interdisciplinary trainings & research in RD

Institut
Marseille
Maladies rares

Aix*Marseille Université

2nd MarMaRa SYMPOSIUM

June 2-3, 2022

Book of Abstracts

BOOK OF ABSTRACTS

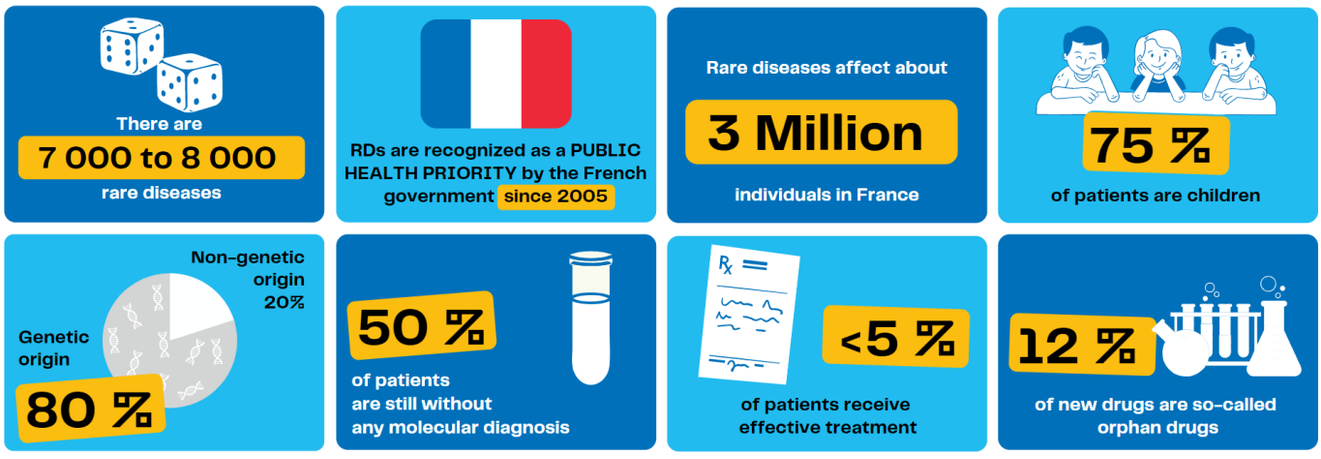
CONTENT

GENERAL INFORMATION

The Marseille Rare Diseases Institute- MarMaRa is one of the Aix-Marseille Université institutes for research and education. AMU institutes aim at developing interdisciplinary training and research by gathering cutting edge research and faculties and the involvement of socio-economic partners, to strengthen its international outreach.

Rare diseases (less than 5 in 10,000 people affected) are at a level of 7,000 to 8,000, of which 80% with a genetic etiology. Recognized as a public health priority by the French government since 2005, rare diseases affect about 3 million individuals in France. However, despite recent successes in diagnosis, care or therapeutic development, 50% of patients are still without any molecular diagnosis and effective treatment exists for only 5% of cases.

The objective of the MarMaRa institute is to gather research laboratories, medical departments, educational teams and industrial partners around cross-cutting actions to develop cutting-edge research for the benefit of patients. By federating new stakeholders, the MarMaRa institute aims at promoting, at the local, national and international levels, multidisciplinary research and training in connection with the socio-economic and cultural environment in the field of rare diseases.



Rare diseases (RDs) in a nutshell

Source : Ministère des solidarités et de la santé - "Les maladies rares". URL: https://solidarites-sante.gouv.fr/soins-et-maladies/prises-en-charge-specialisees/maladies-rares/article/les-maladies-rares#:~:text=Les%20maladies%20sont%20dites%20rares,millions%20de%20personnes%20en%20Europe.

Involved structures

13 Laboratories

ADES (MRU 7268)
(Bio-cultural anthropology, law, ethics & health)

IRPHE (MRU 7342)
(Institute for Research on Out-of-Balance Phenomena)

LMA (MRU 7031)
(Mechanics & Acoustics Laboratory)

FRESNEL institute (MRU 7249)

CEReSS (MRU 7310)
(Center for Studies & Research on Health Services & Quality of Life)

MMG (MRU 1251)
(Marseille Medical Genetics)

C2VN
(CardioVascular & Nutrition Research Center)

CRCM (MRU 7258)
(Marseille Cancer Research Center)

I2M (MRU 5295)
(Institute of Mathematics of Marseille)

LP3 (UMR 7341)
(Lasers, Plasmas & Photonic Processes)

IBDM (UMR 7288)
(The Developmental Biology Institute of Marseille)

INMED (UMR 1249)
(Mediterranean Neurobiology Institute)

TAGC (UMR 1090)
(Theories & approaches of genomic complexity)

4 Doctoral Schools (DS)

Engineering sciences (DS 353)

Mathematics & Informatics (DS 184)

Life and health sciences (DS 62)

Physics and matter sciences (DS 352)

2 Faculties

Faculty of science

Faculty of medical & paramedical sciences

MRU : Mixed Research Unit

Our actions

PhD program 2022 with Rare diseases trainings & cross-cutting trainings

13 funding / scholarships «master» (internships grants)

5 funding / scholarships «training» (acquire new skills)

Education

Summer schools

11 funding / scholarships «end of thesis» (extension up to 6 months)

Tutored seminars

Interdisciplinary research group "3M" with the institute SoMuM (Mediterranean Societies in Transition)

Annual symposium

4 funding / scholarships «incentive action» (support innovative & high-quality projects from different research units)

7 funding / scholarships «mission» (participation to scientific events or undertake short to mid-term scientific visits to collaborators)

Research

4 funding / scholarships «research year» (1 year of research for medical & paramedical students)

14 funding / scholarships «publication» (support dissemination of the research)

3 funding / scholarships «invited researcher» (to host an invited research form 1 week to 3 months)

4 funding / scholarships «post-doc» (up to 10 months)

2020 - 2022

Institut
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Aix*Marseille Université

MarMaRa 2022 Symposium

The Marseille Rare Diseases Institute organises a two-day symposium on **Thursday 2nd and Friday 3rd of June 2022**, in Marseille, at the amphitheatre Grisoli of the Faculty of medical and paramedical Sciences.

This second symposium **aims** to highlight **the projects of the 2021 laureates of the institute's scholarships**. This event is also a time to discuss and develop **collaborations** between the research units and the others AMU structures for the next years of MarMaRa.

The steering committee:

-Thierry Brue, Director
-Frédérique Magdinier, Deputy Director for Research
-Denis Puthier, Deputy Director for Education
-Laurence Colleaux, Grants and calls for tender coordinator
-Cécile Bernard, Project manager
-Rodolphe Moreau, Administrative and financial manager MMG

The scientific committee :

-Thierry Brue, MMG
-Frédérique Magdinier, MMG
-Denis Puthier, TAGC
-Laurence Colleaux, MMG
-Cécile Bernard, MMG
-Rodolphe Moreau, MMG
-Pascal Auquier, CEReSS
-Adrien Casanova, LP3
-Christophe Chevillard, TAGC
-Laurent Fasano, IBDM
-Nathalie Lalevée, C2VN
-Fabienne Lescroart, MMG
-Serge Mensah, LMA
-Françoise Muscatelli, INMED
-Jean-Christophe Roux, MMG

PROGRAM

1st DAY | Thursday 2nd June 2022

9:00-09:30 **Welcome coffee**

09:30-10:00 **MarMaRa news**
Thierry Brue, Director (RST)
Frédérique Magdinier, Deputy Director for Research
Denis Puthier, Deputy Director for Education

SESSION I : End of PhD & research year

Moderator : Nathalie Lalevée

10:05-10:20 **RNA interference-based therapeutic development for KCNQ2-related epileptic and developmental encephalopathies,** Florence Ricardi, *MMG*

10:20-10:35 **MRI quantitative assessment of changes associated to a rehabilitation strategy in FSHD patients,** Camille Noël, *MMG*

10:35-10:50 **High-throughput discovery of silencers element,** Nori Sadouni, *TAGC*

10:50-11:05 **Modeling congenital ACTH deficiency using 3D-organoid culture derived from human induced pluripotent stem cells (hiPSCs) modified by CRISPR-Cas9 editing,** Thi Thom Mac, *MMG*

11:05-11:20 **Comment on "Career Day",** Corentin Porada & Lucile Brun, *MMG*

11:20-11:45 ***Coffee break***

SESSION II : Interactions with other AMU Institutes

Moderator : Françoise Muscatelli

11:50-12:00 **Institute of Mediterranean societies in transition: the contribution of social sciences and humanities in a Mediterranean context,** Isabelle Renaudet, *SoMuM*

12:00-12:10 **Autism Spectrum Disorder: anything but rare?**
Laurent Fasano, *NeuroMarseille-MarMaRa*

12:10-12:20 **Life Habits Restrictions among Patients with Systemic Lupus Erythematosus: A Psychosocial Qualitative Study,** Marie-Anastasie Aim, *ISSPAM*

12:20-12:50 **Round Table,** Isabelle Renaudet, *SoMuM*, Laurent Fasano, *NeuroMarseille-MarMaRa*, Emmanuelle Le Barbenchon, *ISSPAM*

12:50-14:30 ***Lunch break***

SESSION III : Incentive actions publications & Post-doc

Moderator : Laurent Villard

14:30-14:45 ***in vitro* stimulation of cardiomyocytes mirrors the nitro-oxidative stress detected in Chagas disease cardiomyopathy myocardium,** João Paulo Nunes, *TAGC*, Publication Frontiers in immunology

14:45-15:00 **Oxytocin administration in neonates shapes hippocampal circuitry and restores social behavior in a mouse model of autism,** Françoise Muscatelli, *INMED*, Publication Mol Psychiatry

15:00-15:15 **Extensive phenotypic characterization of mouse models of rare neurodevelopmental disorders,** Laurent Fasano, *IBDM*, Incentive action *(INMED-IBDM)*

15:15-15:30 **Study of valve endothelial-interstial interactions during microenvironmental changes,** Stéphane Zaffran, *MMG*, Incentive action *(MMG-IRPHE)*

15:30-15:45 **Creation of iPSC from fibroblasts of patients with monogenic KCC2-related autosomal recessive neurodevelopmental disorders,** Igor Medyna, *INMED*, Incentive action *(INMED-MMG MaSC)*

15:45-16:00 **Exploration and Identification of TPE-OLD in Pathologies,** Jérôme Robin, *MMG*, Post Doc (Victor Murcia Pienkowski)

16:00-16:20 ***Coffee break***

SESSION IV : Artificial Intelligence & rare diseases

16:20-16:50 **Artificial Intelligence for Rare Disease research,** Anaïs Baudot, *MMG*

16:50-17:00 **Conclusion of the 1st day**

2nd DAY | Friday 3rd June 2022

9:00-09:30 ***Welcome coffee***

SESSION V : MarMaRa Training actions

9:30-10:00 Denis Puthier, Deputy Director Education

SESSION VI : Interactions with other structures

Moderator : Marc Bartoli

10:00-10:30 **My journey into the world of LAMAs: Why parents decide to create an association to support research in an ultra-rare neuromuscular disease - LAMA2-DM (merosin deficient congenital muscular dystrophy),** Céline Damon, *LAMA2*

10:30-11:00 **Technology Transfer and Innovation,** Laure Carrichon , *SATT Sud Est*

11:00 -11:30 **Drug Development for the treatment of rare neurodegenerative diseases,** Nuno Ribeiro Palha, *Servier*

SESSION VII : Lecture from a STAB member

11:30-12:20 **Endothelin Pathway and Shaping the Face,** Lecture by Jeanne Amiel, *Imagine Institute*

12:20-13:45 ***Lunch break***

SESSION VIII : Short talks selected from submitted abstracts

Moderator : Frédérique Magdinier

13:45-14:00 **Role of the cAMP-dependent protein kinase A type 1 in cardiac-related Carney Complex syndrome alterations,** Corentin Porada, *MMG*

14:00-14:15 **Developmental origins of Lmna-related dilated cardiomyopathies and impact of FGF10 treatment,** Laetitia Bouchard, *MMG*

14:15-14:30 **A rare case of monogenic KCC2-related autistic spectrum disorder: a new benchmark for the validation of causality and treatment screening,** Mira Hamze, *INMED*

14:30-14:45 **Combination of two laser processes for the creation of relevant bio-models for therapeutical applications,** Lucas Duvert, *LP3*

14:45-15:00 **Characterization of the functional role of Piezo1 coding variant associated with the most severe clinical manifestations of malaria infection,** Mathieu Adjemout, *TAGC*

15:00 -15:15 **Contribution of the adipocyte hormone leptin in the pathogenesis of Rett syndrome,** Yasmine Belaidouni, *INMED*

CLOSING SESSION

15:15 -15:30 **Discussion with the participants on 2022 main actions**

15:30-15:40 **Conclusions by the RST**

RNA interference-based therapeutic development for KCNQ2-related epileptic and developmental encephalopathies (DEE)

Florence Riccardi *1,2*, **Cécile Mignon-Ravix** *1*, **Florence Molinari** *1*, **Laurent Villard** *1,3*
1 Aix Marseille Univ, INSERM, MMG, Marseille, France
2 Service de génétique médicale, hôpital Sainte Musse, CHITS, Toulon, France
3 Département de génétique médicale, hôpital La Timone, AP-HM, Marseille, France

Developmental and Epileptic Encephalopathies (DEE) are rare and severe diseases affecting infants. They are characterized by seizures and a neurodevelopmental disorder. In patients with neonatal onset, the KCNQ2 gene is the most frequently involved. To date, there are neither curative treatment nor prenatal signs to prevent this condition. Dominant negative and gain-of-function variants in the KCNQ2 gene cause DEE. Interestingly, KCNQ2 haploinsufficiency leads to neonatal seizures with a normal neurodevelopment.
We hypothesize that the inactivation of the KCNQ2 mutated allele could change the patient prognosis from severe to benign. Specific mRNA degradation can be obtained using small non-coding RNA molecules according to the RNA interference cellular mechanism. We will test this approach in a knock-in mouse model developed in our team and three unrelated iPSC-derived patients' neurons. We designed small interfering RNA (siRNA) for each variant of interest. For the knock-in mouse, we started the preliminary tests in CHO cells before considering in vivo studies. We take advantage of altered restriction sites to discriminate the wild type and the mutated allele. The first results do not show a decrease of the mutated allele in transfected CHO cells. In patient cells, we demonstrated that Neural Stem Cells (NSC) contain the KCNQ2 mRNA, and we are developing siRNA transfections. When an efficient siRNA will be identified, functional experiments will be performed. In iPSC-derived human neurons, we will record electrical activities using microelectrode arrays and direct recording using patch clamp. In the mouse model, we will build an AAV9-KCNQ2 shRNA vector that can be delivered to the brain of knock-in mice in combination with focused-ultrasounds (FUS) to increase efficacy as previously demonstrated in the team.

MRI quantitative assessment of changes associated to a rehabilitation strategy in FSHD patients

Camille Noël *1,3* **, Constance P. Michel** *1*, **Amira Trabelsi** *1*, **Sébastien Vansteenkiste** *3*, **Emmanuelle Salort-Campana** *4*, **Maëva Cotinat** *2,3*, **Virginie de Bovis Milhe** *3,4*, **Laurent Bensoussan** *2,3,5*, **Shahram Attarian** *4*, **David Bendahan** *1*

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2 Aix Marseille Université, CNRS, INT UMR 7289, 13385 Marseille, France
3 APHM, Physical and Rehabilitation Medecine Departement, Sainte Marguerite Hospital, Marseille, 13014, France
4 Reference Centre for neuromuscular diseases and ALS, Timone University Hospital, Aix-Marseille Université, CHU Timone, 264 rue Saint Pierre, 13385, Marseille Cedex 05, France
5 UGECAM Institut Universitaire de Réadaptation de Valmante Sud

Background: Facio-scapulo-humeral muscular dystrophy (FSHD) is a progressive and asymmetric genetic myopathy. So far, the only interventional option is rehabilitation. The aim of the present study was to quantitatively assess the effects of a personalized rehabilitation strategy using MRI. Fatty infiltration and contractile muscle volume were quantified over time.

Methods: Quantitative MRI of thighs and legs were performed in 10 FSHD patients before and after a 8-week rehabilitation program. Intervention effects were analyzed on the basis of clinical and radiological parameters. Clinical parameters were peak oxygen uptake, knee flexors and extensors isokinetic strength, 6-minute walk test (6MWT), 10 meters walk test (10MWT) and functional, neurological and psychological tests. Fat infiltration and contractile volume of individual muscles were quantified in the lower limbs and potential correlations with strength, aerobic and functional measures were analyzed.

Results: Fat fraction did not significantly change with a 0.67% decrease in thigh muscles and a 0.14% decrease in leg muscles. Similarly, contractile volume did not significantly change over time with a 0.74 cm3 decrease in thigh and a 2.59 cm3 decrease in leg muscles .On the contrary, a significant improvement of clinical parameters such as walk tests, strength and mood was observed. Knee flexors and extensors contractile volume was significantly correlated with their strength with correlation coefficients ranging from 0.5 to 0.89. Knee flexors and extensors strength was also significantly correlated with fat fraction (correlation coefficients ranging from 0.44 to 0.80).

Conclusions: Neither fat fraction nor individual muscle volumes did change throughout the rehabilitation program whereas clinical parameters did. These results are in agreement with the positive effects reported previously throughout a different rehabilitation program (Janssen and al, 2016). With correlations results, we can consider that both fat fraction and contractile volume could be useful biomarkers of clinical evolution in FSHD.

High-throughput discovery of silencer elements

Thi Thom Mac *1,4*, **Teddy Fauquier** *1*, **Nicolas Jullien** *2*, **Frédéric Castinetti** *1,3*, **Thierry Brue** *1,3*

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2 INP – Institut de neurophysiopathologie, UMR 7051, Faculté de médecine, Marseille, France
3 Service d'endocrinologie, hôpital de la Conception – APHM, Marseille, France
4 Service d'endocrinologie, hôpital de l'Université de médecine de Hanoï, 01, Ton That Tung, Hanoï, Vietnam

Congenital adrenocorticotrophic hormone (ACTH) deficiency is a rare disease, defined as the presence of low plasma ACTH and cortisol levels, characterized by neonatal death or cholestatic jaundice, and hypoglycemic seizures. Mutations of TPIT (TBX19) represent the major genetic cause of congenital isolated ACTH deficiency. Several genes are involved in ACTH deficiency in association with other pituitary hormone deficiency (e.g. LHX3). Our group described for the first time (1 Quentien et al 2012) in patients with ACTH deficit a rare association of deficient anterior pituitary and variable immune deficiency as DAVID syndrome; that was later found by us and others to be due to NFKB2 mutations (2 Chen 2013, Brue 2014). However, the mechanisms underlying several congenital pituitary hormone deficiencies remain unknown, and in vitro human models for these diseases are lacking. In this study, we established an in vitro disease model using 3D-organoid culture technique, derived from human induced pluripotent stem cells (hiPSCs) edited by CRISPR-Cas9. In the first step, we used CRISPR-Cas9 system to produce in hiPSCs three mutations (p.K146R TBX19, p.L196P LHX3, p. D865G NFKB2) that cause congenital ACTH deficiency. Next, we developed pituitary organoids from these mutant and non – mutant hiPSCs. As expected, TBX19 mutant organoids showed decreased POMC expression and impaired differentiation into corticotropes cells. Thus, we established an in vitro model, which recapitulates the process of pituitary differentiation, and represents a suitable method to understand the complex cascade of causes leading to congenital pituitary diseases.

Modeling congenital ACTH deficiency using 3D-organoid culture derived from human induced pluripotent stem cells (hiPSCs) modified by CRISPR-Cas9 editing

Saadat Hussain *1**, **Nori Sadouni** *1**, **Dominic van Essen** *3*, **Pascal Lopez** *3*, **Lan T.M. Dao** *1,2,4*, **Guillaume Charbonnier** *1*, **Magali Torres** *1,2*, **Charles Lecellier** *5*, **Tom Sexton** *6*, **Simona Saccani** *3*, **Salvatore Spicuglia** *1,2*

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**these authors contributed equally to this work*

Keywords :
High-throughput reporter assay, regulatory DNA element, gene expression, silencer, epigenetics

Abstract :
Gene repression by cis-acting silencers, defined as genetic elements that negatively regulate gene transcription in a position independent fashion, is not well understood. Despite the widely-held belief that silencers likely represent important and critical general regulators of gene expression, their genome-wide distribution, mechanisms of action are largely unknown. In the lab we repurposed an existing high-throughput reporter assay in order to functionally identify silencers genome-wide. As a newly developed technology, the first objective was to build a bioinformatic pipeline to statistically identify genomic regions displaying silencer activity. Subsequently, a comprehensive genomic and epigenomic characterization of the identified silencers was performed, including: motif enrichment, genomic distribution, histone marks enrichment, repetitive elements enrichment, etc.). Multi-omics integration of identified silencers with transcriptomic and epigenomic ressources provided a comprehensive catalogue of silencer elements in the genome. My results also shed-light into the mechanism of regulation of silencer elements, which have been experimentally validated in the lab.

INTERACTIONS WITH OTHER AMU INSTITUTES

The Institute for Changing Societies in the Mediterranean (SoMuM)

Institut Sociétés en Mutation en Méditerranée Aix*Marseille Université

The strength of the institute is to cover a large disciplinary fi eld in the social sciences and humanities at the Aix-Marseille University site counting on an international network of scientists and socio-economic and cultural stakeholders, all specialists in the Mediterranean as an observatory of the major global challenges to be met.

The contribution of knowledge in the Social sciences and humanities is more necessary than ever in the face of the doxa and stereotypes that impact political and socio-economic discourse. Supported by the Mediterranean social science centre (MMSH), the Institute of Mediterranean Societies in Transition aims to describe, analyse and anticipate profound and sustainable transformations in the Mediterranean rim at the interface of Europe, Africa and the Middle East. The production and processing of survey data and the collection of Big data, as well as their archiving and dissemination, are at the heart of the scientific and educational approach. In an interdisciplinary framework, they allow the creation of digital platforms and tools for new conceptualisations.

Speaker : Isabelle Renaudet
Contact : Chloé Chatelin, chloe.chatelin@univ-amu.fr

Institut NeuroMarseille Aix*Marseille Université

NeuroMarseille Institute

Gathering research and training in neuroscience to meet the challenges of tomorrow.

Understanding the development, organization and functioning of the brain is one of the great challenges of the 21st century. Marseille is particularly well pre-pared for this task thanks to its unique expertise in France, covering all levels of analysis, from molecular and cellular pproaches to cognitive psychology and behavioral sciences. The 9 research laboratories, the School of neurosciences (NeuroSchool), the University Hospital (AP-HM) and biotechnology companies have joined forces to increase the attractiveness of the university, international collaborations, interdisciplinarity, links with the clinical and industrial world and the integration of students into professional life. NeuroMarseille aims to inter-act with citizens and to address current challenges, in order to frame the pres-ent in a historical perspective to invent the future.

Speaker : Laurent Fasano
Contact : Gabrielle Gallon, gabrielle.gallon@univ-amu.fr

The Institute of Public Health Sciences (ISSPAM)

The institute of public health sciences anchors its actions in a modern, digital and globalized world to contribute to clinical and public health decision-making, to the assessment of population health policy, informing decision-makers and impacting public health policy decisions.

The institute has research and training missions characterized by a multidisciplinary and interdisciplinary approach to the public health sciences. It aims to synergize and potentiate the site's strengths in different areas: from health democracy and empowerment to community and population research; social inequalities in health and public policy responses; digital health and augmented humanity; global health; artificial intelligence for public health. It interacts strongly with patient associations and committees, health agencies and the socio-cultural world. Intending to strengthen its international outreach, the institute mainly concentrates on the developing countries in the South, with a priority on the Francophone community and the Mediterranean basin.

Speaker : Marie-Anastasie Aim
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INCENTIVE ACTIONS PUBLICATIONS & POST-DOC

In vitro stimulation of cardiomyocytes mirrors the nitro-oxidative stress detected in Chagas disease cardiomyopathy myocardium

João Paulo Silva Nunes *1,2,3**; **Pauline Andrieux** *4*, **Pauline Brochet** *4*, **Karla Deysiree Alcântara Silva** *1,2*, **André Kenji Honda** *1*, **Jorge Kalil** *1,2,3*, **Christophe Chevillard** *4*, **Edecio Cunha-Neto** *1,2,3*

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Chagas disease cardiomyopathy (CCC) is an inflammatory dilated cardiomyopathy and occurs in 30% of patients chronically infected by Trypanosoma cruzi. Myocardial tissue from CCC patients is an inflammatory-rich environment with augmented expression of IFN-γ and TNF-α. Mitochondrial dysfunction and host genetic factors are depicted as key mediators of heart failure severity, where mitochondrial damage seems to be especially severe in CCC. Our group found rare heterozygous pathogenic variants in mitochondrial genes associated exclusively with CCC and absent in asymptomatic (ASY) siblings, in multiple Chagas families. Our hypothesis is that persistent production of inflammatory cytokines in CCC damages the cardiomyocytes by inducing mitochondrial dysfunction. The objective of this study was to evaluate the nitrosative profile of human CCC myocardium and the in vitro effects of IFN-γ and TNF-α stimuli on human cardiomyocyte's mitochondria. Human left ventricular heart tissue was collected from end-stage heart failure CCC patients (n=40) and non-chagasic dilated cardiomyopathy (DCM, n=31). We measured nitrite (NO_2^-) by chemiluminescence, nitrotyrosine (3-NT) by immunoblotting and mtDNA by real time amplification of mitochondrial gene MT-ND1. We found that CCC tissues displayed higher amounts of nitrite (132%; $p < 0.001$) and 3-NT (27%; $p < 0.01$), and lower copy number of MT-ND1 (44%; $p < 0.001$) compared to DCM patients. In a similar fashion, in vitro stimulation of AC16 cardiomyocytes with IFN-γ (10 ng/ml) and/or TNF-α (5 ng/ml) for 48 hours increased NO_2^- and 3-NT and reduced MT-ND1. Additional in vitro experiments revealed more mitochondrial damage induced by the cytokines. We measured ATP production by Seahorse and luciferase-based assay, reactive species production (ROS) by fluorescence, mitochondrial membrane potential ($\Delta\Psi m$) by high content fluorescence and fuel oxidation by Seahorse. We identified that cytokines-stimulated AC16 have decreased dependency of fatty-acid oxidation as compared to not-stimulated cells. Additionally, the cytokines decreased both $\Delta\Psi m$ and ATP, while increasing ROS production. These results indicate a nitro-oxidative profile of CCC myocardium and that IFN-γ/TNF-α have a direct effect on cardiomyocytes' mitochondrial function, which seems to recapitulate the profile observed in CCC tissue. This may provide a link between inflammation and mitochondrial dysfunction observed in CCC and supports studies to identify mitochondria-based compounds for CCC therapy.

Key words : mitochondrial dysfunction; Chagas disease; IFN-γ/TNF-α;

Oxytocin administration in neonates shapes hippocampal circuitry and restores social behavior in a mouse model of autism

Alessandra Bertoni *1*, **Fabienne Schaller** *1*, **Roman Tyzio** *1*, **Stephane Gaillard** *2*, **Francesca Santini** *3*, **Marion Xolin** *1*, **Diabé Diabira1**, **Radhika Vaidyanathan** *5*, **Valery Matarazzo** *1*, **Igor Medyna** *1*, **Elizabeth Hammock** *5*, **Jinwei Zhang** *6*, **Bice Chini** *4*, **Jean-Luc Gaiarsa** *1* **and** **Françoise Muscatelli** *1*

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4 Institute of Neuroscience, National Research Council (CNR),Vedano al Lambro, Italy. NeuroMI Center for Neuroscience, University of Milano-Bicocca, Milan, Italy.
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6 Institute of Biomedical and Clinical Sciences, College of Medicine and Health, Hatherly Laboratories, University of Exeter, Exeter, UK.

Oxytocin is an important regulator of the social brain. In some animal models of autism, notably in Magel2tm1.1Mus-deficient mice, peripheral administration of oxytocin in infancy improves social behaviors until adulthood. However, neither the mechanisms responsible for social deficits nor the mechanisms by which such oxytocin administration has long-term effects are known. Here, we aimed to clarify these oxytocin-dependent mechanisms, focusing on social memory performance. Using in situ hybridization (RNAscope), we have established that Magel2 and oxytocin receptor are co-expressed in the dentate gyrus and CA2/CA3 hippocampal regions involved in the circuitry underlying social memory. Then, we have shown that Magel2tm1.1Mus-deficient mice, evaluated in a three-chamber test, present a deficit in social memory. Next, in hippocampus, we conducted neuroanatomical and functional studies using immunostaining, oxytocin-binding experiments, ex vivo electrophysiological recordings, calcium imaging and biochemical studies. We demonstrated: an increase of the GABAergic activity of CA3-pyramidal cells associated with an increase in the quantity of oxytocin receptors and of somatostatin interneurons in both DG and CA2/CA3 regions. We also revealed a delay in the GABAergic development sequence in Magel2tm1.1Mus-deficient pups, linked to phosphorylation modifications of KCC2. Above all, we demonstrated the positive effects of subcutaneous administration of oxytocin in the mutant neonates, restoring hippocampal alterations and social memory at adulthood. Although clinical trials are debated, this study highlights the mechanisms by which peripheral oxytocin administration in neonates impacts the brain and demonstrates the therapeutic value of oxytocin to treat infants with autism spectrum disorders.

Extensive phenotypic characterization of mouse models of rare neurodevelopmental disorders

Idrisse Kabore *1, 2*, **Xavier Caubit** *1*, **Fabienne Schaller** *2*, **Mathias Lechelon** *3*, **Séverine Dubuisson** *4*, **Françoise Muscatelli** *2*, **Laurent Fasano** *1*

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2 Aix-Marseille Univ, INSERM UMR 1249, INMED (Institut de Neurobiologie de la Méditerranée), Parc Scientifique de Luminy, Marseille, France.
3 CENTURI Multi-Engineering Platform, Aix-Marseille Univ, Campus Luminy, Marseille, France
4 Aix-Marseille l'Université - Université de Toulon, CNRS UMR 7020, LIS (Laboratoire d'Informatique et Systèmes)

Summary:
Our research focuses on different mouse models of rare neurodevelopmental diseases, which present autism spectrum disorder (ASD) symptoms. ASD is diagnosed on the basis of difficulties in two areas: social communication and restricted, repetitive behavior or interests. Accordingly, our mouse models went through extensive behavioral phenotyping. This was done using manual scoring, which suffers from a number of limitations such as observation which spans short periods and the observation of either one individual for various and separate behavioral tests (i.e. anxiety, learning, memory, repetitive behaviors) or two animals for social interactions, all tests are performed in a different contextual space and mice are not observed in their "normal" conditions of life. To overcome these limitations, we built, validate and started to improve a Live Mouse Tracker system (LMT-https://livemousetracker.org), which allows automatic detection and quantification of the behavior of multiple mice. In this presentation, I will present the LMT we now have and some ideas to improve it.

Study of valve endothelial-interstitial interactions during microenvironmental changes

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The aortic valve maintains unidirectional blood flow between the left ventricle and the ascending aorta. Aortic valve leaflets are composed of three highly organized layers of extracellular matrix populated by valve interstitial cells and covered by a monolayer of valve endothelial cells (VECs). These cells are exposed to different stresses, in particular wall shear stress (WSS). Biomechanical stimuli actively regulate valve tissue structure and induce remodeling events leading to valve dysfunction. However, the biomechanical response of cells at different sides of the leaflets has not been clearly characterized. To analyze the mechanical response of VECs we developed a unique fluid activation device that applies physiologically relevant pulsatile WSS. Using this unique fluid activation device, we characterized the molecular response of adult porcine aortic VECs derived from the opposite sides of aortic valve leaflets following exposure to different pulsatile WSS. Our data reveal functional differences in VECs derived from opposite sides of the aortic valve leaflets and contribute to better understand how heterogeneity of VECs influences pathophysiological behavior under particular conditions.

Creation of iPSC from fibroblasts of patients with monogenic KCC2-related autosomal recessive neurodevelopmental disorders

Igor Medyna *1*, **Mira Hamze** *1*, **Christophe Porcher** *1*, **Natacha Broucqsault** *2*, **Frederique Magdinier** *2*, **Gaetan Lesca** *3*

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A neuron-restricted K+/Cl- co-transporter KCC2 is an important molecule controlling neuronal chloride homeostasis [Cl-]i and associated with etiology of different Neurodevelopmental disorders (NDD). However KCC2-dependent mechanisms leading to different pathologies are not clear and there is no effective treatment of NDD. Recent analysis of the properties of cortical neurons differentiated from Rett syndrome patient's induced pluripotent stem cells (iPSC), that was performed in the laboratory of Dr. Tang (Boston, USA), revealed changes in the properties of KCC2 and neuronal chloride homeostasis. The same laboratory succeeded in screening several compounds that effectively correct KCC2 dysfunction, opening up new prospects for treatment development, at least for patients with Rett syndrome.
Dr. Lesca and collaborators have identified among patients suffering from different NDDs two families associated with different missense variants of SLC12A5 gene encoding KCC2. The first family includes single child "Sacha" affected with a very severe developmental epileptic encephalopathy comorbid with drug-resistant focal seizures. Whole-exome sequencing revealed in Sacha two missense variants of SLC12A5 (called thereafter Sasha1 and Sasha2), each inherited from one of the parents that do not show any detectable symptoms. The second family ("Dylan") includes four siblings with moderate Autistic Spectrum Disorder (ASD) and drug-resistant partial epilepsy in three of them. All siblings disclose two missense variants on SLC12A5 gene (called thereafter Dylan1 and Dylan2). Each variant was inherited from one healthy parent. The four mutations are not known yet and are located within different putative transmembrane regions of KCC2. The functional consequences of the heterozygous combination of KCC2's mutations, occurring in patients, remain unclear.
In the project we propose creation from patients' fibroblasts iPSC, differentiate them in cortical neurons and study which of neuron's properties will differ compared to those obtained from healthy individuals. Soon characterized, the differentiated neurons will be used for screening of the compounds enhancing KCC2 function with perspective of selection candidates for therapeutic treatment.

Exploration and Identification of TPE-OLD in Pathologies

Victor Murcia Pienkowski *1*, **Raphael Chevalier** *1*, **Maciej Sykulski** *2*, **Frédérique Magdinier** *1*, **Jérôme D. Robin** *1*

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Copy number variants (CNV) are characterized as a vast gain or loss of a DNA fragment. These mutations can be divided into (I) benign variants present in healthy individuals and (II) pathogenic variants found in individuals with diseases. In general, CNV associated pathologies are caused by changes in dosage sensitivity of genes encompassed by the variant. However, other mechanisms might impact CNV pathogenicity in subtelomeric context, such as telomere position effect over long distances (TPE-OLD). TPE-OLD is a telomere length-dependent mechanism that consists of telomere loops formation that modulate gene expression through direct interactions. My project entitled: Exploration and Identification of TPE-OLD in Pathologies (EpITOP) proposes a step towards a new model for diagnosis and predictions of CNV-associated pathologies.

By combining clinical data, high-throughput genomics and disease modelling from patients' cells EpITOP aims to identify genes and epigenetic changes governing subtelomeric CNV pathologies with uncertain status. EpITOP is divided into the following steps: Generation of neural progenitor cells derived from carriers of subtelomeric copy number variants, Identification of the CNV structure and length of its abutting telomeres with a novel Oxford nanopore sequencing protocol, and investigation of the related patho-mechanism. In the last step apart from verifying differentially expressed genes and loss/gain of enhancers we will check if TPE-OLD might be partially linked to the pathological phenotype of the patient.

INTERACTIONS WITH OTHER STRUCTURES

LAMA 2 FRANCE

We are an association of families impacted by **LAMA2 Congenital Muscular Dystrophy**, also known as **merosin deficient muscular dystrophy** or **MDC1A**.

Our goals are to :

- list all European french speaking patients (France, Belgium, Luxembourg, Switzerland, Monaco...) that could benefit from a cure or treatment for merosin deficiency muscular dystrophy.

- get in touch and establish relationships with clinicians, hospitals, industrials, other non-profits who could work or help in any way on possible cure / treatment for merosin deficient CMD.

- inform the LAMA2/merosin deficient community of ongoing research and studies on the disease.

An initiative supported by OrphanDev, the national platform for the support of clinical trials in rare diseases.

Speaker: Céline Damon
Website : https://www.lama2.fr/home

SERVIER

Servier is a global pharmaceutical group governed by a Foundation. A leader in cardiology, the ambition of the Servier Group is to become a renowned and innovative player in oncology. Its growth is based on a sustained commitment to cardiovascular and metabolic diseases, oncology, neuroscience and immuno-inflammatory diseases. To promote access to healthcare for all, the Servier Group also offers a range of quality generic drugs covering most pathologies.

Neuroscience and Immuno-inflammation Therapeutic Area
In the field of neuroscience, Servier focuses its research on neurodegenerative diseases. Servier targets proteinopathies, characterized by abnormal accumulation of certain proteins, such as Parkinson's disease or rare diseases such as amyotrophic lateral sclerosis.
Immune-inflammatory diseases are characterized by an inadequate response to the immune system that turns against the patient's own tissues. Servier concentrates its research and development efforts on three autoimmune diseases with very high medical needs: systemic lupus erythematosus, scleroderma and Sjögren's syndrome.

Speaker: Nuno Ribeiro Palha
Website: https://servier.com/en/

The SATT Sud-Est (South-East)

The SATT Sud-Est, "The Technology Transfer Accelerator", is a privileged interface between businesses and public research in the PACA and Corsica Regions.

Its core business is the maturation of inventions from the regional research laboratories on the legal (intellectual property), economic (market) and technological (technological maturation) levels. Its objective is to transfer the innovative technologies of its shareholders to the industrial world by granting operating licences to companies.

The SATT Sud-Est focuses its investment strategy on innovative projects in line with the scientific skills of its shareholders around 5 priority areas of interest:

- Connected information society;
- Environment, energies & territories;
- Health & life technologies;
- Industrial processes;
- Digital Culture, Heritage & Humanities

Speaker : Laure Carrichon
Website : https://www.sattse.com/en/

LECTURE FROM A STAB MEMBER

JEANNE AMIEL

Jeanne AMIEL (PU-PH) is a clinical geneticist and leads since 2019 the team “Embryology and Genetics of Malformations” in INSERM U1163 affiliated to the Imagine Institute (https://www.institutimagine.org/fr/jeanne-amiel-75). She has conducted a number of studies aiming at gene identification for neural crest cell derived congenital malformations and tumour predisposition, in particular in Hirschsprung disease, congenital central hypoventilation, neuroblastoma, conotruncal heart defects and mandibulofacial dysostoses. She is or has been the coordinator or associate investigator in a number of research programs funded by the French National Agency for Research (ANR) and the Fondation pour la Recherche Médicale (FRM). She is coordinating the CRMR Anomalies du Développement at Necker Hospital affiliated to the Filière AnDDI-Rares and the Master Européen de Génétique at Université de Paris.

Lecture: Endothelin Pathway and Shaping the Face

The endothelin system is a vertebrate-specific innovation expressed in many neural crest cell derivatives. I will focus on its role in shaping the face via exploration of some rare and ultra-rare human diseases that are the consequence of homeotic transformations of the jaw.

SHORT TALKS SELECTED FROM SUBMITTED ABSTRACTS

Role of the cAMP-dependent protein kinase A type 1 in cardiac-related Carney Complex syndrome alterations

Corentin Porada *1*, **Fabien Hubert** *1*, **Grégoire Vandecasteele** *2* **and Francesca Rochais** *1*

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2 Signaling and Cardiovascular Pathophysiology, INSERM UMR-S 1180, University Paris-Sud, University Paris-Saclay, Châtenay-Malabry, France.

During the early phase of heart development, second heart field (SHF) progenitor cells allow the rapid elongation of the embryonic heart tube. The precise control of SHF proliferation/differentiation balance is a prerequisite for correct heart tube elongation and any alteration results in severe congenital heart defects (CHD). A second extracardiac cell population, called the cardiac neural crest (CNC), plays a critical role in heart morphogenesis and septation. Interaction between CNC cells and SHF progenitors is essential for the regulation of SHF cell addition to the heart tube.
We previously identified the transcriptional repressor Hes1 as a critical regulator of SHF proliferation and preliminary results suggest that cAMP signaling may control Hes1 expression in the SHF. Using a candidate approach, early embryonic gene expression profiling of diverse cAMP pathway components was achieved. A predominant and regionalized SHF expression of the cAMP-dependent protein kinase (PKA) regulatory subunit RIα (Prkar1a) was identified. In the adult heart, the PKA constitutes one of the master regulators of heart contraction nevertheless its role during heart development still remains to be determined. In human, mutations in PRKAR1A gene cause haploinsufficiency which results in Carney Complex syndrome, a rare disease associated with endocrine tumors and non-endocrine manifestations including cardiac myxomas. Interestingly, cardiac myxomas have been associated with congenital heart defects, including Tetralogy of Fallot.
In order to evaluate the role of R1α during early heart morphogenesis, transgenic mouse lines displaying conditional deletion of Prkar1α in diverse cardiac progenitor cell lineages, including SHF and CNC, have been developed. Our results firstly demonstrate a key role for Prkar1α in controlling early SHF progenitor cell deployment. Indeed, Prkar1a deletion in SHF progenitors results in impaired SHF proliferation, associated with early embryonic lethality at late heart tube stage. Our results revealed Prkar1a mutant embryos display impaired Hes1 expression in SHF, suggesting a potential genetic interaction between Prkar1a and Hes1. We then demonstrated that R1α is required for proper CNC cell deployment. Indeed, CNC conditional Prkar1a mutant embryos display severe CHD including common arterial trunk and ventricular septal defects. Interestingly, heterozygous Prkar1a conditional deletion in CNC leads to an early 5 weeks-old lethality associated with cardiac hyperplasia. Preliminary results using CNC progenitor cell tracing (Sox10CreERT2-RosadT) reveals the existence of subendocardial CNC progenitors in the adult heart which may suggest a potential role for CNC derivatives in the development of cardiac myxomas.
Altogether, this study reveals a critical role for R1α in cardiac progenitor cell deployment and unveils its requirement for correct heart morphogenesis.

Developmental origins of Lmna-related dilated cardiomyopathies and impact of FGF10 treatment

Laetitia Bouchard *1*, **Gaëlle Odelin** *1*, **Antoine Muchir** *2* **and Francesca Rochais** *1*

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2 Sorbonne University, INSERM, Institute of Myology, Paris, France.

Dilated cardiomyopathies (DCM) including ischemic- and genetic-related DCM are the most common form of cardiomyopathies. DCM are characterized by cardiomyocyte necrosis and fibrosis associated with impaired cardiac function leading to severe heart failure. LMNA is commonly mutated in dilated cardiomyopathies accounting for up to 10% of DCM cases in humans and is responsible for rapidly progressing dilated cardiomyopathies with severe cardiac defects. While the role of LMNA has been extensively studied in the adult heart, its role during heart development still remained to be determined. The stimulation of terminally differentiated cardiomyocyte proliferation represents one of the main therapeutic approach for heart regeneration. We recently identified the fibroblast growth factor 10 (FGF10) as a potential target to promote cardiac regeneration and repair in ischemic DCM.
This study thus aims to uncover the role and the cell-type requirement of Lmna during heart development, maturation and homeostasis and to evaluate the relevance of FGF10 as a therapeutic target for cardiac regeneration in Lmna-related DCM.
LMNA expression profiling, in the developing, postnatal and adult heart, was first achieved using immunofluorescence, westernblot and qRT-PCR experiments. Our results revealed increased Lmna expression levels, with low expression at fetal stages and maximal expression at post-natal day 6. We identified that LMNA preferentially accumulates in cardiac fibroblasts in fetal heart. In contrast, in the adult heart, LMNA is predominantly expressed in cardiomyocytes. Using transgenic mouse lines, we then investigated the impact of Lmna cardiomyocyte-specific deletion during heart development, maturation and in adult. Our results revealed that while Lmna deletion in embryonic and adult cardiomyocytes leads to a rapidly progressing and severe DCM, a moderate phenotype is observed in postnatally deleted cardiomyocytes, unveiling a critical requirement in developing and adult cardiomyocytes. Interestingly, preliminary results, showing that specific Lmna-deletion in embryonic cardiac fibroblasts leads to embryonic lethality, revealed an unsuspected role for LMNA in cardiac fibroblasts. Finally, using transgenic mouse lines or adenoviral-gene transfer approaches, we then evaluated the impact of FGF10 expression upregulation on the progression of the Lmna-related DCM. Preliminary results suggest that FGF10 may preserve cardiac fibrosis infiltration and cardiac remodelling in Lmna-related DCM.
Altogether, this study will thus determine the role of LMNA in cardiac development, maturation and homeostasis and will evaluate the relevance of FGF10 as a therapeutic target for cardiac regeneration in genetic-related dilated cardiomyopathies.

A rare case of monogenic KCC2-related autistic spectrum disorder: a new benchmark for the validation of causality and treatment screening.

Mira Hamze *1*, **Christophe Porcher** *1*, **Igor Medyna** *1*, **Gaetan Lesca** *2*

1 Institut de Neurobiologie de la Méditerranée (INMED), INSERM, UMR1249, Marseille.
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The SLC12A5 gene code for a neuron-restricted K+/Cl- co-transporter KCC2, which is an important molecule controlling neuronal chloride homeostasis [Cl-]i and associated with etiology of different Neurodevelopmental disorders (NDD), however KCC2-dependent mechanisms leading to different pathologies are not clear. Dr.Lesca and collaborators have identified among patients suffering from different NDD one family associated with 2 missense variants of SLC12A5 gene. This family named "Dylan" includes four siblings with moderate Autistic Spectrum Disorder (ASD) and drug-resistant partial epilepsy in three of them. All siblings disclose two missense variants on SLC12A5 gene (called thereafter Dylan1 and Dylan2). Each variant was inherited from one healthy parent. The discovered mutations are not known yet and are located within different putative transmembrane regions of KCC2.
To evaluate mutation's impact on KCC2 function we have created different sets of cDNA constructs encoding separately each of the mutants and transiently expressed these constructs in neuroblastoma N2a cells. The transfected cells were assayed using gramicidin perforated-patch clamp recordings, live-cell immunolabeling of KCC2 and Ti+ flux assay. Analysis showed that each of the mutants alone modified both ion-transport ability of KCC2 and surface expression of the protein. Co-expression of each mutant with wild-type KCC2 cDNA (mimicking the heterozygous status of the parents) produced a functional co-transporter but with significantly reduced amount of the surface expressed protein as compared to the homozygous wild type condition. The expression of mutant's combination (Dylan1 plus Dylan2) mimicking patient's genotype showed a reduction (15-20%) in ion transport activity of KCC2 and a significant decrease in the surface expression of the protein.
To further characterize the impact of mutation on the level of organism, we have created transgenic mice harboring Dylan1 and Dylan2 mutations. The mouse mimicking genotype of Dylan's patient (Dylan1 plus Dylan2) develops well and is a subject of extensive neurobehavioral and neurophysiology investigations.

Combination of two laser processes for the creation of relevant bio-models for therapeutical applications

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Printing techniques applied to biology have begun to develop in the 2000s and have since been greatly improved and perfected. Based on interdisciplinary approaches they make use of cell biology, chemistry, engineering and a combination of sophisticated protocols to create organized 2D or 3D patterns of biomaterials or living cells. Their applications range from tissue engineering or organ creation to regenerative medicine and new drug discovery.
In this context, at LP3 and in close collaboration with MMG, we took advantage of our experience on the Laser-Induced Forward Transfer (LIFT) technique (previously developed for electronic purpose) to print bio-inks containing living cells for the creation of in vitro bio-models. This work will be focused on the printing of muscular stem cells and the process optimisation for stem cell differentiation in the prospect of creating a versatile tool aimed at improving differentiation toward the skeletal muscle lineage and formation of neuromuscular junctions (NMJ).
LIFT is a two-part printing method using laser-matter interaction to transfer tiny amounts of material from a thin donor film to a receptor substrate, both separated by a few hundreds of micrometres. A short laser pulse induces the formation of a controlled jet propagating perpendicularly to the donor substrate. The bio-ink previously spread as a thin film (few tens of microns) on this donor substrate is thus collected as a droplet on the receiver.
This method allows us to precisely control the amount and the location of the targeted material deposited and, by extension, the number of living cells printed. In contrary to conventional bio-printing methods using extrusion or ink-jet systems, LIFT is a nozzle-free process that allows the use of a large range of bio-inks viscosity and a high cell concentration without clogging.
Here, we will present the LIFT process and its optimisation allowing us to achieve a controlled, reliable, precise printing of muscle progenitor cells, ensuring a high post-printing cell survival rate and proliferation. The cell survival rate will be controlled by fluorescence staining of printed cells and the monitoring of the cell development over several days.
In parallel with the optimisation of the LIFT process, a laser surface structuring technique is currently being developed to topographically modify the surface of the receiver substrate to improve the survival rate, the proliferation and even the differentiation of the printed cells. Two different kinds of structuration have been investigated: (i) the creation of micro-channels to guide the growth of muscle progenitors to force them to stretch and should thus promote their differentiation into myotubes and (ii) the creation of nano-porosity at the surface of the receiver to make them better suited for cell development.

Characterization of the functional role of Piezo1 coding variant associated with the most severe clinical manifestations of malaria infection.

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In malaria endemic countries, the majority of children infected by Plasmodium falciparum remains asymptomatic, while an estimated 10% of infections progress to fever. Of these, only a small fraction develop severe clinical manifestations that can be lethal. Several studies suggest that host genetic factors are among the factors that play a key role in the occurrence of clinical forms. In particular, red blood cell polymorphisms have been shown to confer innate protection against severe disease. Hereditary xerocytosis, a rare genetic disorder, is characterized by red blood cell dehydration with mild hemolytic anemia. Most cases of hereditary xerocytosis are associated with gain-of-function mutations in PIEZO1, a mechanically activated ion channel. Recently, a coding mutation in the PIEZO1 calcium channel has shown increased activity in Ca^{2+} transport to the inside of erythrocytes. Interestingly, this mutation is extremely rare in all populations (frequency of less than 1%) except for the African populations (frequency of 18%). The existence of the PIEZO1 mutation at such high frequencies suggests strong positive selective pressure in Africa where malaria is endemic.

We therefore conducted a case-control study in the Senegalese population to determine whether the PIEZO1 mutation is associated with severe malaria and then to study its physiological function and role in malaria infection. The study of the PIEZO1 coding mutation showed protection for heterozygous individuals, with a 2.8-fold reduction in the risk of developing cerebral malaria. To study this gain-of-function mutation, the agonist Yoda1 was used to activate PIEZO1 and simulate the effect of the mutation. In vitro experimental showed i) that red blood cells with an active PIEZO1 channel had a 10-fold increase in intracellular Ca^{2+} concentration ii) that parasitemia is strongly decreased in the presence of Yoda1. This, shows the impact of increased intracellular calcium on Plasmodium development. Finally, statistical analysis indicates an interaction between the protective genotypes of PIEZO1 and ATP2B4 which encodes the calcium pump PMCA4 also expressed on red blood cells and previously associated with severe malaria. Indeed, individuals with the protective genotypes of both genes have a 3.5-fold reduced risk.

In conclusion, the gain-of-function mutation in PIEZO1 is associated with protection against cerebral malaria. Activation of PIEZO1 leads to an increase in Ca^{2+} and decreased parasitemia in vitro. Together these results suggest that calcium homeostasis in the red blood cell is a key element in the development of the most severe forms of malaria. Furthermore, the functional characterization of PIEZO1 mutations will also be useful to better understand some rare diseases related to the function of this ion channel.

Contribution of the adipocyte hormone leptin in the pathogenesis of Rett syndrome

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Rett syndrome (RTT) is a non-inherited chromosome X-linked neurodevelopmental disorder characterized by a loss of acquired speech, hand stereotypies and gait abnormalities which appear following a period of apparently normal postnatal development. Other frequent symptoms include breathing difficulties, seizures, scoliosis and growth retardation. This syndrome is caused by mutations in the X-linked chromosome gene Methyl-CpG-binding protein 2 (MECP2) encoding a transcriptional regulator. RTT accounts for up to 10% of severe intellectual disability of genetic origin in women. Currently there are no cures to treat this disease.
In spite of different causative mutated gene and biological pathways affected, epidemiological and animal studies revealed abnormally elevated circulating levels of the adipocyte hormone leptin in patients with RTT and Mecp2-deficient mice. Besides its canonical role in the control of satiety and energy expenditure, leptin acts on many brain areas, and in doing so modulates cognitive functions, anxiety, breathing and more. Consequently, altered levels of leptin may contribute to the RTT-associated neuronal network dysfunctions.
In the present study, we show that serum leptin levels are elevated in early (postnatal day (P) 30) and late symptomatic (P60) male Mecp2-null mice (Mecp2tm1-1 bird, a well-established rodent model of RTT). We also show that daily subcutaneous injections of a validated leptin antagonist (Peg-SMLA, a competitive inhibitor of leptin BBB transport), during 10 days from P40, prevent the body weight loss, restore the hippocampal excitatory/inhibitory (E/I) balance (electrophysiological recordings on slices), slows down the progression of breathing dysfunctions (plethysmography) in the symptomatic male Mecp2-null mice. Conversely, leptin-treatment of wild type mice mimics some of the phenotypic manifestations observed in Mecp2-null mice, i.e. decreased GABAergic activity, increased hippocampal E/I balance, increased seizures susceptibility and increased number of apneas.
These data provide further insights on the possible contribution of leptin in RTT pathogenesis and offer therapeutic perspective to alleviate RTT symptoms.

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NOTES

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Thank you all for your participation !
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