell line is derived from the retrotranscription of human fibroblasts, made available by the NeuroMyoGene Institute, Lyon, and obtained from the MaSC, Marseille. Cells are maintained in mTeSR pluripotency medium (STEMCELL) for proliferation. After pelleting the cells (centrifugation 100g for 2 min), pellets were gently incorporated into AG-nX formulation by gentle homogenization for 10 min at 37°C. The bioinks thus were cross-linked with a 1% (w/w) Ca2+ solution for 10 min.

The AG bioinks developed show significantly different viscoelastic properties (AG-1X vs AG-3X vs AG-5X) after crosslinking by varying the proportions. Moreover, a same shear-thinning behaviour of the AG-1X, AG-3X and AG-5X formulations can be found by varying temperature, which allows to bioprint them avoiding cell injuries. HiPSC were able to self-organize in the AG hydrogels to form embroid bodies, as can be seen in Figure 1. Over culture time, the process of organisation shows growth of spheroids in plultipotency medium (D1 to D3) following by a variation in morphology after 6 days in DMEM medium (allowing differentiation).

Mots-Clés: Tissue engineering – 3D bioprinting, Induced pluripotent spheroids, Biomaterials mechanical characterization – Cell, Material interactions

Microfluidization: an eco-friendly process to improve oral bioavailability of poorly soluble API

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Résumé

Oral drug administration is the preferred route because it ensures better patient compliance to their therapies. However, many factors limit the effectiveness of oral treatments, including the poor bioavailability of some Active Pharmaceutical Ingredients (API) (1). Considering these issues, encapsulation of BCS class IV or II API, as our model drug spironolactone (SPI), in biocompatible lipid-based nanoparticles (Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC)) has become an innovative strategy (2). They are set by the Microfluidizer® technology (high pressure homogenization), an ecologicalfriendly manufacturing process without any solvents, presenting also the advantage to be easily scaled-up (3). The final aim of this project is to transpose the encapsulation process to an industrial scale at Skyepharma and propose new innovative and efficient oral delivery systems for BCS II or IV API.

The particle size characteristics of blank lipid-nanoparticles were satisfactory with mean diameter less than 180 nm (PDI = 0.18) and they all presented spherical shapes (TEM analysis). After SPI encapsulation, no significant difference on particle size or spherical shape were observed, compared to blank SLN or NLC. Concerning the NLC formula, the liquid lipid addition did not impact the size features but significantly improved the encapsulation efficiency (EE) of SPI (EE > 72%), compared to SLN (EE = 50%). The feasibility of the nanosuspension drying was also realized, by two different techniques (spray-drying and wet granulation). The first results were promising as they allowed the obtention of powders with excellent flowability and their compression into tablets (compliant with Ph.Eur.).

The stability of SLN and NLC in simulated digestive fluids and *in vitro* release studies will be performed, likewise their cellular permeability (*in vitro*) and bioavailability enhancement (*in vivo*).

- (1) Sciolo Montoto S. et al. 2020
- (2) Dumont C. et al. 2018
- (3)Ganesan P et al. 2018

Mots-Clés: Lipid nanoparticles, microfluidization, poorly, soluble API

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An innovative phyllosilicate-based hydrogl for skin decontamination against chemical warfare agents

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Résumé

Organophosphate neurotoxins are chemical agents that can enter the body through skin absorption. Decontamination is therefore crucial to prevent significant uptake and avoid a cholinergic crisis. Hence, we hypothesized that a composite hydrogel allowing (i) an easy application and removal on the skin through the formation of a film, and (ii) the incorporation of a phyllosilicate, would ensure an efficient adsorption, sequestration and disposal of an organophosphorus compound. To assess this hypothesis and develop biocompatible hydrogels, different formulations of polyvinyl alcohol (PVA), fuller's earth (FE) and surfactants (S) have been investigated. Hydrogel were prepared by mixing various concentrations of PVA, FE and S (PVA12S3 %, PVA20S3 %, PVA12FE15S3 % and PVA20FE9S3 % w/w) in a solvent composed of 10% ethanol at 90°C. All hydrogels, with and without FE, were easy to apply and formed cohesive films in max 7 minutes at 32°C, which could easily be removed. This drying time allows to envisage a potential use even in emergency situations by the military. Mechanically, an increase in PVA concentration of the formulations improved the resulting film stiffness with a young's modulus of 9.5 MPa for PVA20S3 % compared to 4.6 MPa for PVA12S3 %. Peeling tests showed that hydrogels adhere better to skin than to glass slides. This stronger adhesion did not prevent their easy removal, the results obtained for the reference hydrogel are similar to our conditions. During the procedure of contamination and decontamination we can notice that the removal of the hydrogel could be done simply while sequestrating the contaminant. Strikingly, formulations containing FE clearly demonstrated their ability to very efficiently decontaminate paraoxon from surfaces, allowing up to 98.5% of retention by the films, versus 82% for hydrogels without FE. We describe here new formulations of hydrogels, easy to obtain, compatible with a skin application, and with high decontamination capabilities.

Mots-Clés: Hydrogel, skin decontamination, organophosphorus compound, phyllosilicate

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Preclinical study of immunomodulating nanoparticles in a Hepatitis B Virus infected mice model

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Résumé

The TLR1/2-ligand Pam3CSK4 has been previously identified by our group as a potent and direct anti-HBV molecule in vitro, but the administration of soluble Pam3CSK4 in HBVinfected liver-humanized mice did not lead to a significant effect (Lucifora et al., 2018). In order to increase the overall efficacy of this innate immune agonist, we chemically optimized its vectorization via polylactic-acid (PLA)-based nanoparticles (NP) and evaluated the structural and functional integrity of these nanovectors (Lamrayah et al., 2019). Therefore, the aim of this work is to study the antiviral properties of the novel NP-Pam3CSK4 candidate as well as provide insights regarding its mechanism of action through immunological correlates of activity. To do so, antiviral properties of NP-Pam3CSK4 were first characterized in vitro on HBV-infected cell models (PHH, dHepaRG). Next, their activity was investigated in AAV-HBV transduced mice, which is particularly useful in that is supports persistent replication of the virus. Six groups of mice were designed as followed: PBS, empty NP (6-8x1011/injection), free form Pam3SCK4 (100 mg/injection), NP-Pam3CSK4 at two different doses (5 vs 20 mg/injection), and commercial control 3TC (100mg/kg/day). Eight intravenous administrations and six samplings were performed for viremia, antigenemia and blood markers transversal monitoring. Liver biopsies were collected at the day of sacrifice for intrahepatic quantification of viral and immunological parameters (CLIA, RTqPCR, IHS). Although read outs are still ongoing, the first analysis shows that the most significant viral decreases were observed within mice treated with NP-Pam3CSK4 formulations. Tissue staining of liver biopsies from Pam3CSK4-treated mice also evidenced strong cellular infiltration of macrophages/inflammatory-monocyte with a cluster-like organization across the sections, indicating a strong immune activation. Altogether, these data hint that TLR-agonists represent a great possible therapeutic tool to improve the rate of HBV cure in patients. Further evaluations and mechanistic studies are warranted to move towards clinical trials.

Mots-Clés: nanoparticles, hepatitis B virus, immunostimulation, therapeutic vaccine

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CURVILINEAR SHEAR WAVE ELASTOGRAPHY FOR CRYSTALLINE LENS ELASTICITY MEASUREMENT IN THE CONTEXT OF PRESBYOPIA TREATMENT BY ULTRASONIC CAVITATION

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Résumé

Presbyopia is the progressive rigidification of the crystalline lens, inducing a loss of accommodation capacity that can affect everyone aged above 40-45 years. Ultrasonic cavitation is being investigated in our group to soften the crystalline lens. To monitor a change in elasticity, curvilinear shear wave elastography method has been developed.

We developed curvilinear elastography around the only speckle available in the lens: the anterior interface. Homemade gelatin beads (10%, 15% of porcine gelatin), mimicking the ultrasound transparency of the crystalline lens, were used as an experimental model to evaluate the feasibility of the proposed method. The samples were half embedded in a phantom agar of 2%. Sweeps of vibrations (0.5–3.5 kHz) were induced to the sample with a mechanical vibrator in contact with the agar sample holder, and the displacements were tracked by ultrafast ultrasound imaging along the interface. We calculated the propagation velocity of waves with the noise correlation algorithm(1). The same experiments were conducted on ex vivo porcine excised lens.

The method enables to obtain an estimation of the speed of waves propagating along a surface over a large frequency range. The speed of waves measured for the calibrated gelatin beads are very close to the literature: for the 15% and the 10%, the correlation method finds 5.5m/s and 2.9m/s at 1.5kHz compared to 7.0m/s and 3.4m/s (2). However, for porcine lens, the value 1.6m/s found in the literature(3) is far from the value computed with the method developed: 3.9 m/s (at 1kHz).

The experiments implemented on the gelatin bead validated the curvilinear shear wave elastography method. The frequency study of propagating wave reflects the complexity of the lens structure: a multilayered medium. It remains to show the sensibility of our method to measure a change in elasticity in lens.

Mots-Clés: Presbyopia, crystallin lens, elastography, ultrasound

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In silico genotoxicity prediction by similarity search and machine learning algorithm: optimization and validation of the method for High Energetic Materials

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Résumé

The European regulation REACh (Registration, Evaluation, Authorization, and restriction of Chemicals) has placed responsibility on industry to manage the risk from chemicals since 2006. In order to ensure a high level of protection of human health and environment, toxicity prediction methods are now a widely used tool for regulatory decision making and selection of leads in new substances design. These in silico methods are an alternative to traditional *in vitro* and *in vivo* testing methods, which are laborious, time-consuming, highly expensive, and even involve animal welfare issues. Many computational methods have been employed to predict the toxicity profile of substance, but they are mostly adapted to pharmaceutical molecules and not to High Energetic Materials (HEM). In line with these restrictions, ArianeGroup set up a collaborative project with the French CNRS to develop optimized tools for the prediction of HEM properties, such as genotoxicity. We therefore developed a genotoxicity prediction tool based on the structural similarity search coupled with a supervised machine learning algorithm and composed by 3 predictive models : Ames test, Chromosomal Aberration test and Mouse Lymphoma Assay. The aim of this paper is to evaluate the performance these models to predict the genotoxicity of HEM. We also present the methodology we applied to build these models and optimize their performances. The dimensional reduction of the training set and the hyperparameters tuning of the different algorithms showed a performance acceleration and a significant reduction of the overfitting, which caused a decline in the generalization capacity of the predictive models. The performance of the predictive models was evaluated on a test set of HEM and compared to the results of other prediction softwares.

Mots-Clés: Machine learning, Prediction, Similarity, genotoxicity

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Development of an innovative lipid vector with a poly(lactic) acid core for the delivery of mRNA

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Résumé

mRNA vaccines have attracted a lot of attention with the approval of two of them as urgent prophylactic treatments against Covid-19. While they appear to be an interesting approach to treat diseases that lack yet alternatives, mRNA vaccines require the use of a dedicated platform to overcome main issues related to mRNA delivery. Indeed, naked mRNA suffers from enzymatic degradation within the body and poor targeted cells penetration. Vectors capable of addressing these issues while allowing endosomal escape are therefore needed. To date, the most promising carriers have been based on the use of lipids. In this study, we have designed an innovative vector called LipoParticles (LP) consisting of poly(lactic) acid nanoparticles coated with DSPC/DOTAP bilayers. The post-formulation of mRNA was performed using a strategy that we named particulate layer-by-layer (pLbL). The latter relies on the use of electrostatic interactions to adsorb successively nucleic acids and LAH4-L1, a cell-penetrating peptide allowing both cellular internalization and endosomal escape. After characterization of the naked vector as well as resulting formulations, their transfection capacity and cytotoxicity were compared both in vitro on different cell lines (DC 2.4, HeLa, CHSE...)(1) and in vivo on a zebrafish model. While LP have been shown to be very promising *in vitro*, with a transfection efficiency significantly better than liposomes and even commercial transfecting agents on some cell lines, the *in vivo* potential of LP is currently limited by the inhibition of mRNA expression in zebrafish. These data illustrate the difficult transposition between in vitro results and in vivo expectations, and an in-depth study has been initiated to explain such results.

(1) Ayad, C., et al. (2021). Lipoparticles: Lipid-coated PLA Nanoparticles enhanced *in vitro* mRNA transfection compared to liposomes. *Pharmaceutics*

Mots-Clés: Delivery systems, LipoParticles, mRNA vaccines, Nanoparticles, Nucleic acids, Transfection

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Additive manufacturing of silicone in a powder matrix for medical devices

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Résumé

Silicone-based materials are commonly used for the production of implantable soft prostheses thanks to their inertness toward the immune system and mechanical similitude with human tissues. The emergence of additive manufacturing techniques, being able to produce, silicone parts with customized shape and mechanical properties, have open the path to the production of patient specific objects and pre-surgery models. Among the existing additive manufacturing techniques, liquid deposition modelling (LDM) stand out as one of the best alternative for implant production. However, in most cases, the very poor firmness of the liquid silicone material is incompatible with the LDM process since the material itself, once deposited, is unable to withstand its own weight leading to printing defects. One of the most promising techniques to overcome this challenge is the freeform 3D printing, defined as a variant of LDM. In this widespread technique, liquid raw materials (termed "ink") are directly deposited within a temporary or permanent second fluid-based material (matrix) that prevents gravitational collapse and then enables freeform. In this presentation, we present the additive manufacturing in powder matrix. This unique matrix material fulfils the Freeform 3D printing requirements such as supporting the printed ink and self-repairing after its disruption by the printing head movements. Composite materials can be in-situ obtained or porous constructs if the powder support is removed. The success of this technique relies on the powder flowability properties but also on the printed material-powder physicochemical interactions and instabilities control. Powder shear tests are carried out to provide a quantitative description of the powder self-repairing property. The fluid-powder interaction is investigated across the viscoelastic properties of the extruded silicone ink and the contact angle. Cytotoxicity tests are performed on the printed constructs as well as dimensionnal and structural tests to quantify the effects of these conditions and instabilities.

Mots-Clés: Additive manufacturing, patient specific, medical silicone, freeform 3D printing, soft prostheses

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Can COS preserve cell from low temperature effects : A preliminary cytotoxicity study

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Résumé

Vitrification has wide potential for long-term storage of living biological samples that may be damaged by ice crystals formation. During a vitrification protocol, the most commonly used cryoprotective agents (CPA) are penetrating CPA. However, these CPA are potentially toxic or even mutagenic, especially at the high doses at which they are used in vitrification protocols. To address this challenge, we aimed to evaluate the potential of a large panel of saccharide molecules (chitosans), specifically chito-oligo-saccharides (COS), to replace penetrating CPA in embryo vitrification solutions. To this end, a defined Matrix of COS with different acetylation (0, 25, 50) and polymerization (10, 20, 30, 100, 1000) degrees was produced and chemically characterized at the laboratory. The evaluation is carried out using an innovative dual approach, combining physical and biological evaluation of the solutions. At first, in vitro toxicity tests have been carried out to ensure the absence of toxicity of COS. Fibroblasts were exposed to different solutions containing COS (100 mg/mL). 48 hours after exposition, viability cells was assessed by CCK-8 assay. Our results demonstrated high cell survival rates (> 70 %) and no cytotoxic effect was observed. Then, the physical evaluation will allow us to target the most interesting COS without using biological material. To achieve this goal, we are using differential scanning calorimetry, which allows the characterization of the thermodynamic properties of cryoprotective solutions (for example, the critical cooling and warming rates that allow the solution to vitrify). Finally, the biocompatibility of the most interesting COS will be evaluated in two steps. First, in vitro embryo development will be performed to ensure that the COS has no toxicity towards embryos under our conditions of use. Secondly, embryo vitrification assay will allow us to evaluate the ability of the COS to replace penetrating CPA in vitrification solutions.

Mots-Clés: cytotoxicity, COS, cryopreservation

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Estimation of the dose delivered by Cone-Beam CT patient positioning system for prostate VMAT treatments using an innovative plastic scintillating dosimeter

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Résumé

Since twenty years, the use of imaging in patient repositioning have grown to become a standard in radiotherapy. Image Guided Radiotherapy using planar acquisitions or Cone-beam CT (CBCT) acquisitions is a required condition for treatments with high dose gradients such as Intensity Modulated Radiation Therapy (IMRT), Volumetric Arc-therapy (VMAT), or stereotactic radiotherapy.

An innovative detector, based on the use of a scintillating optical fiber (IVICBCT[®], FIBERMETRIX, France) allows to measure the delivered dose and the CT dose indexes (CTDI and DLP) during CBCT exams. The study was carried on a Truebeam (Varian Medical system, Palo Alto, USA) with a IVICBCT (Fibermetrix, Strasbourg, France) dosimeter. The sensitive part of the dosimeter is 1mm of diameter and 1m long in order to take account of the complete length of the CBCT acquisition field. The measurements were compared to the dose measured by a pencil ionization chamber (IC) of 100mm in a CTDI fantom.

The differences observed for all protocols were between -7,9% (Image gently : 2,14mGy to 1,97mGy) and -13% (Pelvis large : 37,91mGy to 32,97mGy between the dose measured by a 100mm pencil ionization chamber and the IVICBCT dosimeter. Based on the results, for a prostate VMAT treatment with daily CBCT the total CTDI could reach 495,3mGy for a pelvis protocol and 981,1mGy for a Pelvis large protocol.

The results are similar between the measurements from an IC and the IVICBCT dosimeter. As expected, the dose is highly dependent of the protocol used. Following these results a clinical study including patients benefiting from VMAT prostate radiotherapy is ongoing to evaluate the impact of the CBCT delivered dose.

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Influence of administration route on mRNA vaccine immunogenicity: role of ionizable lipids

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Résumé

mRNA-based vaccines leap forward since Sars-Cov2 pandemic and have already shown their benefits to prevent other infectious diseases. Selection of delivery system and optimized-mRNA sequence are two keys factors to reach in vivo efficacy but optimal administration route for those vaccines remains unclear. Thus, we investigate the influence of lipid components and immunization route regarding intensity and quality of humoral immune responses in mice. DLin-mc3-dma or GenVoy ionizable lipids were used to encapsulate a mRNA encoding HIV p55Gag polyprotein using LipidNanoParticles (LNP) self-assembly process. Immunogenicity has been compared after intramuscular or subcutaneous routes following three sequential mRNA vaccine administration and a heterologous boost with p24 HIV-1 gag protein loaded onto polylactic acid nanoparticles.

4 groups of 8 mice were immunized at 4 weeks interval, and humoral immune responses has been monitored in sera samples through ELISA assay to quantify IgG responses and to analyze antibodies quality. Total IgG titers revealed the same kinetic profiles with a plateau effect after the third injection and for all tested conditions. IgG subtypes analysis showed Th1/Th2 balance towards humoral immune response when both LNP were administrated by intramuscular route after completed mRNA-based immunization. Surprisingly, subcutaneous route showed a Th1/Th2 biased cellular immunity in an ionizable lipids dependent manner which was improved by the second boost. Heterologous protein-based vaccine injection seems to reverse this balance to a strictly humoral response as noticed with a slight increase of antibodies avidity According to those results, intrinsic adjuvant effect of ionizable lipids appears to be dependent on delivery route and new experiments are ongoing to test such hypothesis.

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Sciences et Techniques des Activités Physiques et Sportives

Effect of hip and knee joint angles on resting hamstring muscles rigidity in men and women

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Résumé

Purpose: Hamstring muscle strains are one of the most common injuries in sports practice, for both men and women. However, sex disparities in the rate of muscle injuries have been observed. As these muscular lesions usually occur at long muscle length, this study aimed to determine the effect of sex on hamstring muscles' resting rigidity, under different stretching conditions.

Methods: The shear wave speed (SWS) of resting hamstring muscles was measured in 12 men and 12 women in different hip and knee positions (hip extended with knee flexed, hip flexed with knee extended, both joints extended and both joints flexed).

Results: Combining all the positions, the SWS of the *semitendinosus* was higher in men than in women (2.95 vs 2.71 m.s-1). Regardless of sex, a significant rise in SWS was systematically observed when the *semimembranosus* was stretched (1.86, 2.36, 2.73 and 4.36 m.s-1) but it was neither the case for the *semitendinosus* (p = 0.82) nor for the *biceps femoris* (p = 0.50). Finally, differences in SWS among the hamstring muscles were only observed at the longest muscle length, with greater SWS values for the *semimembranosus* and *semitendinosus* in comparison with the *biceps femoris* (4.36 and 4.12 vs 3.36 m.s-1 respectively).

Conclusion: In conclusion, a sex-difference was only observed in the resting semitendinosus rigidity. Independently of sex, the increase in resting hamstring muscles SWS with stretch was muscle specific.

Mots-Clés: Elasticity, Hamstrings, Sex difference, Shear wave elastography, Ultrasound
Influence of marker weights on scapular kinematics in a multibody kinematic optimization

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Résumé

<u>Introduction</u>: Assessing the shoulder kinematics, and in particular the scapular motion, is interesting in many research and practical fields. Skin markers are generally used to track scapular kinematics, but it suffers from misestimations because of soft tissue artefacts. Experimental then numerical methods have been developed to improve the kinematic estimates. Recently, multibody kinematic optimization (MKO), for which adjustable weights are applied to markers, has emerged. This study aimed to assess the influence of weights applied to scapular markers during MKO on scapular kinematics accuracy.

<u>Methods</u>: Fifteen healthy volunteers were equipped with 24 reflective markers. They performed fourteen movements decomposed in five static poses to allow the positioning of a scapula palpator. Two kinematics models were implemented through OpenSim and scaled to participant's anthropometry. The reference model reconstructed scapula positions using the scapula palpator, and the studied model used the skin markers in MKO. In the latter, weights applied to scapular markers were optimized for each movement of each participant to minimize the differences in orientation between both models. To evaluate the influence of weights, these differences were compared to those obtained with homogeneous weights. Specificity to movements and participants was studied. The average of all optimized weighting sets was computed and applied to all trials to investigate a common weighting set.

<u>Results</u>: Optimized weighting sets reduced the difference in orientation for all movements and all participants (mean misorientation with optimized weights of $14.6\pm4.0\circ vs.~18.3\pm6.3\circ$ for homogeneous weights (p< 0.0001)). Weighting sets were subject- and movement-specific. Additionally, the average optimized weighting set did not significatively reduce the difference in orientation.

<u>Conclusion</u>: Optimizing weighting sets for MKO improves scapular kinematic estimates. Nevertheless, the subject- and movement-specificity makes this method inappropriate for clinical use as not appliable in routine. Using homogenous weights for estimating scapular kinematics is recommended in MKO.

Mots-Clés: scapular kinematics, multibody kinematic optimization, shoulder

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The effect of acute physical and cognitive exercise on sequential motor learning

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Résumé

Mots-Clés: Motor Learning, Physical Exercise, Cognitive Exercise

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Imagerie



Impact of the contrast of CT images and FLAIR MRI for stroke lesion segmentation with deep neural networks

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Résumé

Introduction: Brain imaging plays a central role in the management of stroke patients. Cerebral MRI is the key imaging carried out in emergency in those patients provided that it does not delay the therapy. If MRI is not available or if contraindication, CT imaging will be performed. The objective of this work is to determine the impact of the contrast of these images for an accurate segmentation of the stroke lesion by deep neural networks, while MRI present a better one compared to CT scans.

Methods: The U-Net reference network is compared to two others architectures: the cGAN which tries to reinforce the U-Net results with a discriminatory network and the Mask R-CNN which uses bounding boxes to put attention on lesions before segmentation. The three algorithms are tested on the same 58 patients that were treated by thrombectomy. The CT images have been acquired 24 hours after treatment and FLAIR MRI five days later. The groung truth was seli-automatically segmented by an expert on FLAIR images.

Results: The global performances are better when the image modality has a better contrast. The Mask R-CNN is more precise on scans dealing between the detection threshold and the precision of the segmentation. While for the MRI, all three algorithms provide comparable results.

Conclusion: contrast has a great impact on the lesion segmentation precision but some methods seems promising concerning valid segmentation on CT images.

Mots-Clés: CT, FLAIR MRI, stroke, segmentation, deep learning

Micro-elastography on spheroid tumor models and the impact of ultrasonic cavitation

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Résumé

In the context of development of a new treatment against pancreatic adenocarcinoma combining chemotherapy and cavitation, it is of high interest to be able to mechanically characterize spheroid tumor models.

Spheroids, which are clusters of cancerous cells (KPC) and fibroblasts (iMEF), were made using magnetic nanoparticles which were linked to the cells. By using magnetic cell culture plates, cells aggregated, until forming a spheroid. Hence magnetic nanoparticles were incorporated inside the spheroid, and could be used to generate elastic waves inside. A pulsed magnetic field generated by a transcranial magnetic stimulator was applied, producing vibrations inside the spheroid. It was observed using an optical microscope and an ultrafast camera. Using particle image velocimetry and noise correlation algorithms, the displacements and the local shear wave velocity were retrieved. The higher the shear wave velocity was, the stiffer the sample was.

Cavitation designates the bubble generation using ultrasound. We showed that ultrasonic cavitation induces a statistically significant decrease of the velocity of shear waves, indicating a softening of the spheroid during the treatment. This could be due to the alteration of the stroma of the tumor model, potentially leading to a better penetration of chemotherapy. With different cavitation treatment parameters, the statistically significant decrease of the shear wave velocity was retrieved. However, the method was not sensitive enough to distinguish between the different cavitation conditions. Finally, the spheroid composition was varied, showing that there was no significant difference between the spheroids before cavitation, but that after cavitation, the fewer fibroblasts there were, the more sensitive to cavitation the spheroids were.

An original method has been developed to estimate the mechanical properties of spheroids. Optical micro-elastography is performed using an original shear wave source, constituted of magnetic nanoparticles stimulated by a magnetic pulse. Ultrasonic cavitation has been shown to soften the samples.

Mots-Clés: elastography, spheroids, pancreatic cancer, medical imaging

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Hemodynamic Changes Before and After Endovascular Treatment of Type B Aortic Dissection by 4D Flow MRI

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Résumé

The standard treatment for complicated Stanford type B aortic dissection (TBAD) is tho-racic endovascular aortic repair (TEVAR). Functional parameters, specifically blood flow, are not measured in the clinical assessment of TEVAR, yet they are of outmost importance in patient outcome. We investigated the impact of TEVAR on the flows in the aorta and its branches in TBAD using 4D Phase-Contrast Magnetic Resonance Imaging (4D Flow MRI).

Seven patients with TBAD scheduled for TEVAR underwent pre and post-operative 4D Flow MRI. We assessed the presence of helical flow in the false lumen (FL) using streamlines and measured net flow at specific locations. Additionally, forward and reverse flows, stasis, helicity, and absolute helicity were computed automatically along the aorta centerline.

FL helical flow was observed proximally in 6 cases and distally in 2 cases pre-operatively. Helical flow disappeared post-TEVAR proximally, but developed distally for 2 patients. Intrastent measures were similar to stent-free with a median difference of 0.1 L/min and an ICC equal to 0.967 (p < 0.01). Forward flow increased from 59.9 to 81.6% in the TL and significantly decreased in the FL from 15.9 to 3.3%. Similarly, reverse flow increased in the TL from 4.36 to 10.8% and decreased in the FL from 10.3 to 4.6%. No significant changes were observed in net flow for aortic branches (p > 0.05). A significant increase in FL stasis was observed (p = 0.04).

TEVAR significantly increased forward flow in the TL and significantly decreased both forward and reverse flows in the FL. Interestingly, reverse flow in the TL increased post-TEVAR, which could be due to increased rigidity of the wall, due to the metallic stent. User independent helicity quantification enabled detection of elevated helicity at the level of secondary entry tears which had been missed by streamline visualization.

Mots-Clés: 4D Phase, Contrast MRI, type B aortic dissection, thoracic endovascular aortic repair (TEVAR), hemodynamic evaluation, helical flow, parametric hemodynamic maps

Selective agonist PET radioligand (18F)F13640 for functional 5-HT1A receptor imaging in humans

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Résumé

F13640 (a.k.a. NLX-112) is a highly selective seroton in 5-HT1A receptor ligand that was identified as a PET radio pharmaceutical-candidate based on in vitro and animal studies. Because of its high efficacy agonist properties, (18F)F13640 binds preferentially to functional 5-HT1A receptors coupled to intracellular G-proteins. In this first-in-human study, we characterize brain labeling of 5-HT1A receptors by (18F)F13640 and propose a simplified model for its quantification.

PET-MRI scans were conducted in a total of 8 healthy male volunteers $(29 \pm 9 \text{ years old})$, with arterial input functions (AIF) and test-retest protocol. Several kinetic models were compared (one tissue compartment, two-tissue compartment and Logan); two models with reference region were also evaluated (simplified reference tissue model, SRTM, - and the Logan reference model, LREF).

(18F)F13640 showed high uptake values in raphe nuclei and cortical regions. SRTM and LREF models showed excellent correlation with kinetic models using AIF. Considering test-retest parameters and the prolonged binding kinetics of (18F)F13640, better reproducibility and reliability were found with the LREF method. Cerebellum white matter and frontal lobe white matter stand out as suitable reference regions.

The favorable brain labeling and kinetic profile of (18F)F13640, its high receptor specificity and its pure agonist properties open new perspectives for studying functionally active 5-HT1A receptors, unlike previous radiopharmaceuticals that act as antagonists. (18F)F13640's kinetic properties allow injection out of the PET scanner with delayed acquisitions, facili-tating the design of innovative longitudinal protocols in neurology and psychiatry.

Mots-Clés: (18F)F13640, 5, HT1A receptors, functional receptor, PET imaging, brain, modelling study

Methods of radiotherapy planning for head and neck tumors with multiparametric MRI

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Résumé

The excellent contrast between soft tissues of MRI is of great interest for radiotherapy planning. Unlike the CT scan, MRI does not give direct access to electronic densities, which is needed for dose calculation. To overcome this difficulty, two approaches allow to build a synthetic CT (sCT): statis-tical methods like bulk density assignment (1), deep learning or atlas registration; physical methods like proton density (PD) (2). My project aims to improve radiotherapy planning of head and neck tumors. We established a 30mn MRI protocol on 19 patients at the Centre Léon Bérard. It con-sists in routine acquisition, research sequences and a CT scan. 3D SPIRAL VIBE UTE and 3D DIXON VIBE sequences were used to classify four fundamental radiological densities: bone, air, water and fat, for the bulk density assignment. The PD method was developed using a phantom with different concentrations of to measure the relationship between theoretical and experimental proton densities. The UTE sequence measures the magnetization at the origin The PD can be computed, considering the sensitivity map of each element of the coils. The protocol gave contrasts between the tumor and the surrounding healthy tissues of 44,7 and 29,9 for MRI and CT respectively. The sCT with the 4 classes of densities gives realistic electronic densities for fat and wa-ter, but susceptibility artifacts make bone segmentation difficult. For the PD tests, the head and neck coil show better results than the body coil. The magnetic susceptibility variations at the air/skin/bone interface generate errors of clas-sification which could be reduced with additional T2* mapping. Further works will be done to determine the source of discrepancies between the two coils for PD mapping.

Mots-Clés: multiparametric MRI, radiotherapy, head and neck tumors

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Oxygen metabolism with MRI: Towards a better prediction of the ischemic penumbra in stroke

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Résumé

In case of acute ischemic stroke (AIS), the infarct core (irreversibly dam-aged tissues) progresses within the ischemic penumbra (tissues with preserved metabolism), but the latter can be salvaged if perfusion is restored. Its mapping, using medical imaging, is critical when managing AIS patients in order to identify those who are the most amenable to reperfusion strategies.

Initially, (150)-PET imaging validated the existence of the ischemic penumbra with metabolic parameters albeit exposed patients to radioactivity. Alternatives, such as CT and MRI, have been introduced to estimate the core progession in clinical routine and emergency settings. However, their reliability in defining the penumbra is questioned as "tissue-based" approaches tailored to each patient, are increasingly favored. In this context, new parameters better defining the penum-bra would greatly improve AIS care. Cerebral metabolism parameters can be obtained in MRI using magnetic suscep-tibility and hemodynamic parameters. A tool combining existing oxygen metabolism mapping methods and advanced image pro-cessing techniques, such as bayesian based deconvolution and motion correction, was developed. The tool was applied to an AIS non-human primate model (n=22)with combined PET-MRI modalities to validate the parameter against the gold-standard (150)-PET reference. Additionally, comparing the parameter with standard MRI practices for AIS penumbra per-formance care enables prediction evaluation. Both ischemic core and penumbra could be identified in preclinical AIS data when compared to physiological conditions imaging. These results correlated with infarct identification by standard MRI procedures on lesion side and presence of salvageable tissues detection with (15O)-PET. Preliminary tests on preclinical data in physiological and AIS conditions have shown promising results. Additional comparison with gold-standard (15O)-PET imaging and tissue-outcome will pave the way for the parameter's clinical validation.

Mots-Clés: MRI, oxygen metabolism, stroke, penumbra

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Assessment of skeletal muscle energy metabolism by 31P MRS in long-term fasting

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Résumé

Evaluating skeletal muscle energy metabolism is of medical interest in monitoring diseases and evaluating muscle1,2. 31P-MRS is a non-invasive technique of choice for dynamically assess the concentration of phosphorylated metabolites, directly related to the respiratory capacity of mitochondria3,4. The aim of this study is to provide evidence-based medicine on the impact of long-term fast (12-days,250kcal/day), on muscle metabolism and integrity in representative subjects. Indeed, fasting could represent a nutritional intervention of tremen-dous interest for public care, which effects on our organs need to be carefully demonstrated5.

The GENESIS (lonG tErm FastiNg Multi-systEm Adaptations In humans) study is a prospective, monocentric, single-arm interventional study on 33 subjects. High-resolution anatomical 3D isotropic Dixon sequence and dynamic 31P-MRS acquisitions were performed on a 3T clinical MRI at three time-points, before, after and 1 month after the end of fasting. After pre-processing and quantification, muscle volume, metabolite concentrations and time constants are extracted. Comparisons between time-points were performed using a repeated-measures ANOVA followed by a post-hoc Bonferroni-test for multiple comparisons (Xlstat) with significance at p < 0.05.

While the subjects lost 10% of their total body weight, there was no significant loss of skeletal muscle mass nor disturbance of muscle metabolism.

The results do not indicate any disturbance of muscle metabolism caused by long-term fasting, with no evidence of a negative impact on mitochondrial respiration or on the general muscle cell function, and minor muscle loss. These results should be compared with complementary analysis such as muscle force and performance to fully demonstrate a harmlessness

or an improvement of the muscular metabolism in the subjects following a long-term fast.

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Mots-Clés: Phosphorus, 31 magnetic resonance spectroscopy, muscle metabolism, fatigue, long, term fasting

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