SOCIÉTÉ FRANÇAISE DE MYOLOGIE

20ÈME ÉDITION

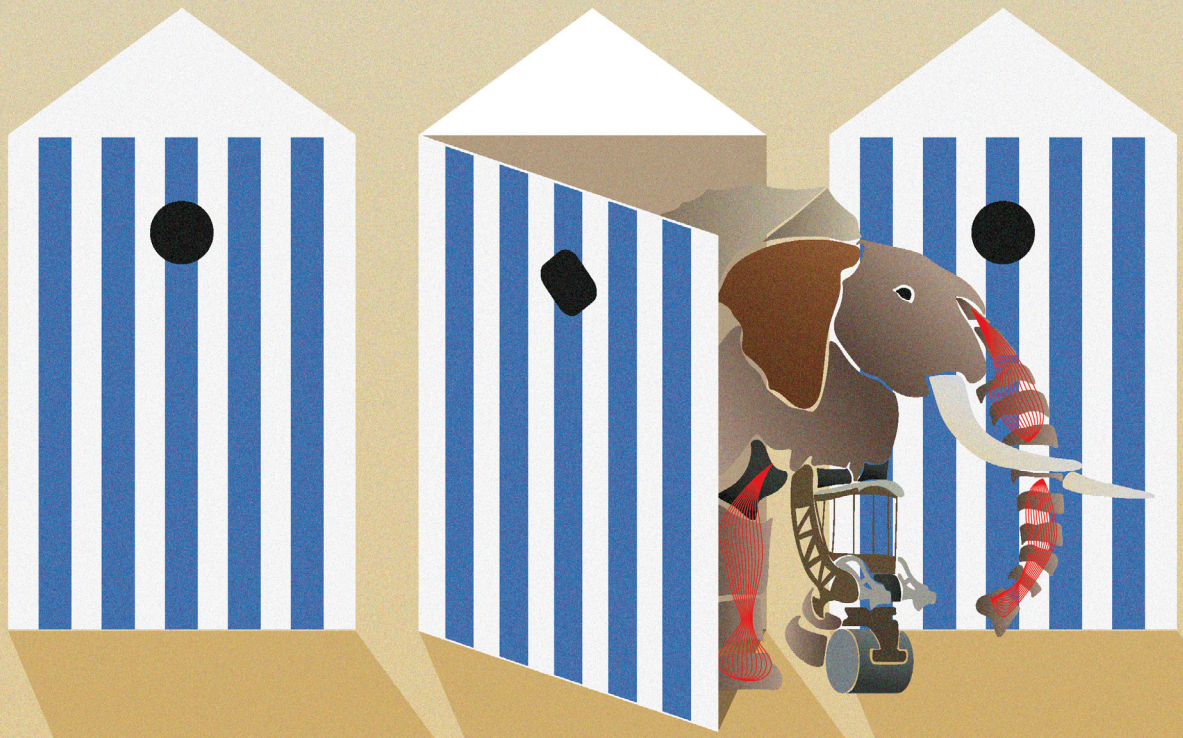
JOURNÉES DE LA SOCIÉTÉ FRANÇAISE DE MYOLOGIE

15 - 17 Novembre 2023

Palais des Congrès - Atlantia

LA BAULE

LIVRET DES RÉSUMÉS



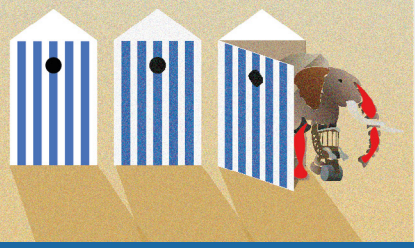
COMITÉ DE PILOTAGE

M.-A. Colle, A. Magot,
Y. Péréon, K. Rouger

Filnemus
Filière Neuromusculaire

COMITÉ D'ORGANISATION

C. de Lattre, C. Huchet,
C. Le Guiner, P. Marcorelles,
S. Mercier, M.-C. Minot-Mihié,
A. Nordez, J.-B. Noury, J. Ropars



REMERCIEMENTS

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Amicus Therapeutics
Biogen
Pfizer
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LUPIN NEUROSCIENCES
PTC THERAPEUTICS
Roche
ALEXION AstraZeneca Rare Disease
argenx
Alnylam PHARMACEUTICALS
CSL Behring Biotherapies for Life
GRIFOLS
LFB L'ENGAGEMENT ÉTHIQUE
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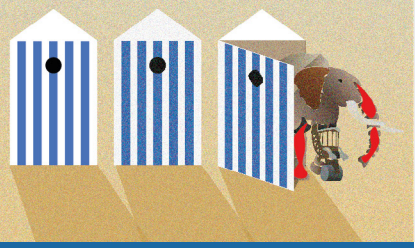


SOMMAIRE

COMITÉS & ÉDITORIAL

COMITÉ DE PILOTAGE


Marie-Anne Colle


Armelle Magot


Yann Péréon


Karl Rouger

COMITÉ D'ORGANISATION

C. de Lattre • C. Huchet • C. Le Guiner • P. Marcorelles • S. Mercier
M.-C. Minot-Mihié • A. Nordez • J.-B. Noury • J. Ropars

ÉDITORIAL DU COMITÉ DE PILOTAGE

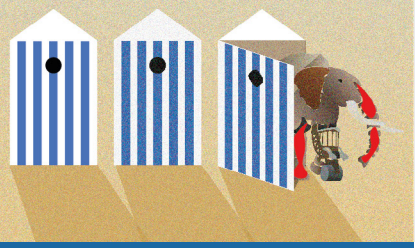
Chers Amis Myologues,

Après Toulouse et son organisation qui nous avait mis la tête dans les étoiles, nous sommes heureux de vous accueillir à La Baule pour les 20èmes Journées de la Société Française de Myologie.

Sur les terres de Jules Verne, cette édition anniversaire vous invitera à un voyage extraordinaire, quasiment les pieds dans l'eau, en revisitant les grands thèmes actuels de la discipline, avec des sessions portant sur la thérapeutique, l'inflammation, l'exercice, l'autophagie… et de belles contributions locales. Vous ferez également le Tour du monde de la Myologie en vingt ans avec quatre séquences 'fil rouge' qui vous accompagneront tout au long du congrès pour vous remémorer les plus belles avancées scientifiques qui ont marqué la discipline ces deux dernières décennies mais aussi aborder ce qui nous attend pour les années à venir. Vous ne manquerez pas non plus les classiques sessions d'enseignement de FILNEMUS, les sessions communes chercheurs-cliniciens, les sessions de posters, le 'Muscle Quizz' maintenant devenu traditionnel, les prix remis aux plus brillants des jeunes participants promis à un bel avenir myologique. Nul doute que ces Journées, comme à chaque édition, seront riches d'échanges entre chercheurs et cliniciens !

Nous sommes ravis de vous voir débarquer sur la Côte d'Amour fort justement surnommée le Midi de la Bretagne pour la douceur de son climat et vous pourrez également y goûter aux bienfaits de la gastronomie bretonne, agrémentée de sel de Guérande : laissez-vous séduire par le fondant Baulois au gré de balades pour découvrir les Bauloises, majestueuses bâtisses du littoral Atlantique.

Breizh atao, eo ma bro !



MOT DU PRÉSIDENT DE LA SOCIÉTE FRANÇAISE DE MYOLOGIE

Chers Amis,

Cette année la Société Française de Myologie organise ses 20èmes Journées. Que de chemin parcouru depuis qu'une petite équipe de pionniers s'est réunie autour de Michel Fardeau pour donner naissance à cette société à l'orée des années 2000 !

Depuis la création de la SFM, les équipes étudiant le tissu musculaire, qu'il soit sain ou pathologique, viennent d'horizons très divers : de la neurologie, de la pédiatrie, de la cardiologie, de la génétique, de la médecine interne, de la rééducation fonctionnelle et de toutes les disciplines biologiques situées en amont : biologie cellulaire et moléculaire, biochimie, histopathologie, imagerie médicale, physiologie, etc… La lecture de cette simple liste à la Prévert illustre la diversité de notre communauté. Dès les premières JSFM à Caen, la société s'est donnée pour but de fédérer toutes ces équipes afin d'accroitre les échanges et d'augmenter la visibilité de la Myologie.

Les JSFM sont progressivement devenues le temps fort annuel où les myologues ont pris l'habitude de se retrouver grâce au travail sans relâche des anciens présidents et présidentes : Michel Fardeau, Claude Desnuelles, Françoise Chapon, Gisèle Bonne et Emmanuelle Campana-Salort.

En 20 ans, les JSFM ont gagné en maturité et chaque comité local d'organisation a apporté sa pierre à l'édifice avec le soutien des partenaires industriels, institutionnels et associatifs dont celui de l'AFM-Téléthon. Le congrès est maintenant structuré autour de temps forts attendus de tous : les journées d'enseignement FILNEMUS, le GEM, les sessions Myologie fondamentale…

Ces dernières ont pris la suite du "Club myogénèse" depuis Grenoble en 2012 et permettent de mettre en valeur les jeunes chercheurs en myologie. Ce soutien tout particulier apporté aux jeunes est une des grandes forces de la SFM. Elle s'exprime aussi à travers la politique des prix SFM : prix master, prix coup de pouce, prix impulsion, prix communications orales et affichées dont le prix Isabelle Penisson-Besnier du nom d'une de nos plus regrettées consœurs. Nous sommes particulièrement fiers de plusieurs lauréats du prix master qui depuis 2007 ont pu poursuivre une carrière remarquée dans le domaine de la Myologie et sont l'avenir de notre discipline.

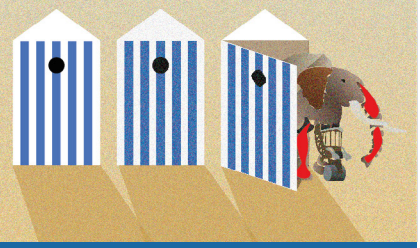
Fédérer les énergies c'est aussi savoir s'ouvrir aux autres. Les JSFM accueillent régulièrement d'autres sociétés savantes comme les sociétés italiennes AIM et IIM à Marseille ou la Société Française de Neuropédiatrie à Toulouse. Cette année, les JSFM seront adossées au congrès international d'ENMG pédiatrique. La SFM est aussi un membre fondateur et actif du CoSSAF, le Collège des Sociétés Savantes Académiques de France.

De nombreux liens d'amitié se sont créés aux JSFM et pour cela rien ne vaut un moment de convivialité. Tous ceux qui y ont participé gardent sûrement un souvenir ému de quelques grands temps forts de nos Journées :
Un dîner sous le regard de statues parfois intimidantes à Angers en 2011, une danse à l'opéra de Montpellier en 2013, un tour de manège ancien à Paris en 2014 ou une déambulation aquatique à Brest en 2018. Que les autres organisateurs ne m'en veuillent pas pour cette liste forcément subjective et incomplète. Cet esprit de convivialité s'est encore renforcé avec la création du muscle quizz qui a, certes, permis de mettre en valeur nos jeunes myologues, mais aussi et surtout d'apprendre de nombreux mots et expressions en marseillais, gaga ou occitan. Gageons que nous parlerons brezhoneg comme de vieux loups de mer cette année.

C'est donc fière de ses 20 ans de journées mais aussi poussée vers l'avenir par le vent breton que la SFM vous accueille à La Baule pour ses 20èmes JSFM.

Myologiquement vôtre.

Guilhem Solé & le Bureau de la SFM



20ÈME ÉDITION

JOURNÉES DE LA SOCIÉTÉ FRANÇAISE DE MYOLOGIE

15 - 17 Novembre 2023 • Palais des Congrès - Atlantia

SYNOPSIS DES JOURNÉES

MERCREDI 15 NOVEMBRE

11h00	**Session d'enseignement mixte SFM / FILNEMUS** - *Auditorium*	
13h00	**Cocktail déjeunatoire de bienvenue**	
14h00	**Introduction** - *Auditorium*	
14h15	**Conférence d'ouverture : Yes we can! Surmonter le coût de l'effort pour adopter un mode de vie actif** - *Auditorium*	
15h00	• SYMPOSIUM Pompe AMICUS - *Auditorium*	• MYOLOGIE FONDAMENTALE Communications orales - *Salle Plénière 2*
16h00	**Pause & Posters Groupe 1**	
17h00	• RÉUNION DU GEM *Auditorium*	• MYOLOGIE FONDAMENTALE Communications orales - *Salle Plénière 2*
18h30	**Muscle-quizz** - *Auditorium*	
19h30	**Cocktail dînatoire de bienvenue & Posters Groupe 2**	

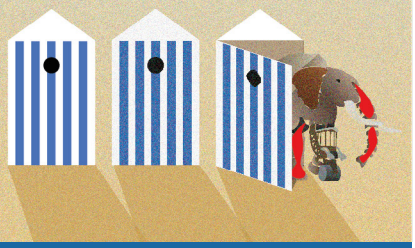
JEUDI 16 NOVEMBRE

08h00	**Atelier Scientifique** - *Salle Plénière 2*	
09h00	**Avancées thérapeutiques dans les maladies neuromusculaires : 20 ans après**	
09h30	**SESSION PLÉNIÈRE 1 :** Thérapie des maladies neuromusculaires - *Auditorium*	
10h30	**Pause & Posters Groupe 3**	
11h00	• SYMPOSIUM SMA BIOGEN *Auditorium*	• MYOLOGIE FONDAMENTALE Communications orales - *Salle Plénière 2*
12h30	**Cocktail déjeunatoire**	
14h00	**Assemblée Générale de la SFM** - *Auditorium*	
14h40	**Déconstruction et reconstruction du développement musculaire humain *in vitro***	
15h10	**SESSION PLÉNIÈRE 2 :** Inflammation et immunothérapie musculaire *Auditorium*	
16h10	**Pause & Posters Groupe 3**	
16h40	**2002 - 2023 : L'Odyssée de... la Myologie**	
17h10	**SESSION PLÉNIÈRE 3 :** Force, exercice & maladies musculaires - *Auditorium*	
18h45	**Départ en bus du Palais Atlantia pour la Soirée du Congrès**	

VENDREDI 17 NOVEMBRE

09h00	**Évolution diagnostique des maladies musculaires depuis 20 ans**	
09h30	**SESSION PLÉNIÈRE 4 :** Glycogenèse & Autophagie - *Auditorium*	
10h30	**Pause & Posters Groupe 4**	
11h00	**Communications orales mixtes** - *Auditorium*	
12h00	•SYMPOSIUM PFIZER *Auditorium*	• MYOLOGIE FONDAMENTALE Communications orales - *Salle Plénière 2*
13h00	**Cocktail déjeunatoire & Posters Groupe 4**	
14h00	**Les myopathies liées à RYR1, que d'évolution sur leur compréhension !**	
14h30	**SESSION PLÉNIÈRE 5 :** Canalopathies - *Auditorium*	
15h40	**Remise des prix Master & SFM** - *Auditorium*	
16h10	**Clôture des journées**	

PROGRAMME SCIENTIFIQUE



MERCREDI 15 NOVEMBRE

10h00 Accueil des participants

11h00-13h00 **Session d'enseignement mixte SFM / FILNEMUS** - *Auditorium*
Modérateurs : Martial Mallaret & Antoine Nordez

11h00-12h00 Embryologie du système musculo-squelettique
Olivier Pourquié

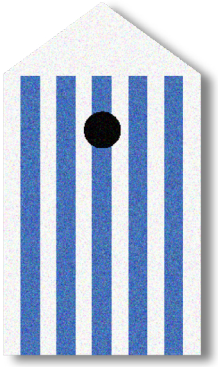
12h00-12h30 De l'hystérie au dysfonctionnement du réseau cérébral
Antoine Daubigney & Julie Bernard

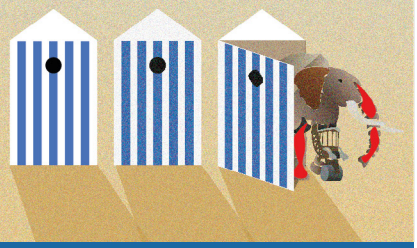
12h30-13h00 Évaluation d'un patient neuromusculaire
Jean-Yves Hogrel

13h00-14h00 Cocktail déjeunatoire de bienvenue autour des partenaires

14h00-14h15 **Introduction** - *Auditorium*
Comité local d'organisation & Guilhem Solé - Président de la SFM

14h15-15h00 **Conférence d'ouverture :**
Yes we can! Surmonter le coût de l'effort pour adopter un mode de vie actif - *Auditorium*
Boris Cheval
Modérateurs : Armelle Magot & Guilhem Solé





MERCREDI 15 NOVEMBRE

15h00-16h00 SESSIONS PARALLÈLES 1

15h00-16h00 SYMPOSIUM Pompe AMICUS - *Auditorium*

Amicus Therapeutics

De nouvelles approches dans la maladie de Pompe

Modérateur : Yann Péréon

15h00-15h20 Rôle de l'autophagie dans la maladie de Pompe
Marie-Anne Colle, Nantes

15h20-15h40 Méthodes d'évaluation de la maladie de Pompe de "nouvelle génération"
Pascal Laforêt, Paris

15h40-16h00 Nouvelles alternatives thérapeutiques pour les patients atteints de LOPD
Françoise Bouhour, Lyon

OU

15h00-16h00 MYOLOGIE FONDAMENTALE - *Salle Plénière 2*

Communications orales issues des abstracts

Modérateurs : Bodvael Fraysse & Capucine Trollet

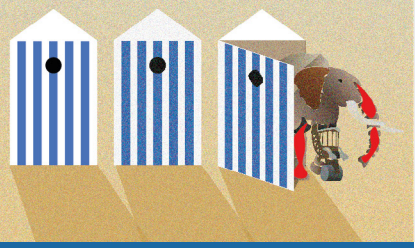
15h00-15h15 *Spatio-Temporal control of myoblast diversity in Drosophila*
Camille Guillermin, Lyon

15h15-15h30 *Distinct satellite cell states are defined by PAX3 expression during regeneration*
Virginia Zoglio, Créteil

15h30-15h45 *Engineered 3D muscle constructs for modeling Duchenne Muscular Dystrophy and high-throughput screening of novel therapeutics*
Ghislain Banos, Créteil

15h45-16h00 *Characterization of the infiltrating polarized macrophages during the onset of heterotopic ossification in a mouse model of Fibrodysplasia Ossificans Progressiva*
Riccardo Gamberale, Lyon

16h00-17h00 Pause et échanges autour des partenaires & Posters Groupe 1



MERCREDI 15 NOVEMBRE

17h00-18h30 **SESSIONS PARALLÈLES 2**

17h00-18h30 RÉUNION DU GEM - *Auditorium*
Groupe d'Étude en Myologie - 4 cas
Modérateurs : Cyril Gitiaux & Jon Andoni Urtizberea

OU

17h00-18h30 MYOLOGIE FONDAMENTALE - *Salle Plénière 2*
Communications orales issues des abstracts
Modératrices : Bénédicte Chazaud & Aude Lafoux

17h00-17h15 *Mechanisms of muscle wasting in a mouse model of sickle cell disease*
Christine Ibrahim, Paris

17h15-17h30 *Investigating potential regulators of PABPN1 in skeletal muscle*
Hadidja-Rose Mouigni, Paris

17h30-17h45 *Study of the role of muscle metabolism in Amyotrophic Lateral Sclerosis*
Flore Cheguillaume, Paris

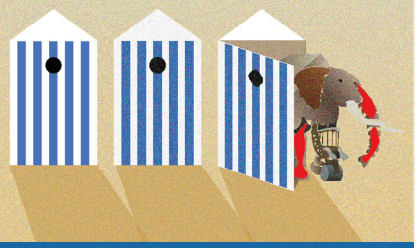
17h45-18h00 *Implication of annexins in the development of muscular dystrophies*
Léna d'Agata, Pessac

18h00-18h15 *Skeletal muscle organoids for preclinical gene therapy with recombinant AAV vectors*
Clémence Lièvre, Nantes

18h15-18h30 *Live imaging reveals perturbed symmetric stem cell divisions in a mouse model of Duchenne Muscular Dystrophy*
Liza Sarde, Paris

18h30-19h30 **Muscle-quizz** - *Auditorium*

19h30 **Cocktail dînatoire de bienvenue autour des partenaires & Posters Groupe 2**



JEUDI 16 NOVEMBRE

07h45 Accueil des participants

08h00-09h00 Atelier Scientifique UCB - *Salle Plénière 2*

Modératrices : Armelle Magot et Céline Tard

- Nouvelles sources de données épidémiologiques de la Myasthénie auto-immune
  Céline Tard

- Myasthénie auto-immune : va-t-on vers une prise en charge personnalisée ?
  Armelle Magot

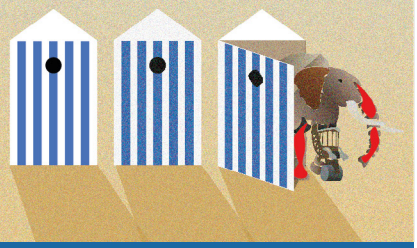
09h00-09h30 Avancées thérapeutiques dans les maladies neuromusculaires : 20 ans après
Jon Andoni Urtizberea
Modérateurs : Bruno Allard & Juliette Ropars

09h30-10h30 SESSION PLÉNIÈRE 1 - *Auditorium*
Thérapie des maladies neuromusculaires
Clinique & fondamentale
Modérateurs : Yann Péréon & Karl Rouger

09h30-10h00 Défi de la thérapie génique AAV pour les maladies neuromusculaires : réussites et perspectives
Caroline Le Guiner

10h00-10h30 Thérapie cellulaire pour la dystrophie musculaire : pourquoi cela peut fonctionner ?
Giulio Cossu

10h30-11h00 Pause et échanges autour des partenaires & Posters Groupe 3



JEUDI 16 NOVEMBRE

11h00-12h30 SESSIONS PARALLÈLES 3

11h00-12h00

Biogen

SYMPOSIUM SMA BIOGEN - *Auditorium*

Voyage au cœur de la jonction neuromusculaire (JNM) et paramètres électrophysiologiques à l'ère des thérapeutiques

Modérateur : Yann Péréon

- Intérêt de l'étude de la JNM dans les maladies musculaires génétiques
  Cyril Gitiaux
- Intérêt de la JNM dans les maladies du neurone moteur : leçon de l'impact thérapeutique
  Pascal Cintas

OU

11h00-12h30

MYOLOGIE FONDAMENTALE - *Salle Plénière 2*

Communications orales issues des abstracts

Modérateurs : Marie-Anne Colle & Thomas Laumonier

11h00-11h15 *Comparative RNA-sequencing analysis to understand muscle pathophysiology of glycogen storage disease type III*
Lucille Rossiaud, Corbeil-Essonnes

11h15-11h30 *Targeting lysosome damage in Duchene muscular dystrophy improves micro-dystrophin gene therapy*
Abbass Jaber, Evry-Courcouronnes

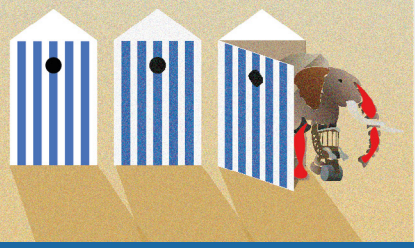
11h30-11h45 *Laser bioprinting: a new tool for skeletal muscle tissue enginnering*
Lucas Duvert, Marseille

11h45-12h00 *Involvement of SH3KBP1 protein in the modulation of ER architecture and autophagy during myofiber formation*
Marine Daura, Lyon

12h00-12h15 *Dystrophin deficiency impairs cell junction formation during embryonic myogenesis*
Jean-Baptiste Dupont, Nantes

12h15-12h30 *Blueprinting myonuclear heterogeneity along the body axis*
Amaury Korb, Paris

12h30-14h00 Cocktail déjeunatoire autour des partenaires



JEUDI 16 NOVEMBRE

14h00-14h35 **Assemblée Générale de la SFM** - *Auditorium*

- Prix Interne 2022 - Agathe Molimard
- Prix Coup de pouce 2022 - Margherita Giannini

14h40-15h10 **Déconstruction et reconstruction du développement musculaire humain *in vitro***
Olivier Pourquié
Modérateurs : Pascale Marcorelles & Vincent Mouly

15h10-16h10 **SESSION PLÉNIÈRE 2** - *Auditorium*
Inflammation et immunothérapie musculaire : clinique & fondamentale
Modérateurs : Pascale Marcorelles & Vincent Mouly

15h10-15h40 Inflammation et réparation du muscle cardiaque
Jean-Sébastien Silvestre

15h40-16h10 Myopathies inflammatoires : bien les classer pour bien les traiter : l'exemple de la myosite à inclusions
Olivier Benveniste

16h10-16h40 **Pause et échanges autour des partenaires & Posters Groupe 3**

JEUDI 16 NOVEMBRE

16h40-17h10 **2002 - 2023 : l'Odyssée de... la Myologie**
Gisèle Bonne
Modérateurs : Gillian Butler-Browne & Guilhem Solé

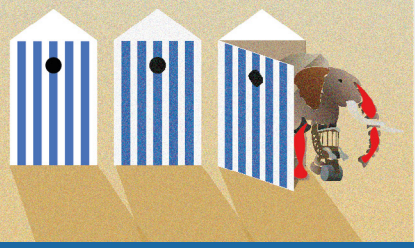
17h10-18h00 SESSION PLÉNIÈRE 3 - *Auditorium*
Force, exercice et maladies musculaires : clinique & fondamentale
Modératrices : Corinne Huchet & Capucine de Lattre

17h10-17h30 Le muscle, une cible du dopage sportif, mais une cible fragile
Xavier Bigard

17h30-17h50 Évaluation structurelle et tissulaire du muscle humain par échographie et élastographie
Antoine Nordez

17h50-18h00 Parasport et maladies neuromusculaires
Orianne Lopez

18h45 Départ en bus du Palais Atlantia pour la Soirée du Congrès



VENDREDI 17 NOVEMBRE

08h45 Accueil des participants

09h00-09h30 **Évolution diagnostique des maladies musculaires depuis 20 ans**
Bruno Eymard
Modérateurs : Pascal Cintas & John Rendu

09h30-10h30 **SESSION PLÉNIÈRE 4** - *Auditorium*
Glycogenèse & Autophagie : clinique & fondamentale
Modératrices : Marie-Anne Colle & Pascale de Lonlay

09h30-10h00 Importance de l'autophagie dans l'homéostasie du muscle squelettique
Perrine Castets

10h00-10h30 Voyage dans le monde des glycogénoses
Pascal Laforêt

10h30-11h00 Pause et échanges autour des partenaires & Posters Groupe 4

11h00-12h00 **Communications orales mixtes** - *Auditorium*
Modérateurs : Vincent Gache & Jean-Baptiste Noury

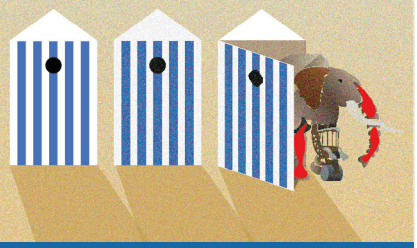
11h00-11h15 *Mitochondrial quality control in muscle stem cells: a determinant of fate decision and tissue repair capacity*
Yan Burelle, Ottawa - Canada

11h17-11h27 *Amyotrophie spinale infantile chez l'homme : une pathologie de la spermatogénèse ?*
Armelle Magot, Nantes

11h28-11h38 *Limb-girdle muscular dystrophy associated with TRIM 32 mutations: a national cohort study and review of the literature*
Alexandre Gueremy, Marseille

11h39-11h49 *Genotype-phenotype correlation of patients with severe congenital titinopathies*
Aurélien Perrin, Montpellier

11h50-12h00 *Myopathies myofibrillaires : impact fonctionnel et qualité de vie*
Geoffroy Julien, Caen



VENDREDI 17 NOVEMBRE

12h00-13h00 SESSIONS PARALLÈLES 4

12h00-13h00 SYMPOSIUM PFIZER - *Auditorium*

Pfizer

Dystrophie musculaire de Duchenne : les enjeux de l'évaluation à l'aube des nouvelles perspectives thérapeutiques

Modérateur : Yann Péréon

12h00-12h20 • Actualités dans la prise en charge de la dystrophie musculaire de Duchenne
Juliette Ropars

12h20-12h40 • Histoire naturelle : les enjeux et limites de l'évaluation
Jean-Yves Hogrel

12h40-13h00 • Suivi au long terme des patients : l'implémentation de biomarqueurs digitaux
Cécile Halbert & Clarissa Gorin - *Équipe Ad Scientiam*

OU

12h00-13h00 MYOLOGIE FONDAMENTALE - *Salle Plénière 2*

Communications orales issues des abstracts

Modérateurs : Rémi Mounier et Kryzystof Jagla

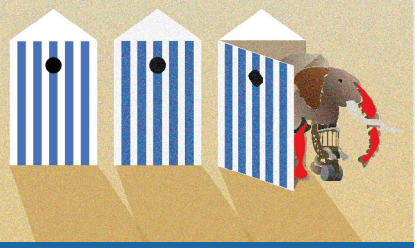
12h00-12h15 *Abnormal autophagy is a critical mechanism in TANGO2-related rhabdomyolysis*
Hortense de Calbiac, Paris

12h15-12h30 *Mutation independent CRISPR/Cas9-induced allele deletion results in vitro in a functional benefit for dominant RYR1 mutation*
Margaux Melka, La Tronche

12h30-12h45 *Design, development and characterization of an innovative extrusion-based 3D bioprinting system for Skeletal Muscle Tissue Engineering applications*
Stefano Testa, Marseille

12h45-13h00 *Orchestration of CaVβ1 expression in adult and embryonic muscle: exploring the role of novel isoforms in neuromuscular development*
Amélie Vergnol, Paris

13h00-14h00 Cocktail déjeunatoire autour des partenaires & Posters Groupe 4



VENDREDI 17 NOVEMBRE

14h00-14h30 **Myopathies liées à RYR1, que d'évolution sur leur compréhension !**
Isabelle Marty
Modérateurs : Caroline Le Guiner & Stéphane Vassilopoulos

14h30-15h40 SESSION PLÉNIÈRE 5 - *Auditorium*
Canalopathies : clinique & fondamentale
Modérateurs : Denis Furling & Sandra Mercier

14h25-14h50 • Approches de séquençage haut débit : apport dans le domaine des canalopathies
Jean-Jacques Schott

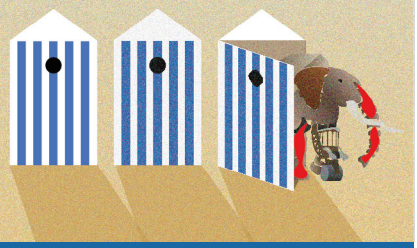
14h50-15h15 • Atteinte cardiaque des dystrophies myotoniques : un exemple de canalopathie sodique cardiaque
Karim Wahbi

15h15-15h40 • Canalopathies calciques et sodiques du muscle squelettique
Bruno Allard

15h40-16h10 **Prix Master & SFM** - *Auditorium*

- Prix Master 2022 - Audrey Saugues
- Prix Master 2021 - Alix Simon
- Prix Impulsion 2022 - Alexis Boulinguiez

16h10-16h30 Remise des prix, résultats AG & clôture des journées



COMMUNICATIONS ORALES
SESSIONS PARALLÈLES 1

Mercredi 15 Novembre
15h00-16h00

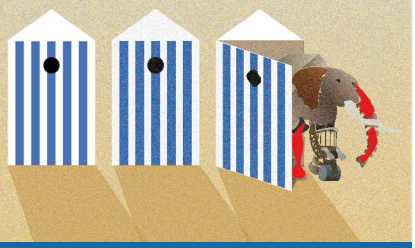
COMMUNICATION ORALE - SESSIONS PARALLÈLES 1
Développement / Cellules souches / Régénération musculaire

Camille GUILLERMIN
Mathilde Bouchet, Violaine Tribollet, Sergio Sarnataro, Laurent Gilquin, Isabelle Stevant, Yad Ghavi-Helm, Benjamin Gillet, Sandrine Hughes, Jonathan Enriquez

IGFL, Lyon, France

Spatio-Temporal control of myoblast diversity in Drosophila

Life is constantly in motion, as the Renaissance philosopher Michel De Montaigne once said. One common behavior animals use to find food, mates, or evade predators is locomotion. In animal appendages, the morphology of muscles is key in ensuring precise movement. These muscles are innervated by a unique wiring of motoneuron axon terminals that control the timing and intensity of muscle contraction. However, how muscles and motoneurons coordinate their development to establish these unique axon-muscle connections and maintain them throughout adult life remains largely unknown. During my thesis, I made a significant discovery regarding the genetic program that governs the morphology of adult muscles. To achieve this objective, I employed single-cell RNA profiling, computational tools, and genetic techniques to visualize and selectively modify the genotype of myoblasts during their development. Additionally, I utilized advanced microscopy techniques to analyze the impact of these genetic manipulations on muscle architecture. The findings from my research demonstrate that muscle progenitors, known as myoblasts, possess a naive state upon joining the epithelial cells of the leg disc. Subsequently, during the early stages of the mid-larval stage, these myoblasts become organized into subpopulations that are gradually determined to produce specific muscles. This progressive determination of myoblasts occurs in two steps. Initially, myoblasts are determined to generate either proximal or distal muscles. Subsequently, myoblasts are gradually determined to produce unique adult muscles 24 hours prior to the onset of the fusion process. Currently, our research endeavors involve exploring the intrinsic and extrinsic factors that control this multistep regulation of muscle morphology. My research has enabled the identification of distinct subpopulations of myoblasts and the identification of specific genes that govern muscle diversity. This project has the potential to contribute novel knowledge and understanding of the intricate mechanisms involved in controlling the diverse array of muscles.

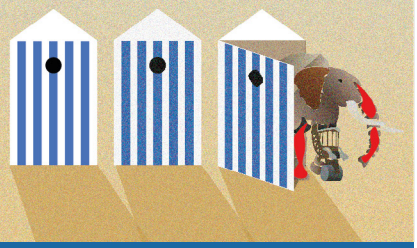


Virginia ZOGLIO
Sarah Chebouti, Sylvie Manin, Frédéric Relaix# and Joana Esteves de Lima#

Univ Paris Est Créteil, INSERM, EnvA, EFS, AP-HP, IMRB, F- 94010 Créteil, France

Distinct satellite cell states are defined by PAX3 expression during regeneration

Muscle adult stem cells, the satellite cells (SCs), play a pivotal role in skeletal muscle maintenance and repair. Key regulators of these cells are the paired-homeobox transcription factors PAX3 and PAX7. In homeostasis, the SCs are in a quiescent state (G0) and are characterized by the presence of PAX7, which controls muscle post-natal growth and regeneration in the adult. A subset of SCs also expresses PAX3 (Relaix et al., 2006), which orchestrates the myogenic progenitor cell specification, their migratory behaviour and survival. Despite PAX3 well characterized role in muscle development, its potential role in a context of muscle homeostasis and regeneration remains poorly investigated. Interestingly, SCs exhibit heterogeneity in terms of PAX3 expression in quiescence (Calhabeu et al., 2013; Kuang et al., 2006; Relaix et al., 2006). Whereas only a low amount of SCs express PAX3 in hindlimb muscles, almost 55% of SCs from the trunk and the forelimb muscles are positive for PAX3 (Der Vartanian et al., 2019). Moreover, a distinct cellular function in the context of environmental stress was associated with the expression of PAX3 in SCs. To explore the role of PAX3 expression in the context of regeneration we used the Pax3nLacZ-IRES-GFP/+ mouse as a model. We performed regeneration studies and analyzed the muscles at 7- and 28-days post injury; and in vitro analysis on FACS-isolated SCs expressing or not PAX3, which unveiled a functional heterogeneity of the SCs depending on PAX3 expression. Consistently, RNA-seq data on FACS-isolated and activated SCs confirmed a distinct transcriptomic signature between the PAX3-positive and PAX3-negative SCs, enhancing a higher commitment towards the myogenic program in the PAX3-expressing SCs. Furthermore, histological analysis on Pax3 cKO mouse model in the context of tissue damage, unveiled a potential key role of PAX3 in tissue repair in PAX3-positive muscles. We will combine histological and scRNAseq analysis to decipher cell-type specific dysregulations linked to tissue damage and identify the PAX3 downstream gene regulatory networks that could explain this functional heterogeneity between SCs.



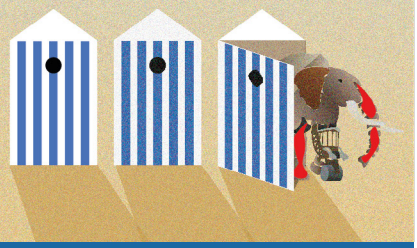
COMMUNICATION ORALE - SESSIONS PARALLÈLES 1
Ingénierie / Biomatériel / Organoïde

Ghislain BANOS[1]
Anaïs Bleuzen[1], *Teoman Ozturk*[1], *Julien Mignot*[1,3], *Thomas Boudou*[4], *Olivier Stephan*[4], *Frédéric Relaix*[1,2,3,5], *Hélène Rouard*[1,2,3], *Nathalie Didier*[1,3]

1. Univ Paris Est Créteil, INSERM, EFS, IMRB, F-94010 Créteil, France
2. EnVA, IMRB, F-94700 Maisons-Alfort, France
3. EFS, IMRB, F-94010 Créteil, France
4. Laboratory of Interdisciplinary Physics (LIPhy), University Grenoble Alpes, CNRS, F-38000, Grenoble, France
5.AP-HP, Hôpital Mondor, Service d'histologie, F-94010 Créteil, France

Engineered 3D muscle constructs for modeling Duchenne Muscular Dystrophy and high-throughput screening of novel therapeutics

With the rapid advances in gene therapy and the constant need to rapidly test new drug candidates, the development of reliable in vitro skeletal muscle models reproducing the main features of muscular disorders has become essential. We have developed innovative hydrogels favoring myogenic differentiation of muscle stem cells (MuSC) and enabling the long-term maintenance of unidirectionally aligned, highly mature and contractile myofibers in vitro.
Using the properties of these hydrogels and MuSC of a rat model of Duchenne Muscular Dystrophy (RDMDdel52),we engineered a 3D DMD muscle model. We observed that purified rat MuSC differentiated on our hydrogels formed aligned and mature myofibers expressing DAPC components, Laminin, adult Myh genes (Myh 1, 2, 4 and 7) and exhibiting striated organization of sarcomeric a-Actinin and AChR clusters. However, we observed that DMD myofibers showed a delayed maturation of their contractile apparatus and a defect in AChR clustering and maturation process evidenced by a reduced expression of AChRe subunit. With this 3DMonolayer system, we have thus developed a rapid and easy-to-use rat myofiber model to monitor myofiber maturation kinetics, AChR assembly/disassembly dynamic and perform calcium transient imaging. Moreover, in order to obtain even more mature myofibers and get closer to the structure of native muscle, we set up a system of PDMS micropillars produced by 3D printing. Thanks to this technology, MuSC-derived myofibers embedded in our hydrogel form 3D muscles wrapped around the micropillars enabling contractile force measurement by live imaging. After low-frequency electrical stimulation (0.5 Hz), we observed that 3D DMD muscles exhibited higher contractile force than 3D WT muscles, but with highly irregular frequency and amplitude and tetany phases. This 3D muscle model will therefore provide a powerful platform for studying defects in dystrophin-deficient myofibers and evaluating the impact of new therapies for the treatment of DMD.



COMMUNICATION ORALE - SESSIONS PARALLÈLES 1
Physiopathologie / Vieillissement

Riccardo GAMBERALE[1,3]
Mauro Bergamaschi[1], *Marta Carminati*[1], *Antonello Spinelli*[2], *Anna Sofia Tascini*[2], *Emanuele Azzoni*[1], *Raffaella Meneveri*[1], *Bénédicte Chazaud*[2], *Silvia Brunelli*[1]

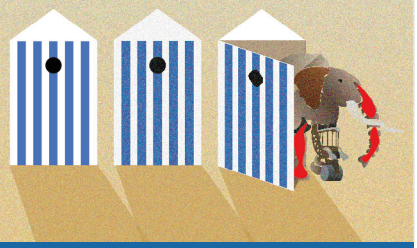
1. University of Milano Bicocca
2. IRCCS Ospedale San Raffaele
3. Institut NeuroMyoGène - Physiopathology and Genetics of Neuron and Muscle, Université Claude Bernard Lyon 1, CNRS 5261, Inserm 1315, Univ Lyon, Lyon, France

Characterization of the infiltrating polarized macrophages during the onset of heterotopic ossification in a mouse model of Fibrodysplasia Ossificans Progressiva.

Fibrodysplasia Ossificans Progressiva (FOP) is a rare congenital disease that results in heterotopic ossification (HO) in skeletal muscles. It arises from a gain-of-function mutation (R206H) in the Acvr1 gene encoding for the activin type I receptor, which leads to the aberrant activation of the bone morphogenetic proteins and activin A signalling pathways. Patients experience episodic inflammatory flare-ups in skeletal muscles that trigger HO. Macrophages still have an unclear role in the tissues where HO occurs and need a better characterization.
To model FOP we used the Acvr1(R206H)loxP;Gt(ROSA26)SorCreERT2 conditional transgenic mouse strain. Computerized tomography (CT) revealed that tamoxifen induced FOP mice develop ectopic bone after receiving muscle injury at 14 and 21 days. Histological analysis showed a consistent inflammatory infiltrate in the injured muscles of induced mice at 14 and 21 days post-injury.
To investigate how the innate immune system is involved in the onset and progression of HO, we depleted circulating monocytes by performing four intravenous injections of clodronate liposomes in FOP mice. CT scans showed that ectopic bone formation in macrophage-depleted FOP mice was significantly lower compared to controls at 14 and 21 days after injury.
To get more insights on the early signalling leading to HO, single-cell RNA sequencing was performed on muscles of FOP mice 5 and 7 days after pinch injury.
Bioinformatic analysis revealed that fibro-adipogenic progenitors (FAPs) were enriched in pathways related to chondro/osteogenesis and hypoxia in FOP mice. Furthermore, FOP macrophages expressed higher levels of osteoclast differentiation markers and displayed an upregulated pro-inflammatory profile.
Overall, these data confirm that FOP mice can reliably reproduce the features observed in patients and that macrophages are crucial for HO. Finally, single-cell transcriptomics indicates that macrophages and FAPs are committed to form a cellular niche that promotes and sustains bone formation already at early timepoints in FOP mice.

COMMUNICATIONS ORALES
SESSIONS PARALLÈLES 2

Mercredi 15 Novembre
17h00-18h30



COMMUNICATION ORALE - SESSIONS PARALLÈLES 2
Développement / Cellules souches / Régénération musculaire

Christine IBRAHIM

Université Paris Cité, Paris, France

Mechanisms of muscle wasting in a mouse model of sickle cell disease

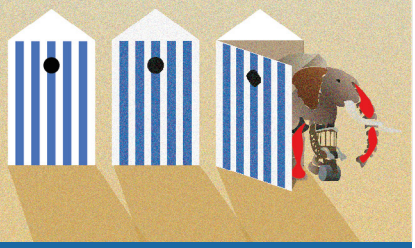
Sickle cell disease (SCD) is the most common genetic blood disorder. It manifests by a deformation of the red blood cells, which causes painful vaso-occlusive crises. Such recurrent ischemic events induce severe end-organ damage, reducing patients' life quality and expectancy. An overlooked skeletal muscle wasting accompanies SCD.

This study aims to explore the muscle phenotype in SCD and understand the implication of the Activin A-ACVR2B pathway in these lesions in the context of SCD. We first studied the kinetics of the muscular injury in our SCD mouse model. Our research shows that SCD mice have myofiber atrophy affecting all fibre types.

Additionally, skeletal muscles from the SCD mice exhibit vascular rarefaction and satellite cell loss after 16 weeks. Interestingly, the immunofluorescence staining on isolated myofibers from the muscles of SCD mice demonstrated a blockade of the remaining satellite cells in a double-positive MYOD PAX7 activated state.

Likewise, RT-qPCR analysis of sorted satellite cells from SCD mice muscle shows a significant decrease in the MyoD mRNA expression.

We then uncovered impaired regeneration capacities of the SCD muscle in response to cardiotoxin injury. Using this model, we are currently studying the mechanims of such alterations, focusing notably on the satellite cells phenotype.
Finally, we wil present the results of a screening of SCD mice and patients for sarcopenia promoting factors and proof of concept for therapeutic reversion of satellite cells phenotype in SCD mice.



COMMUNICATION ORALE - SESSIONS PARALLÈLES 2
Physiopathologie / Vieillissement

Hadidja-Rose MOUIGNI
Nami Altin, Jessica Ohana, Maria Kondili, Jamila Dhiab, Laura Muraine, Megane Lemaitre, Pierre Meunier, Gillian Butler-Browne, Vincent Mouly, Anne Bigot, Elisa Negroni, Capucine Trollet

Sorbonne Université, Inserm, Association Institut De Myologie, Centre De Recherche En Myologie, 75013 Paris, France.

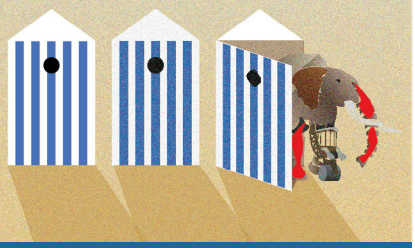
Investigating potential regulators of PABPN1 in skeletal muscle

Poly(A) binding protein nuclear 1 (PABPN1) is an ubiquitous polyadenylation factor with multiple roles in RNA metabolism, such as activation of the poly(A) polymerase (PAP), or control of mRNA poly(A) tail length. A short expansion in N-terminal of the protein leads to Oculopharyngeal muscular dystrophy (OPMD), a rare muscle genetic disease characterized by ptosis and dysphagia. In OPMD muscles, expanded PABPN1 aggregates lead to a loss of functional PABPN1 (Roth et al Acta Neuropath 2022). Interestingly, the level of PABPN1 protein is extremely low in skeletal muscle both in humans and in mice, as compared to other organs, and decreases with age. Loss of function experiments using RNA interference have shown that decreasing levels of PABPN1 leads to defects in myogenesis, degeneration, muscle atrophy and altered RNA metabolism. Today little is known about the mechanisms that regulate and control PABPN1 expression in human skeletal muscle.

In this context, using a comprehensive database that analyzes high-throughput sequencing data from cross-linking and immunoprecipitation (CLIP-seq) available datasets, we selected several RNA binding proteins (RBPs) that could potentially regulate PABPN1 expression. Using siRNA and/or overexpression systems, we tested these candidates for their ability to regulate PABPN1, both in vitro in human muscle cell lines and in vivo by AAV intramuscular injection in mice. Downstream analyses are on-going, including force measurements, histological and molecular analyses.

In parallel, we generated CRISPR-Cas9 human muscle cell lines to reduce or abrogate PABPN1 protein and analysed the consequences on cellular function. Surprisingly, these genetically modified cells were functional, with no defect in proliferation nor differentiation. We recently identified a compensatory mechanism in these cells which we are currently further investigating.

Altogether our data identified potential molecular targets for intervention to slow down disease progression in OPMD as well as in muscle ageing.



COMMUNICATION ORALE - SESSIONS PARALLÈLES 2
Physiologie / Fonction musculaire / Biomécanique / Métabolisme

Flore CHEGUILLAUME[1]
Delphine Sapaly[1], *Laure Weill*[1], *François Etienne*[1], *Gaëlle Bruneteau*[2,3], *Frédéric Charbonnier*[1]

1. Faculty of Basic and Biomedical Sciences, University Paris Cité & Inserm UMR_S1124, Paris, France
2. Paris ALS expert center, Assistance publique-Hôpitaux de Paris, Sorbonne university, Pitié-Salpêtrière Hospital, 75013 Paris, France
3. Centre de Recherche en Myologie, UMRS974, Association Institut de Myologie, Sorbonne Université, INSERM, Paris, France

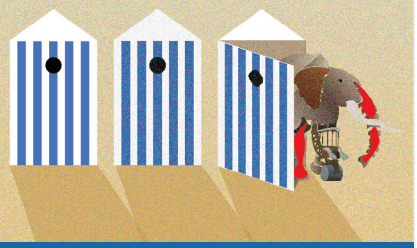
Study of the role of muscle metabolism in Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS) is a fatal adult-onset neurodegenerative disease with no efficient therapy. It is characterized by motor neurons death and skeletal muscle atrophy leading to paralysis and results in patient death due to respiratory failure. Familial forms (fALS) have been identified but 90% of the patients are sporadic (sALS), with causes that remain largely unknown. Also, the disease onset, progression and the presence of non-neurological symptoms, such as energetic metabolism defects, differs between patients. This heterogeneity makes it difficult to identify common pathogenic mechanisms.

Multiple studies indicate that skeletal muscle dysfunction, and particularly alterations in skeletal muscle metabolic pathways, participate in the disease pathogenesis.

In the present study, we analysed the energy metabolism in primary myotube cultures from deltoid biopsies of sALS patients, and compared the results with their clinical data (PULSE study, Paris ALS center, Hopital de la Pitié-Salpetrière, Paris). H1 Nuclear Magnetic Resonance (NMR) analysis showed alteration of several major metabolites of the catabolic pathways in ALS myotube cultures compared to controls. We notably observed an alteration in the citrate homeostasis, with an increase of citrate secretion in the extracellular medium. Interestingly, this alteration in sALS myotubes is associated with a down-regulation of ANKH, the only currently known membrane transporter involved in citrate cell exit. Moreover, using sALS patient's muscle biopsies, we found that ANKH mRNA expression was significantly down-regulated compared to controls. Most importantly, ANKH mRNA expression negatively correlates with the disease progression in sALS patients, suggesting that citrate metabolism is likely involved in ALS pathogenesis.

Taken together, these data highlight an original mechanism potentially involved in sALS-induced alteration of the skeletal muscle functioning.



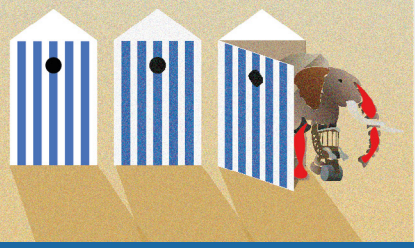
COMMUNICATION ORALE - SESSIONS PARALLÈLES 2
Physiopathologie / Vieillissement

Léna D'AGATA
Céline Gounou, Flora Bouvet, Phoebé Rassinoux, Anthony Bouter

Institute of Chemistry and Biology of Membranes and Nano-objects, UMR 5248, CNRS, University of Bordeaux, IPB, Pessac, France - Bordeaux (France)

Implication of annexins in the development of muscular dystrophies

Sarcolemma disruption, caused by mechanical stress in muscle fibers, triggers a repair process in normal muscle cells. Membrane resealing is an active Ca2+-dependent process based on the formation of a membrane patch by aggregation and fusion of intracellular vesicles with the disrupted membrane. Membrane repair process involves the active implication of various proteins, including Annexins (ANX). Defective membrane repair lead to cell death and may contribute to the development of degenerative diseases, such as muscular dystrophies. In this context, Limb-girdle muscular dystrophy type R2 and Miyoshi myopathy result from a defect of membrane repair. Other myopathies, also resulting from a defect in the membrane repair, may remain unidentified. Additionally, the severity of muscular dystrophy may vary due to the existence of secondary factors. Among the proteins involved in membrane repair, ANX are suspected to be dysregulated in many muscular dystrophies and so to be a genetic modifier.
From muscle cell lines established from control or patients suffering from muscular dystrophies (LGMDR2, RMD, DMD and FSHD), our research project first aimed at identifying pathological muscle cells suffering from a defect in membrane repair. This was achieved by the development a micro-fluidic approach allowing to submit shear stress to muscle cells, with the advantage to damage a large number of cells in a short time-lapse. Resting and mechanically stressed samples were submitted to western blotting experiments to identify dysregulations of annexins expression.
We have identified DMD and LGMDR2 as two pathological conditions resulting from defect of membrane repair. Furthermore, DMD and LGMDR2 are associated with dysregulations of the expression of ANXA5 and ANXA6 after mechanical constraints.



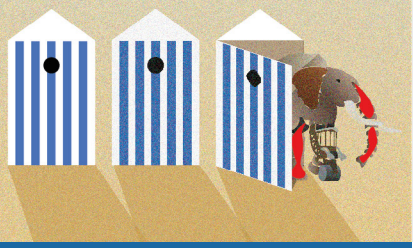
COMMUNICATION ORALE - SESSIONS PARALLÈLES 2
Ingénierie / Biomatériel / Organoïde

Clémence LIÈVRE[1]
E. Mozin[1], *D. Mack*[2], *C. Le Guiner*[1], *J-B. Dupont*[1]

1. Laboratoire TaRGeT, INSERM, UMR1089, IRS2-NBT, 22 Boulevard Benoni Goullin, 44200 Nantes, France
2. Institute for Stem Cell and Regenerative Medicine, Department of Rehabilitation Medicine, University of Washington, Seattle, WA, USA

Skeletal muscle organoids for preclinical gene therapy with recombinant AAV vectors

Duchenne Muscular Dystrophy (DMD) is an X-linked genetic disease caused by mutations in the DMD gene coding for dystrophin. Young boys suffer from marked muscle degeneration, and no curative treatment exists to date. Among the therapeutic approaches currently investigated, gene therapy using vectors derived from the adeno-associated virus (AAV) has been successfully tested in animal models of DMD. In patients, promising results have been obtained in clinical trials, but serious adverse events also emerged, sometimes with a fatal issue. Therefore, a new generation of AAV vectors with a better therapeutic index is urgently required, together with appropriate preclinical models with a higher throughput and an improved predictive power. In this context, human induced pluripotent stem cells (hiPSCs) derived from patient samples could provide a reliable alternative, as they can be differentiated into any cell type and into 3D organoids recapitulating the structure and function of the native tissues. Our project aims to develop a preclinical testing platform for DMD gene therapy using skeletal muscle organoids. We first optimized a protocol to generate large batches of myogenic progenitors from hiPSCs, that we use as building blocks to generate contractile skeletal muscle organoids in fibrin hydrogels. Using a reporter transgene, we determined the most efficient vector embedding strategy for successful AAV transduction in organoids, together with the minimal dose and efficient serotypes. Importantly, we observed that transgene expression was maintained over 4 weeks post transduction, proving that our preclinical organoid model allows for medium-term monitoring of AAV efficacy in vitro. Future perspectives include the evaluation of a therapeutic AAV-microdystrophin gene therapy in DMD organoids, to demonstrate the feasibility of in vitro preclinical gene therapy in patients hiPSCs. In the future, it could be used to screen libraries of next generation AAV vectors and accelerate the discovery of the most promising candidates.



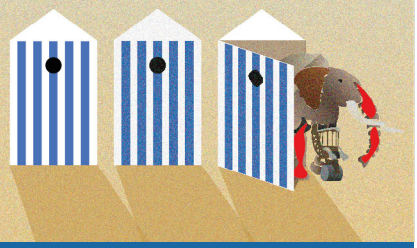
COMMUNICATION ORALE - SESSIONS PARALLÈLES 2
Développement / Cellules souches / Régénération musculaire

Liza SARDE[1,2,3]
Gaëlle Letort[4], *Wissal Manai*[1,2,3], *Stéphane Rigaud*[4], *Vincent Laville*[1,2,5], *Tarik Najib*[6], *Shahragim Tajbakhsh*[1,2*], *Brendan Evano*[1,2*]

1. Stem Cells and Development, Department of Developmental and Stem Cell Biology, Institut Pasteur, Université Paris Cité, 75015 Paris, France
2. CNRS UMR 3738, Institut Pasteur, 75015 Paris, France
3. Sorbonne Université, Complexité du Vivant, F-75005 Paris, France
4. Image Analysis Hub, Research and Resource Centre for Scientific Informatics, Institut Pasteur, 75015 Paris, France
5. Bioinformatics and Biostatistics Hub, Research and Resource Centre for Scientific Informatics, Institut Pasteur, 75015 Paris, France
6. Fab Lab, Institut Pasteur, 75015 Paris, France
** Co-corresponding authors*

Live imaging reveals perturbed symmetric stem cell divisions in a mouse model of Duchenne Muscular Dystrophy

Adult muscle stem cells (MuSCs) can self-renew or differentiate through symmetric (SCD) and asymmetric (ACD) cell divisions. These fate decisions have been investigated in the mouse mostly using static imaging of MuSCs in artificial niches or on isolated muscle fibres, leaving their dynamic behaviour to be inferred. We are analysing the cellular and molecular regulation of the modes of MuSC divisions using several readouts including distribution of Pax7 (stem) and Myogenin (differentiated) transcription factors. Specifically, we developed a unique ex vivo assay where primary muscle fibres and their associated MuSCs can be cultured and filmed in microwells for several days, allowing live tracking of cell fate decisions. Interestingly, we noted that ACD and SCD were not obligate in individual clones in consecutive divisions. We also observed that MuSCs have impaired SCDs and migration kinetics a mouse model of Duchenne Muscular Dystrophy (mdx). To evaluate the relative impact of intrinsic and extrinsic factors, we cross-grafted MuSCs between mdx and WT myofibres. While fate decisions appeared as mostly stem cell-intrinsic, the migration behaviour of MuSCs results from interacting cues between the stem cell and the fibre. This study highlights the importance of perturbed SCDs and niche alterations in a disease model and raises the possibility that similar mechanisms act in diverse stem cell populations.



COMMUNICATIONS ORALES
SESSIONS PARALLÈLES 3

Jeudi 16 Novembre
11h00-12h30

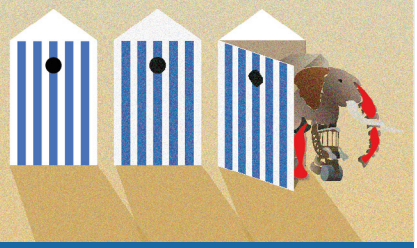
COMMUNICATION ORALE - SESSIONS PARALLÈLES 3
Développement / Cellules souches / Régénération musculaire

Lucille ROSSIAUD
Quentin Miagoux, Margot Jarrige, Helene Polveche, Emilie Pellier, Louisa Jauze, Mallaury Vie, Xavier Nissan, Giuseppe Ronzitti and Lucile Hoch

I-STEM, Institute for Stem Cell Therapy and Exploration of Monogenic Diseases, 91100 Corbeil-Essonnes, France

Comparative RNA-sequencing analysis to understand muscle pathophysiology of glycogen storage disease type III

Glycogen storage disease type III (GSDIII) is a rare disease caused by a deficiency of glycogen debranching enzyme (GDE), which leads to glycogen accumulation in liver, skeletal muscles and heart. Although the disease manifests with severe liver impairments, the progressive myopathy is the major disease burden in adult patients, without curative treatment. To understand the molecular mechanisms underlying GSDIII muscle pathophysiology, we took advantage of the self-renewal and differentiation capabilities of human induced pluripotent stem cells (hiPSCs) to generate muscle cellular models of GSDIII. First, GSDIII hiPSCs were reprogrammed from patient's fibroblasts and then differentiated into skeletal muscle cells. Analysis of glycogen content in hiPSC-derived muscle cells revealed a persistent accumulation of glycogen under glucose starvation conditions. Secondly, we performed a comparative RNA-sequencing analysis between GSDIII and healthy hiPSC-derived muscle cells to identify differentially expressed genes that contribute to GSDIII muscle impairments. To highlight potential therapeutic targets, we correlated these data with RNA-sequencing analysis of muscle tissues from a GSDIII mouse model treated or not with recombinant AAV vectors expressing the human GDE.



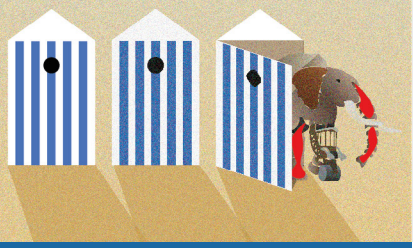
COMMUNICATION ORALE - SESSIONS PARALLÈLES 3
Thérapie

Abbass JABER
Rania Bakour, Ai Vu Hong, Laura Palmieri, Nathalie Bourg, Sonia Albini, Isabelle Richard, David Israeli

Université Paris-Saclay, Univ Evry, Inserm, Généthon, Integrare research unit UMR_S951, 91000, Evry-Courcouronnes, France

Targeting lysosome damage in Duchene muscular dystrophy improves micro-dystrophin gene therapy

Duchene muscular dystrophy (DMD) is a muscle degenerative disease that affects mainly boys, which is caused by the loss or drastic reduction in the expression of dystrophin. Gene therapy for the restoration of a functional shortened form of dystrophin (μ-dystrophin) have provided encouraging results in animal models. Nevertheless, the therapeutic benefit of this approach is still questionable in treated DMD patients. We therefore attempted to explore the limitations of μ-dystrophin gene therapy. To find molecular and cellular pathways which failed to be corrected by the treatment, mdx mice were treated with AAV9-μ-dystrophin, muscles were subjected to RNA sequencing, which was analyzed by Gene Set Enrichment Analysis (GSEA). We found indications for lysosomal perturbation in the dystrophic muscle, which was only partially corrected by μ-dystrophin gene therapy.
Recently, Galectin-3 (LGALS3) was proposed as a biomarker for lysosomal damage. We found that LGALS3 is upregulated in the dystrophic muscle, in a puncta pattern on the membranes of enlarged lysosomes of the myofiber. Thus, LGALS3 upregulation and expression pattern indicate lysosome membrane permeabilization in dystrophic muscle, and the LGALS3 puncta assay can be used for the evaluation of this lysosomal damage.
To assess the therapeutic potential of lysosome correction in muscular dystrophy, mdx mice were treated with the Drug-X, which is an activator of lysosomal biogenesis, alone and in combination with AAV9-μ-dystrophin. Drug-X alone reduced dystrophic features, although to a lesser extent than AAV9-μ-dystrophin alone. Inversely, lysosomal damage was better corrected by Drug-X alone than by AAV-μ-dystrophin alone. Importantly, mice subjected to the combined treatment showed the highest benefit, including normalization of circulating biomarkers, histological features, lysosomal damage and increased muscle force. We concluded that lysosomal damage is not completely corrected by μ-dystrophin gene therapy and that targeting the endo-lysosomal compartment in the setup of a combined therapy might be beneficial in DMD.



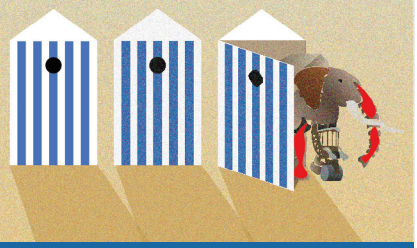
COMMUNICATION ORALE - SESSIONS PARALLÈLES 3
Ingénierie / Biomatériel / Organoïde

Lucas DUVERT
Clarissa Muru[2], Adrien Casanova[2], Stefano Testa[1], Frédérique Magdinier[1], Anne-Patricia Alloncle[2]

1. Aix-Marseille University, INSERM, Marseille Medical Genetics, MMG, 27 Bd Jean moulin 13385 Marseille, France
2. Aix-Marseille University, CNRS, UMR 7341, LP3, Campus de Luminy, Case 917, 13288, Marseille cedex 9, France

Laser bioprinting: A new tool for skeletal muscle tissue enginnering

Bio-printing methods are based on interdisciplinary approaches aiming at the creation and patterning of organized 2D and 3D cell scaffolds. First developed for electronic purposes, Laser-Induced Forward Transfer (LIFT) is a laser-based technique now applied to the transfer of biomaterials and even living cells, on a substrate. This technique uses a short laser pulse to transfer tiny amounts of material from a thin donor film to the desired location with high precision, resolution and reproducibility. In this context, thanks to an interdisciplinary collaboration between the LP3 lab [LIFT process] and the MMG [primary and IPS derived neuro-muscular progenitors] we are able to safely print cell-laden bioinks for the creation of biological models with application ranging from tissue engineering to disease modelling. Here, we will present the complete study of the LIFT process allowing us to achieve a controlled, reliable, precise printing of muscle progenitor cells while ensuring a high post-printing cell survival rate. We will present the potential of co-culture printing that further improves the fidelity of the bio-models created and open the door for neuro-muscular disease modelling with precise printing of different cell types on a single substrate.
In parallel, laser structuration by direct laser ablation of hydrogels was developed and combined to the printing process. Muscle progenitors can now be printed precisely in pre-made micro-structured channels that guide and align the resulting myotubes according to the channels orientation. Besides being able to precisely print living cells, we can reproducibly produce muscle fibres of about 200µm width and several millimetres long from affected and non-affected human progenitors. Once validated, these models will be a useful tool for personalised medicine applications.

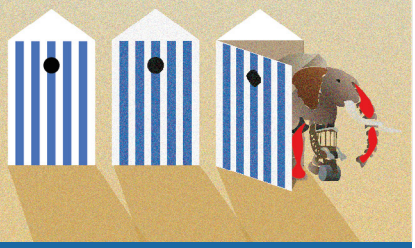


Marine DAURA
Leslie Andromaque, Vincent Gache, Carole Remy-Kretz

PGNM - Institut NeuroMyoGene - *UCB Lyon 1 - CNRS UMR5261 - INSERM U1315*

Involvement of SH3KBP1 protein in the modulation of ER architecture and autophagy during myofiber formation

During muscle fibers formation, the organization and maintenance of cellular organelles is essential for the proper functioning of the fibers. The endoplasmic reticulum (ER) and its muscle-specific form, the sarcoplasmic reticulum (SR), are crucial organelles in muscle fibers involved in calcium regulation, structural support and muscle contraction.
SH3KBP1 is an adaptor protein well described to be involved in membrane trafficking, but its function in muscle cells/fibers has never been investigated. In the team, we determined that SH3KBP1 expression is transiently increased during the differentiation of myoblasts into myotubes. We also demonstrated that SH3KBP1 binds to calnexin, a transmembrane chaperone of the endoplasmic reticulum (ER). Moreover, we observed that, during the early phases of muscle fiber formation, SH3KBP1 under-expression alters the perinuclear architecture of the ER.
Of interest, a well-known process involved in the ER remodeling is the reticulophagy (also called ER-phagy), which is a selective form of autophagy. During this process, a portion of the ER is targeted for degradation by ER-phagy receptors, which are proteins allowing the recruitment of the autophagic machinery at ER sites. ER portions are thus engulfed in autophagosomes that fuse with lysosomes to form autolysosomes, in which the ER is degraded.
We thus asked whether SH3KBP1 could be involved in the maintenance of ER through modulation of bulk autophagy and/or ER-phagy processes. Our results indicate that under-expression of SH3KBP1 modulates the bulk autophagic and ER-phagic activities. Moreover, we identified that SH3KBP1 possesses many hallmarks of ER-phagy receptors. Thus, we suggest that SH3KBP1 is involved in the maintenance of muscle fiber integrity and function through modulation of ER architecture via autophagy.



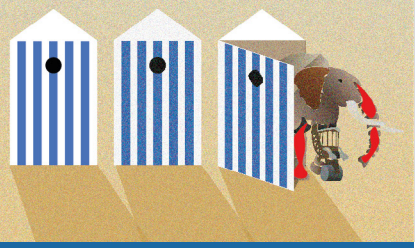
COMMUNICATION ORALE - SESSIONS PARALLÈLES 3
Développement / Cellules souches / Régénération musculaire

Jean-Baptiste DUPONT[1]
Elise Mozin[1], *Emmanuelle Massouridès*[2], *Virginie Mournetas*[3], *Clémence Lièvre*[1], *Audrey Bourdon*[1], *Dana L Jackson*[4], *Jonathan S Packer*[4], *Cole Trapnell*[4], *Caroline Le Guiner*[1], *Christian Pinset*[2], *David L Mack*[5]

1. Nantes Université, CHU Nantes, INSERM, TARGET, F-44000 Nantes, France
2. Centre d'Etude des Cellules Souches, I-Stem, AFM, F-91100 Corbeil-Essonnes, France
3. ADLIN Science, F-91058 Evry, France
4. Department of Genome Sciences, University of Washington School of Medicine, Seattle, WA 98105, USA
5. Institute for Stem Cell and Regenerative Medicine, Department of Rehabilitation Medicine, University of Washington, Seattle, WA, USA

Dystrophin deficiency impairs cell junction formation during embryonic myogenesis

Mutations in the DMD gene lead to Duchenne muscular dystrophy (DMD), a severe X-linked neuromuscular disorder affecting young boys as they acquire motor functions. DMD is diagnosed after 2 to 4 years but early studies in patients and animal models indicated that symptoms are already detected in neonates and initiate before birth. This poses a serious challenge in the optimization of standards of care for DMD patients, as the disease goes unnoticed during the first years of life and possibly leads to irreparable damage in skeletal and cardiac muscles. Therefore, it is crucial to determine the earliest disease phenotypes and investigate the functions of the DMD gene during embryonic development.
Here, we used human induced pluripotent stem cells (hiPSCs) as a model to recapitulate the successive steps of myogenesis in a dish and to determine the developmental dynamics of DMD at the molecular level. We first established the single-cell trajectory followed by hiPSCs in the course of their differentiation into the skeletal muscle lineage and we showed that DMD mutant cells bifurcate towards an alternative transcriptomic endpoint when they reach the "somite" developmental stage. Importantly, dystrophin deficiency in somite progenitors resulted in marked dysregulations of a large number of genes involved in the formation of tight junctions, adherens junctions and desmosomes. Specifically, several gene families such as claudins (CLDN), desmocollins (DSC) and desmogleins (DSG) were found downregulated in DMD somite cells, while protocaderins (PCDH) were mostly upregulated. As a result, DMD cells showed an altered ability to form epithelial islets expressing somite markers, suggesting that dystrophin might have a direct impact on the remodelling of cell junctions during the cell state transitions associated with somite development. Altogether, our work demonstrates that dystrophin deficiency has early consequences during myogenic development, which should be considered in future therapeutic approaches for DMD.



COMMUNICATION ORALE - SESSIONS PARALLÈLES 3
Génétique / Omique

Amaury KORB
Stephan Fischer, Shahragim Tajbakhsh, Glenda Comai

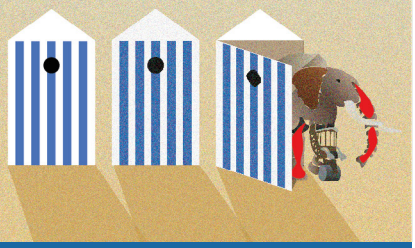
Stem Cells & Development, Department of Developmental & Stem Cell Biology, 2 CNRS UMR 3738, Institut Pasteur, Paris, France,

Blueprinting myonuclear heterogeneity along the body axis

Although all muscles of the body share the same structural organization, with multinucleated myofibers as the basic functional unit, an unexpected heterogeneity distinguishes head and trunk muscles. This is manifested by their different embryological origins, innervation patterns, myosin composition, susceptibility to myopathies, and properties of their resident muscle stem cells (MuSCs). It remains unclear whether these phenotypical differences are due to their different embryological origins and molecular signatures of myogenic progenitors that give rise to myofibers, and/or whether it is the local micro-environment that modulates the properties of cranial myofibers and MuSCs.
We used unbiased genomic approaches to assess the relative roles of intrinsic/extrinsic factors differentially deployed during lineage progression using cranial (EOM, Esophagus) and limb (TA) muscles as comparative. We constructed a cell cartography of transcriptional diversity among adult cranial muscles using single nuclei RNA-seq (sn-RNAseq) and identified critical regulators of myogenic and non-myogenic cell types (eg. FAPs, tenocytes). Unexpectedly, while cranial myonuclei shared a common program with the TA counterparts, they displayed unique structural, metabolic and receptor/ligand signatures. To our knowledge, this is the first comprehensive analysis of the gene regulatory networks operating in anatomically distinct muscles and a starting point for understanding the differential susceptibility of muscles groups to disease.

COMMUNICATIONS ORALES MIXTES

Vendredi 17 Novembre
11h00-12h00



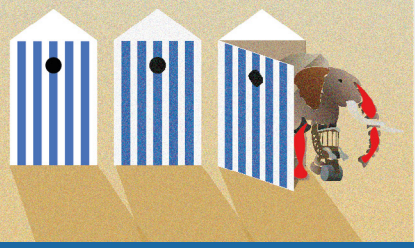
COMMUNICATIONS ORALES MIXTES
Développement / Cellules souches / Régénération musculaire

Yan BURELLE[1]
George Cairns, Madhavee Thumiah Mootoo, Mah Rukh Abbasi, Jeremy Racine, Melissa Gourlay, Nikita Larionov, Alexandre Prola, Mireille Khacho

1. University of Ottawa, Canada
2. Université de Lausanne, Suisse

Mitochondrial quality control in muscle stem cells: a determinant of fate decision and tissue repair capacity

Maintenance of optimal mitochondrial function plays a crucial role in the regulation of Muscle Stem Cell (MuSC) behavior, but the underlying maintenance mechanisms remain ill defined. Our lab aims to delineate the importance of mitophagy as a mitochondrial quality control regulator in MuSCs and the role this process plays in maintaining optimal muscle regenerative capacity. Our recent work indicates that in the quiescent state key mitophagy regulating genes including Pink1 and Parkin are actively expressed, and mitochondrial localization to autophago(lyso)somes is prominent, representing 10-20% of mitochondrial biomass at steady state. Furthermore, transition to an activated state results in a rapid downregulation of several mitophagy transcript, and loss of mitochondrial colocalization to autophagolysosomes, which altogether indicate that mitophagy is dynamically regulated in MuSCs during state transitions. Experiments also reveal that genetic disruption of PINK1 reduces mitophagy in quiescent MuSCs, which is accompanied by increased mitochondrial ROS release and mitochondrial network fragmentation. These abnormalities lead to hampered self-renewal of MuSCs which can be rescued by mitochondrial-targeted antioxidants, and impaired muscle regeneration following in vivo injury. However, proliferation and differentiation capacity is unaltered in the absence of PINK1, pointing to altered fate decision as the main mechanism underlying impaired muscle regeneration in this model. Preliminary work indicates that genetic inactivation of Parkin, or the mitophagy receptor BNIP3L/NIX recapitulate many of the phenotypic characteristics observed in PINK1 deficient mice, particularly the impaired self-renewal, which altogether suggest that overlapping pathways regulate mitophagy in and influence fate decision in MuSCs.



COMMUNICATIONS ORALES MIXTES
Pathologie du nerf et motoneurone

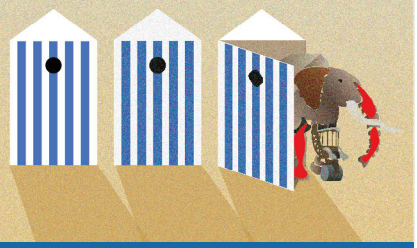
Armelle MAGOT[1]

Arnaud Reignier[2], *Olivier Binois*[3], *Anne Laure Bedat-Millet*[4], *Jean-Baptiste Davion*[5], *Louise Demurger*[6], *Karima Ghorab*[7], *Lucie Guyant*[8], *Emilie Laheranne*[6], *Claire Lefeuvre*[9], *Martial Mallaret*[10], *Maud Michaud*[11], *Jean Baptiste Noury*[12], *Alexandra Nadaj-Pakleza*[13], *Guillaume Nicolas*[9,14], *Antoine Pégat*[15], *Morgane Péré*[16], *Emmanuelle Salort-Campana*[17], *Guilhem Solé*[6], *Marco Spinazzi*[18], *Céline Tard*[19], *Carole Vuillerot*, *Yann Péréon*[1]

1. Centre de Référence Maladies Neuromusculaires AOC, CHU de Nantes, Filnemus, Nantes, France
2. Service de médecine et biologie de la reproduction, gynécologie médicale, CHU de Nantes, Nantes, France
3. Service de Biologie de la Reproduction - CECOS, Hôpital Antoine Béclère, AP-HP, Université Paris Saclay, Clamart, France
4. Centre de référence des maladies neuromusculaires Nord-Est-Ile de France, Services de neurologie et neurophysiologie, CHU Charles Nicolle, Rouen, France
5. Centre de référence des Maladies Neuromusculaires Nord-Est-Ile de France, CHU Lille, Lille, France
6. Centre de référence des maladies neuromusculaires AOC, service de Neurologie et des maladies neuromusculaires, CHU de Bordeaux, Filnemus, Euro-NMD, Bordeaux, France
7. Centre de Référence des Maladies Neuromusculaires AOC, CHU de Limoges, Limoges, France
8. Service de Neurophysiologie et Service de Génétique Clinique, CHU de Rouen, France
9. Service de Neurologie, CHU Raymond Poincaré, APHP, Garches, France
10. Centre de référence des maladies neuromusculaires, Service de neurologie, CHU Grenoble Alpes, Univ. Grenoble Alpes, Inserm, U1216, Grenoble Institut Neurosciences, Grenoble, France
11. Service de neurologie, centre de référence maladies neuromusculaires Nord-Est-Ile de France, CHRU Central, Nancy, France
12. Inserm, LBAI, UMR1227, centre de référence des maladies neuromusculaires AOC, CHRU de Brest, Brest, France
13. Centre de Référence des Maladies Neuromusculaires NEIdF, Service de Neurologie, Hôpitaux Universitaires de Strasbourg, France
14. Université de Versailles Saint Quentin en Yvelines, Garches, France
15. Service ENMG et de pathologies neuromusculaires, centre de référence des maladies neuromusculaires PACA-Réunion-Rhône Alpes, Hôpital Neurologique P. Wertheimer, Hospices Civils de Lyon, France
16. Plateforme de Méthodologie et de Biostatistique, Centre Hospitalier Universitaire de Nantes, Nantes, France
17. Centre de référence PACA Réunion Rhône Alpes, AP-HM, Hôpital La Timone, Filnemus, Marseille, France
18. Centre de Référence des Maladies Neuromusculaires, Service de Neurologie, CHU d'Angers, France
19. U1172, centre de référence des maladies neuromusculaires Nord-Est-Ile-de-France, Service de neurologie, CHU de Lille, Lille, France
20. Centre de référence PACA Réunion Rhône Alpes, Hospices Civils de Lyon, Hôpital Femme-Mère-Enfant, L'Escale, Service de Médecine Physique et de Réadaptation Pédiatrique, Bron, France; NeuroMyogen Institute, CNRS UMR 5310 - INSERM U1217, University of Lyon, Lyon, France

Amyotrophie spinale infantile chez l'homme: Une pathologie de la spermatogénèse?

Introduction : Les patients atteints d'amyotrophie spinale (SMA) bénéficient de traitements modificateurs d'épissage du pré-ARNm du gène SMN2, avec l'objectif d'obtenir une augmentation de la production de SMN fonctionnelle. La mise en évidence d'une toxicité animale sur la spermatogénèse associée à un de ces traitements, nous a conduit à nous questionner sur la spermatogénèse des patients masculins atteints de SMA.
Matériels et Méthode : Il s'agit d'une étude descriptive, transversale, concernant des patients adultes masculins atteints de SMA prouvée génétiquement (délétion homozygote SMN1) suivis dans 13 centres neuromusculaires français. Des données générales, de sévérité motrice, d'antécédents urologiques, d'exposition à certains facteurs, de parentalité et les spermogrammes ont été recueillies.
Résultats : 68 patients ont été inclus (33 SMA2 et 35 SMA3). Les 2 groupes de patients différaient de façon significative, de façon attendue, sur leur sévérite motrice, le temps passé en fauteuil, le poids et la taille. Les données de fertilité (antécédents de paternité et données de spermogrammes) ont pu être obtenues pour 41 patients (33 spermogrammes). Des anomalies de spermogramme existaient chez 27/33 (81%) de ces patients (19 SMA2, 8 SMA3), dont 40 % présentaient une azoospermie. Les anomalies étaient liées de façon significative au type de SMA (plus fréquentes pour les patients type 2, p=0.0007), la sévérité motrice de la maladie (p=0.005), l'âge de la perte de la marche et le temps passé au fauteuil (p=0.0003). Le nombre de spermatozoïdes était corrélé à la sévérité de la maladie mesurée par la mesure de fonction motrice (MFM) (p=0.01).
Discussion : Les troubles de la fertilité dans notre population sont très nettement supérieurs à ceux de la population générale (environ 7.5%). L'absence de protéine SMN pourrait être délétère pour la spermatogénèse, conséquence négative étayée par des études chez la drosophile et la souris. L'absence de régulation adéquate de la température scrotale due à la position prolongée au fauteuil peut également être suspectée.



COMMUNICATIONS ORALES MIXTES
Dystrophie musculaire

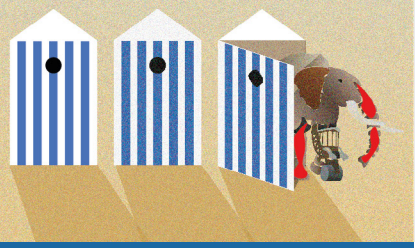
Alexandre GUEREMY

A. Guérémy[1], S. Gorokhova[2,3], T. Stojkovic[4], F. Bouhour[5], A Nadaj Pakleza[6], J. Nectoux[7], E. Fortanier[1], A. Magot[8], S. Sacconi[9], B. Eymard[4], C. Metay[10], F Duval[11], ML Martin-Negrier[12], M. Cerino[3], L Michel[13], R. Menassa[13], M. Cossée[14], L. Barbat du Closel[1], A. Behin[4], F. Leturcq[7], J .B Noury[15], M Krahn[2,3], G Sole[15,16], S. Attarian[1,3,16], E. Salort-Campana[1,3,16]

1. Centre de référence des maladies neuromusculaires PACA Réunion Rhône alpes, CHU de Marseille-hôpital de la Timone, Marseille, France
2. Aix Marseille Univ, Inserm, MMG, Marseille Medical Genetics, Translational Neuromyology, Marseille, France
3. Département de génétique médicale, Hopital La Timone enfants, Marseille, France
4. Groupe Hospitalier (GH) Pitié-Salpêtrière, Centre de Référence des Maladies Neuromusculaires Paris Est, Institut de Myologie, AP-HP, Paris, France
5. Hôpital Neurologique Pierre Wertheimer, Service d'électroneuromyographie et de pathologies neuromusculaires, CHU de Lyon—Hospices Civils de Lyon (HCL) groupement Est, Bron, France
6. Centre de Référence des Maladies Neuromusculaires NEIdF, Service de Neurologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France
7. Service de Médecine Génomique des Maladies de Système et d'Organe, Hôpital Cochin, AP.HP.CUP, Paris, France
8. Centre de référence des maladies neuromusculaires AOC, Laboratoire d'Explorations Fonctionnelles, CHU de Nantes, Nantes, France
9. Université Côte d'Azur (UCA), Centre Hospitalier Universitaire de Nice, Peripheral Nervous System and Muscle
10. UF de cardiogénétique et myogénétique moléculaire et cellulaire, Groupe Hospitalier (GH) Pitié-Salpêtrière, AP-HP, Paris, France
11. Centre de référence des maladies neuromusculaires AOC, Pellegrin Hospital, Bordeaux, France
12. Laboratoire d'anatomopathologie, CHU de Bordeaux, Bordeaux, France
13. service de biochimie et biologie moléculaire, hospices civils de Lyon, Lyon, France
14. Laboratoire de génétique moléculaire, CHU de Montpellier, Montpellier, France
15. Centre de référence des maladies neuromusculaires CHRU Brest, 29200 Brest, France
16. Filnemus

Limb-girdle muscular dystrophy associated with TRIM 32 mutations: A national cohort study and review of the literature

Introduction: Limb girdle muscular dystrophies (LGMDs) are rare genetic diseases characterized by a progressive atrophy of the shoulder and pelvic muscles. LGMD subtype linked to TRIM32 mutation, known as LGMDR8 or sarcotubular myopathy (STM), is an uncommon form of LGMD. This mild and progressive myopathy was initially described in the Hutterite population and is characterized by a wide phenotypic heterogeneity. Most of variants previously reported are located in the region coding for the C-terminal NHL domain. Little is known about this very rare myopathy in non-Hutterite population.
Methods: We retrospectively collected data from patients diagnosed with LGMDR8 or STM followed in neuromuscular reference centres in France and compared them to patients from literature review. Clinical, electrophysiological, genetic, MRI and histological data were collected.
Results: Data from 15 Caucasian probands were studied. Mean age at inclusion was 53.5 (33-73) years and sex-ratio was 6 females per 7 males. Motor weakness in lower limbs was the initial symptoms for most of the patients (93.3%) and began at 26.0 (8-40.0) years. CK levels were mildly elevated (3.2 times normal). Histological studies revealed a dystrophic pattern in all patients and features of mitochondrial dysfunction in two of them. Both protein truncating and missense variants were identified. 3/17 variants were located in the "Coil-coiled" region, where very few pathogenic variants have been previously reported without detailed clinical data. Twelve patients harboured homozygous variants and 3 were compound heterozygotes. The phenotype associated to these variants was more severe than those associated with the typically reported variants, with a higher proportion of patients experiencing loss of walking and an earlier onset of symptoms.
Conclusion : The description of our LGMDR8 patient cohort highlights the phenotypic and genetic diversity of this population. We also report novel genetic variants that provide new insights into the genetic-phenotype correlation.

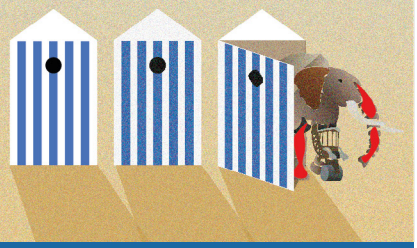


COMMUNICATIONS ORALES MIXTES
Myopathie congénitale

Aurélien PERRIN

Rocio Garcia Uzquiano[3], Céline Tard[4], Corinne Metay[5], Valérie Biancalana[7], Anne Bergougnoux[1,2], Charles Van Goethem[1], Corinne Thèze[1], Marion Larrieux[1], Ana Maria Navarro[1,2], Florence Esselin[8], Marie-Christine Arné-Bes[9], Anne-Laure Bedat Millet[10], Anne Claire Bréhin[11], Ana Camacho Salas[12], Claude Cances[13], Jean Baptiste Davion[14], Julien Durigneux[15], Héloise Faure-Gautron[1,2], Léonard Féasson[16], Ana Ferreiro[17,18], Martha Gomez Garcia de la Banda[3], Arnaud Isapof[19], Médéric Jeanne[20], Pascal Laforet[21], Annie Laquerriere[22,] Guillaume Lefebvre[23], France Leturcq[24], Franck Letournel[25], Edoardo Malfatti[26], Pascale Marcorelles[27,28], Xénia Latypova[29,30], Arnaud Molin[31], Juliette Nectoux[32], Marie-Christine Nougues[33], Florence Petit[34], Marguerite Preud'homme[35], John Rendu[29], Isabelle Richard[36], Tanya Stojkovic[37], Vincent Tiffreau[38], Sandra Whalen[39], Christian Jorgensen[40], Martin Krahn[41,42], Raul Juntas Morales[43,] Michel Koenig[1,2], Susana Quijano-Roy[3,44], Robert Yves Carlier[45*], Mireille Cossée[1,2**]*

1. Laboratoire de Génétique Moléculaire, Centre Hospitalier Universitaire de Montpellier, 34093 Montpellier, France
2. PhyMedExp, Université de Montpellier, INSERM, CNRS, 34093 Montpellier, France
3. APHP, GH Université Paris-Saclay, Neuromuscular Center, Child Neurology and ICU Department, Raymond Poincare Hospital, Garches, France
4. Department of Neurology and Movement Disorders, U1172, Centre Hospitalo-Universitaire (CHU) de Lille, CT, Centre de Référence des Maladies Neuromusculaires Nord Est Ile de France, Lille, France
5. AP-HP, UF Molecular Cardiogenetics and Myogenetics, Sorbonne Université and Sorbonne Université UPMC Paris 06 Inserm UMRS974, Research Center in Myology, Pitié-Salpêtrière Hospital, Paris, France
6. Laboratoire de Diagnostic Génétique, Université de Strasbourg, 67084 Strasbourg, France
7. Laboratoire de Diagnostic Génétique, Faculté de Médecine, CHRU, Nouvel Hôpital Civil, 1 place de l'Hôpital, 67091, Strasbourg, France
8. Explorations Neurologiques et Centre SLA, Centre de Référence des Maladies Neuromusculaires AOC (Atlantique-Occitanie-Caraïbe), Centre Hospitalier Universitaire de Montpellier, 34295 Montpellier, France.
9. Explorations Neurophysiologiques, Centre SLA, Centre de référence de pathologie neuromusculaire, CHU Toulouse, France
10. Department of Neurology, Rouen University Hospital and University of Rouen, France
11. Department of Genetics, Normandy Centre for Genomic and Personalized Medicine, Normandie University, UNIROUEN, Inserm U1245 and Rouen University Hospital, F 76000, Rouen, France
12. Sección de Neurología Infantil, Servicio de Neurología, Hospital Universitario 12 de Octubre, Madrid, España
13. Service de Neuropédiatrie, Centre Hospitalier Universitaire de Toulouse, Centre de référence des Maladies Neuromusculaires AOC (Atlantique-Occitanie-Caraïbe), 31059 Toulouse, France
14. Centre de Référence des Maladies Neuromusculaires Nord/Est/Ile de France, Service de Neuropédiatrie, Hôpital Salengro CHU Lille, Lille, France
15. Centre de Référence des Maladies Neuromusculaires AOC, CHU d'Angers, Angers, France
16. Univ Lyon, UJM-Saint-Etienne, Laboratoire Interuniversitaire de Biologie de la Motricité, EA 7424, F-42023 Saint-Etienne, France
17. APHP, Centre de Référence des Pathologies Neuromusculaires Nord-Est-Ile de France, Institut de Myologie, GHU Pitié-Salpêtrière, Paris, France
18. Basic and Translational Myology laboratory, Université de Paris BFA, UMR 8251, CNRS, Paris, France
19. Centre de Référence des Maladies Neuromusculaires Nord/Ile de France/Est, Service de Neuropédiatrie, Hôpital Trousseau, APHP, Paris, France
20. UMR 1253, iBrain, Université de Tours, Inserm, 37032 Tours, France
21. Nord/Est/Ile de France Neuromuscular Reference Center, PHENIX FHU, Hôpital Raymond-Poincaré, AP-HP. INSERM U1179, Garches, France
22. Department of Pathology, Normandy Centre for Genomic and Personalized Medicine, Normandie University, UNIROUEN, Inserm U1245 and Rouen University Hospital, F 76000, Rouen, France
23. Service d'Imagerie musculo-squelettique, CCIAL, CHU de Lille, rue Emile Laine, 59037, Lille, France
24. Department of Genetics and Molecular Biology, AP-HP, Cochin Hospital, Paris, France. 25 Laboratoire de neurobiologie et neuropathologie, Centre Hospitalier Universitaire d'Angers, Angers, France
26. UPEC, Paris Est University, IMRB INSERM U955, APHP, Centre de référence neuromusculaire, HU Henri Mondor, Créteil, France
27. Department of Pathology, Brest University Hospital, Brest, France
28. Laboratory of Neurosciences of Brest, Faculté de Médecine et des Sciences de la Santé, Université de Bretagne Occidentale, Brest, France
29. Université Grenoble Alpes, Inserm, U1216, CHU Grenoble Alpes, Grenoble Institute of Neurosciences, 38000 Grenoble, France
30. Department of Genetics, Assistance Publique-Hôpitaux de Paris, France - Université de Paris, UMR7216, Epigenetics and Cell Fate, 75013, Paris, France.
31. Normandy University, UNICAEN, Caen University Hospital, Department of Genetics, Reference Center of Rare Diseases of Calcium and Phosphorus Metabolism, EA 7450 BioTARGen, Caen, France
32. Service de Génétique et Biologie Moléculaires, Hôpital Cochin, DMU BioPhyGen, Assistance Publique-Hôpitaux de Paris, AP-HP. Centre-Université de Paris, Paris, France
33. Pediatric Neurology Department, Reference Centre for Neuromuscular Diseases, Armand Trousseau Hospital, APHP, Sorbonne University, 26, avenue du Docteur Arnold Netter, 75012 Paris, France
34. CHU Lille, Clinique de Génétique Guy Fontaine, Lille, France
35. Centre de référence Nord Est Ile-de-France, Service de rééducation fonctionnelle, CHU de Lille
36. INTEGRARE, Genethon, Inserm, Université Evry, Université Paris-Saclay, 91002 Evry, France
37. Reference Center for Neuromuscular Disorders Nord/Est/Île-de-France, Sorbonne Université, AP-HP, Hôpital Pitié-Salpêtrière, 75013 Paris, France
38. Physical and Rehabilitation Medicine Unit, University Hospital, Lille, France, URePSSS (Pluridisciplinary Research Unit: Sports, Health, Society) EA, 7369, Lille University
39. UF de génétique Clinique et Centre de Référence Anomalies du Développement et Syndromes Malformatifs, Assistance Publique-Hôpitaux de Paris (APHP) Sorbonne Université, Hôpital Armand Trousseau, ERN-ITHACA, Paris, France
40. IRMB, Univ Montpellier, INSERM, Montpellier, France. 41 INSERM, Marseille Medical Genetics, U1251, Aix-Marseille Université, 13385 Marseille, France
42. Département de Génétique Médicale, Hôpital Timone Enfants, APHM, 13385 Marseille, France
43. Neurology Department, Vall d'Hebron University Hospital, Barcelona, Spain.
44. Université de Versailles, U1179 INSERM-UVSQ, Montigny, France
45. Radiology Department, DMU Smart Imaging, Raymond Poincaré University Hospital, APHP, Garches, France; APHP-Université Paris-Saclay, Garches, France.



COMMUNICATIONS ORALES MIXTES
Myopathie congénitale

Aurélien PERRIN ***(Suite)***

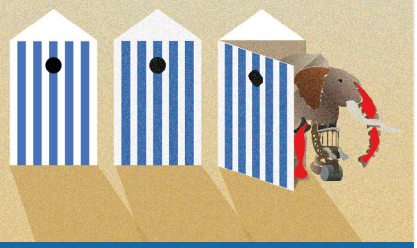
Genotype-phenotype correlation of patients with severe congenital titinopathies

Objective
Variants in the titin gene (TTN) which is composed of 364 coding exons, are expressed differently before and after birth and are associated with a great phenotypic variability. The molecular bases of this variability are incompletely elucidated. Among the 55 patients with congenital titinopathy reported to date, the pathogenic variants are inherited in an autosomal recessive fashion. They are located mainly in metatranscript-only exons (exons not included in main cardiac and skeletal pots natal isoforms). The objective of this study was to describe additional patients and define new titinopathy genotype-phenotype correlations.

Methods
We studied 28 patients from 21 families with a phenotype of congenital myopathy and/or neonatal hypotonia, contractures and/or arthrogryposis, and at least one pathogenic or suspected pathogenic TTN variant localized in a metatranscript-only exon. The phenotypic diagnosis of myopathy was done in the antenatal period, at birth or in the first months of life.

Results
21 patients have a recessive titinopathy with 2 TTN variants in trans, 7 with 1 single variant in the metatranscript and 4 with 2 variants in the metatranscript.
For 7 patients from 4 families, a single TTN variant was identified leading to the suspicion of a dominant inheritance. Clinically they showed signs of prenatal immobility (arthrogryposis, adduct thumb, feet deformities). MRI analysis identified a specific pattern of muscle damage in these patients: all-or-none changes, porcelaine-like texture in Gluteus maximus, triceps, thigh and sometimes tibialis anterior), supporting the identification of a new congenital dominant titinopathy phenotype. The patients do not show major cardiac involvement, however respiratory involvement may be an important criterion in the management of these patients.

Interpretation
This study reinforces the genotype-phenotype correlations of congenital titinopathies due to mutations in metatranscript-only exons and allowed the identification of a new congenital dominant titinopathy phenotype.



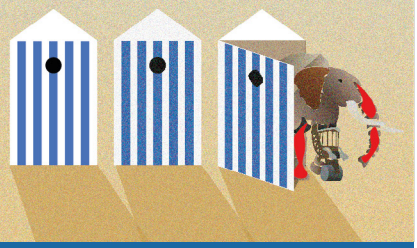
COMMUNICATIONS ORALES MIXTES
Autre myopathie héréditaire (mito, myofibrillaire…)

Geoffroy JULIEN[1]
Pr Tiffreau[2], *Pr Chapon*[3]

1. CHU de Caen
2. SFM
3. SOFMER

Myopathies myofibrillaires : Impact fonctionnel et qualité de vie

Introduction : Les myopathies myofibrillaires (MMF) constituent un groupe de myopathies rares, défini par une myopathologie commune (agrégats protéiques et une désorganisation myofibrillaire). Si la clinique est désormais bien décrite pour les principaux gènes, l'histoire naturelle et fonctionnelle l'est moins. La littérature est pauvre également concernant l'impact des MMF sur la qualité de vie. Cette étude vise à mieux comprendre l'histoire naturelle des MMF et son impact sur la QDV.
Méthode : Étude rétrospective des données cliniques, paracliniques et fonctionnelles sur 127 patients atteints de MMF en lien avec mutation de gène déjà associés à une MMF, suivis entre 2010 et 2022 dans 7 centres de référence/ compétence en France. Passation de questionnaires MIF, ACTIVLIM, QoLgNMD. Analyses de QDV en sous-groupes phénotypiques par test de Student ou Wilcoxon-Mann-Whitney, études de corrélations entre sous-scores de QoLgNMD et ACTIVLIM, entre sous-scores de QoLgNMD et MIF.
Résultats : Description de l'histoire naturelle clinique et fonctionnelle des entités. Qualité de vie bonne ou excellente dans 50% des cas. Altération significative des dimensions de QDV en lien avec l'atteinte axiale et proximale. Pas de différence de QDV en lien avec l'atteinte cardiaque ou respiratoire évidente. Corrélation entre QDV, autonomie et limitations d'activité. Importance de la prise en rééducation précoce axiale et proximale et du suivi psychologique des patients.
Proposition d'un livret d'auto-rééducation pour les patients, d'un guide d'orientation diagnostique et de recommandations de prise en charge et suivi pour neurologues et MPR.
Discussion : Importance de redéfinir les contours du concept. Intérêt d'une étude prospective avec recueil standardisé des données sur les aspects fonctionnels. Intérêt d'analyses multivariées ultérieures sur les facteurs influençant la qualité de vie dans les MMF. Intérêt d'un registre clinique, paraclinique et fonctionnel international.



COMMUNICATIONS ORALES
SESSIONS PARALLÈLES 4

Vendredi 17 Novembre
12h00-13h00

COMMUNICATION ORALE - SESSIONS PARALLÈLES 4
Physiopathologie / Vieillissement

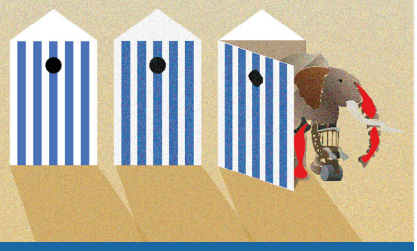
Hortense DE CALBIAC[1,2]

Sebastian Montealegre[1], *Marjolène Straube*[1,2], *Hugo Debruge*[1,2], *Loïc Chentout*[1,2], *Sorana Ciura*[3], *Apolline Imbard*[4], *Edouard Le Guillou*[4], *Anca Marian*[3], *Nicolas Goudin*[5], *Laure Caccavelli*[1,2], *Sylvie Fabrega*[6], *Arnaud Hubas*[7], *Peter van Endert*[1,8], *Nicolas Dupont*[1], *Julien Diana*[1], *Edor Kabashi*[3], *Pascale de Lonlay*[1,2]

1. Université Paris Cité, INSERM, CNRS, Institut Necker Enfants Malades, F-75015 Paris, France
2. Reference Center of Inherited Metabolic Diseases, Hôpital Universitaire Necker-Enfants Malades,, AP-HP, Institut Imagine, Filière G2M, MetabERN, F-75015, Paris, France
3. Translational Research for Neurological Diseases, Institut Imagine, INSERM UMR 1163, Université Paris Cité, F-75015, Paris, France
4. Metabolic biochemistry, Hôpital Universitaire Necker-Enfants Malades, AP-HP, Institut Imagine, Filière G2M, MetabERN, Université Paris Cité, F-75015, Paris, France
5. Cell Imaging & flow cytometry core facilities, Structure Fédérative de Recherche Necker, INSERM US24/CNRS UMS3633, F-75015, France
6.Platform, Structure Fédérative de Recherche Necker, F-75015, Paris, France
7.Genetics and Molecular Biology, Laboratoire de culture cellulaire, Hôpital Universitaire Cochin, AP-HP, F-75014, Paris, France
8. Service Immunologie Biologique, AP-HP, Hôpital Universitaire Necker-Enfants Malades, F-75015, Paris, France

Abnormal autophagy is a critical mechanism in TANGO2-related rhabdomyolysis

Patients with pathogenic variants in the TANGO2 gene suffer from severe and recurrent rhabdomyolysis (RM) episodes precipitated by fasting. Since starvation promotes autophagy induction, we wondered whether TANGO2-related muscle symptoms result from autophagy insufficiency to meet cellular demands in stress conditions. Autophagy functioning was analyzed in vitro, in primary skeletal muscle cells from TANGO2 patients in basal and fasting conditions. In addition, we developed a tango2 morphant zebrafish model to assess the effect of tango2 knockdown (KD) on locomotor function and autophagy efficiency in vivo. We report that TANGO2 mutations are associated with decreased LC3-II levels upon starvation in primary muscle cells. In zebrafish larvae, tango2 knockdown induces locomotor defects characterized by reduced evoked movements which are exacerbated by exposure to atorvastatin, a compound known to cause RM. Importantly, RM features of tango2 KD are also associated with autophagy defects in zebrafish. Calpeptin treatment, a known activator of autophagy, is sufficient to rescue the locomotor function and improves autophagy in zebrafish. LC3-II levels of primary muscle cells of TANGO2 patients are also ameliorated by calpeptin treatment. Overall, we demonstrate that TANGO2 plays an important role in autophagy, and that autophagy efficiency is critical to prevent RM, thus giving rise to new therapeutic perspectives in the prevention of these life-threatening episodes in the context of TANGO2 pathology.



COMMUNICATION ORALE - SESSIONS PARALLÈLES 4
Thérapie

Margaux MELKA[1]
Mathilde Beaufils[1*], *Julie Brocard*[1], *Clement Benoit*[2], *Nagi Debbah*[2], *Kamel Mamchaoui*[3], *Norma B. Romero*[4], *Anne Frédérique Dalmas-Laurent*[5], *Susana Quijano-Roy*[6], *Julien Fauré*[1,2], *John Rendu*[1,2*], *Isabelle Marty*[1*]

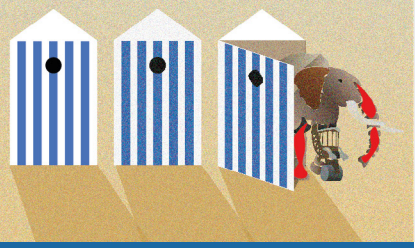
1. Univ. Grenoble Alpes, INSERM, U1216, CHU Grenoble Alpes, Grenoble Institut Neurosciences, Grenoble, France.

Mutation independent CRISPR/Cas9-induced allele deletion results in vitro in a functional benefit for dominant RYR1 mutation

The Ryanodine Receptor Type 1 (RyR1) is a calcium channel that plays a pivotal role in the contraction of skeletal muscle cells. A multitude of mutations in the gene encoding this channel have been identified as causative factors in a group of rare myopathies, collectively referred to as «RyR1-related myopathies.» These conditions manifest as muscle weakness of varying degrees of severity in affected individuals. Despite ongoing research, there is currently no curative treatment available for these disorders. One of the primary challenges in developing gene therapy for these conditions is the extensive number of mutations found in the RYR1 gene, as well as their widespread distribution throughout the gene. In addition, gene replacement therapy is not a viable option for RYR1 due to its large size.

In light of these challenges, we propose a versatile approach aimed at rectifying RyR1 calcium release, irrespective of the specific patient mutation. Our methodology involves the targeted deletion of the pathogenic allele, enabled by the use of CRISPR-Cas9 technology. For the proof-of-principle, we concentrated our efforts on a dominant mutation identified in a French family afflicted with Central Core Disease. Our approach entailed the design of a pipeline to select the most effective guide RNAs for targeting the pathogenic allele. Subsequently, we transduced immortalized myoblasts derived from the patient using lentiviruses expressing both Cas9 and the selected guide RNA. Throughout the course of our study, we assessed the efficacy of the treatment at the DNA, RNA, and functional levels.

Our findings represent the first successful application of genome editing techniques for the treatment of RyR1-related myopathies. Given that our approach is applicable to any dominant pathogenic variant, we intend to continue our research using animal models.



COMMUNICATION ORALE - SESSIONS PARALLÈLES 4
Développement / Cellules souches / Régénération musculaire

Stefano TESTA[1]
E. Fornetti[2], *F. De Paolis*[3], *D. Seliktar*[4], *F. Magdinier*[1], *S. Cannata*[3], *C. Gargioli*[3]

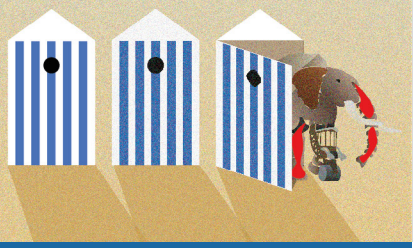
1. Aix-Marseille Univ-INSERM, MMG, 13005 Marseille, France
2. Center for Life Nano and Neuro Science, Istituto Italiano di Tecnologia (IIT), Rome, Italy
3. Department of Biology, Rome University Tor Vergata, Rome, Italy
4. Department of Biomedical Engineering, Techion Institute, Haifa, Israel

Design, development and characterization of an innovative extrusion-based 3D bioprinting system for Skeletal Muscle Tissue Engineering applications

Over the past two decades, 3D bioprinting has emerged as a valid and reliable tool for skeletal muscle tissue engineering applications. Among the different bioprinting techniques, the one based on extrusion has proven to be the most suitable for reproducing the architecture of skeletal muscle tissue. In fact, the continuously extruded printing fiber can be specifically organized in parallel lines, layer upon layer, recreating the organization of muscle tissue. Furthermore, the extrusion mechanism forces the orientation of cells and scaffold molecules along the printing axis, promoting the organization of the resulting myotubes into aligned bundles.

The key concept of this technique is “printability”, a combination of qualities that the biomaterial chosen for the bioink must possess and that is often related to poor biological compatibility. Nowadays, the most adopted solution to this problem is the use of a combination of two different biomaterials, one suitable for the machine and one for the cells, a strategy that has proven effective, despite revealing limitations in the results, especially in vivo.

Here we report the multi-step process culminating in the design and development of a novel extrusion 3D bioprinting system capable of using a cell-friendly biomaterial (PEG-fibrinogen) as the unique component of the bioink. Different bioprinting systems will be illustrated, highlighting the strengths and weaknesses of each. Subsequently, the new bioprinting system will be presented demonstrating: i) its ability to generate highly organized muscle constructs in vitro; ii) the ability to restore volumetric muscle damage when implanted in mice, as revealed by the presence of adequately organized, vascularized and innervated newly formed muscle tissue.



COMMUNICATION ORALE - SESSIONS PARALLÈLES 4
Génétique / Omique

Amélie VERGNOL[1]
E. Batsché[2], *E. Allemand*[3], *M. Traoré1, S. Falcone*[1]*and *F. Piétri-Rouxel*[1]

1. Sorbonne Université, Inserm, Institut De Myologie, Centre De Recherche En Myologie F-75013 - Paris, France
2. Sorbonne Université, CNRS, Institut de Biologie Paris-Seine (IBPS) - Paris, France
3. Inserm, U1163, Institut Imagine - Paris, France

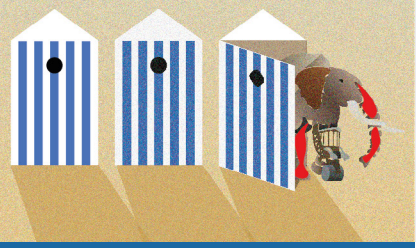
Orchestration of CaVβ1 expression in adult and embryonic muscle: exploring the role of novel isoforms in neuromuscular development

CaVβ1, encoded by Cacnb1 gene, exists as several transcript variants in skeletal muscle. Our recent work demonstrates CaVβ1D as the constitutive adult isoform, localized with CaVα1 at the triad. On the other hand, we show that CaVβ1E and CaVβ1A are expressed at late embryogenesis and peri-natal stages. Interestingly, our results revealed the existence of another undescribed CaVβ1 isoform: at early embryogenesis stages (E12.5), Cacnb1 exon 7A is excluded leading to a premature stop codon in exon8 and giving rise to the Cacnb1_early mRNA. In addition, we were able to show Cacnb1_early expression at protein level. Between E12.5 and E16, a progressive inclusion of exon7A leads to a gradual switch toward adult Cacnb1 mRNAs. These results support the existence of a new CaVβ1 isoform, expressed early during embryogenesis and for which function remains to be characterized.

In adult muscle, the re-expression of these embryonic CaVβ1E and/or CaVβ1A isoform(s) plays a crucial role in muscle mass homeostasis when electrical activity is impaired by preventing loss of muscle mass. We showed that both the embryonic CaVβ1E, CaVβ1A and the newly discovered CaVβ1_early transcripts begin at exon1 while the mRNA of the adult constitutive isoform CaVβ1D begins at exon3. We found that the expression of these isoforms derives from the activation of two distinct promoters at exon1 and exon3, respectively. Finally, we showed that the epigenetic marks H3K4me3 and H3K9ac, characteristics of active promoters, are increased at exon1 and reduced at exon3 following denervation. This suggests that the exon1/exon3 promoter switch induced by denervation can be regulated through the restoration of an embryonic epigenetic program.

These results bring insights on the mechanism behind the induction of embryonic CaVβ1 isoform expressions in adult skeletal muscle after impaired electrical activity and rise questions regarding the role of CaVβ1 isoforms both in embryonic and adult skeletal muscles.

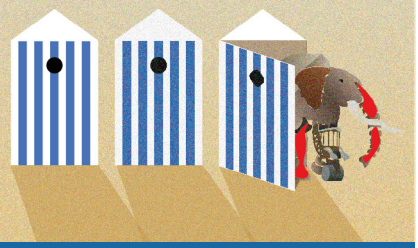
POSTERS



LISTE DES POSTERS

#	GROUPE	NOM	PRÉNOM	TITRE DE L'ABSTRACT
P59*	Groupe 3	ANDRADE	Ricardo J.	Noninvasive quantification of elastic anisotropy factor by steered ultrasound pushing beams: towards a novel imaging biomarker of muscle health
P35	Groupe 1	AUTHIER	François-Jérôme	Myological evaluation of patients with post-acute COVID-19 syndrome
P2*	Groupe 2	BABARIT	Candice	Activation précoce de la voie de réparation/ stabilisation du réseau membranaire dans la maladie de Pompe
P4*	Groupe 2	BELOTTI	Edwige	The histone variant H2A.Z is required for DNA repair in muscle fibers and prevents premature aging
P48*	Groupe 2	BENARROCH	Louise	Cellular and genomic features of myo-converted fibroblasts, an alternative cellular model to myoblasts
P61*	Groupe 3	BENOIST	Marion	Mechanosensitive clathrine platforms regulate YAP/TAZ signaling.
P78*	Groupe 4	BERLING	Edouard	Développement de Biomarqueurs Digitaux Permettant l'Auto-évaluation à Distance des Patients Atteints de Myasthénie Généralisée : Preuve de Concept
P1	Groupe 1	BIGOT	Anne	Myogenic and non-myogenic cellular models to study neuromuscular diseases
P63	Groupe 3	BIONDI	Olivier	Exercise-specific effects on the motor performance, glycaemia regulation and muscle phenotype of a mouse model of Limb-Girdle Muscular Dystrophy R1 (Calpainopathy)
P3*	Groupe 1	BLEUZEN	Anaïs	Human engineered skeletal muscles derived from iPSC for the modeling of neuromuscular disorders and the development of a high-throughput screening cellular platform
P6	Groupe 2	BOHM	Johann	DPAGT1 mutations in limb-girdle congenital myasthenic syndrome (LG-CMS) associated with tubular aggregates and ORAI1 hypoglycosylation
P8*	Groupe 2	BON	Émeline	Flunarizine influences transcriptome expression in spinal muscular atrophy
P27	Groupe 1	BONCOMPAIN	Gaëlle	Adaptability of the Golgi-dependent protein secretory routes
P5*	Groupe 1	BOUCHE	Axelle	Intracellular autofluorescence allows the isolation of functional human MuRC subpopulations with distinct stem cell states.
P7*	Groupe 1	BOUCHEREAU	Wilhelm	Dysregulation of myogenesis by chronic inflammation
P10*	Groupe 2	BOURAGBA	Dounia	Human muscle cell in Dysferlinopathy

*Éligible pour le prix du meilleur Poster



LISTE DES POSTERS

#	GROUPE	NOM	PRÉNOM	TITRE DE L'ABSTRACT
P89*	Groupe 3	BOURGUIBA	Aly	Unraveling the role of GDF5 therapeutic potential in Amyotrophic Lateral Sclerosis
P107*	Groupe 3	BOUVET	Marion	Innovative injectable and porous hydrogel as support for striated skeletal muscle tissue engineering.
P65*	Groupe 3	BOWEN	Maximilien	Application of a force-velocity-endurance model to in situ muscle evaluation in mouse model
P91*	Groupe 3	BRUGE	Céline	Identification of bazedoxifene for the treatment of LGMD R2 by high throughput screening
P58	Groupe 4	CANCES	Claude	JEWELFISH : tolérance, pharmacodynamie et données d'efficacité exploratoires dans une population de patients atteints d'amyotrophie spinale (SMA) déjà traitée, recevant risdiplam - analyse à 24 mois
P93*	Groupe 3	CARLIER	Andréa	Pan-therapy, CRISPR/Cas13-mediated, for Centronuclear myopathies by targeting DYNAMIN 2
P12*	Groupe 2	CASTELLANO	Léa	NuMA1 promotes microtubule organisation and controls myonuclear spreading and dynamics in skeletal muscle
P9*	Groupe 1	CERVERA	Chloé	Étude de l'évolution d'une lésion musculaire radio-combinée sur modèle de rat
P14*	Groupe 2	CHENANE	Linda	Deciphering the Link Between Interferon Stimulated Genes and Regeneration by Spatial Transcriptomics
P80	Groupe 4	CHOLLET	Grégory	Safety and tolerability of zilucoplan in RAISE-XT: A multicenter, open-label extension study in patients with myasthenia gravis
P11*	Groupe 1	CICCIARELLO	Delia	PHF2 Demethylase controls muscle stem cell fate modulating lipid droplets turnover
P67	Groupe 3	CIENIEWSKI-BERNARD	Caroline	Impact of proteotoxic stress on αB-crystallin partition, post-translational modifications, and interaction with desmin intermediate filaments protein
P82	Groupe 4	CIUMAS	Mariana	Étude pharmacodynamique de non-infériorité comparant les injections sous-cutanées d'efgartigimod pH20 avec les perfusions intraveineuses d'efgartigimod : résultats de l'étude de phase 3 ADAPTsc
P16*	Groupe 2	CLERC	Zoé	Development of molecular tools for fast-motorneuron-specific RNA isolation
P69	Groupe 3	COIRAULT	Catherine	A-type lamins are crucial to preserve chromatin states during mechanical loading in skeletal muscle

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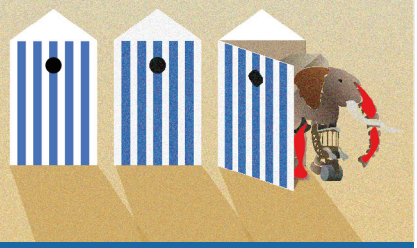

LISTE DES POSTERS

#	GROUPE	NOM	PRÉNOM	TITRE DE L'ABSTRACT
P88	Groupe 4	COSSEE	Mireille	Le mosaïcisme confiné au placenta, un piège dans le diagnostic prénatal des dystrophinopathies : à propos d'un cas
P18*	Groupe 2	CRISOL	Barbara	Effects of aging and sex-difference on the muscle secretome
P71*	Groupe 3	DABADIE	Carole	Striated skeletal muscle resistance to metastasis: understanding the molecular and cellular mechanisms
P73*	Groupe 3	DARGAR	Tanushri	Decoding the Contribution of Microtubule Network Organization in Cardiac Muscle Cell Functioning
P50*	Groupe 2	DE FERAUDY	Yvan	Myocapture: exome sequencing in undiagnosed congenital myopathies reveals new genes and expand the clinical phenotypes associated with known myopathy genes
P60*	Groupe 4	DE FERAUDY	Yvan	Projet préfigurateur DEPISMA : étude de faisabilité du dépistage néonatal de l'amyotrophie spinale infantile en France
P52*	Groupe 2	DE PONTUAL	Laure	Deciphering the mechanisms of CTG repeat contractions induced by an inhibitor of histone deacetylase in myotonic dystrophy type 1
P54*	Groupe 2	DEBBAH	Nagi	Classifying RyR1 Variants
P90	Groupe 4	DELAGE	Erwan	Robust preclinical data support development of DYNE-251 as a potential treatment for individuals with DMD mutations amenable to exon 51 skipping
P102	Groupe 4	DELAGE	Erwan	Preclinical Data Support the Initiation of the ACHIEVE Trial of DYNE-101 in Individuals with Myotonic Dystrophy Type 1 (DM1)
P62	Groupe 4	DELAUNAY	Elise	Developing a digital physical exercise solution for people living with neuromuscular disease: results from a co-creation process
P64	Groupe 4	DELAUNAY	Elise	Interim results from the ongoing respond study evaluating nusinersen in children with spinal muscular atrophy previously treated with onasemnogene ABEPARVOVEC
P13*	Groupe 1	DELLA GASPERA	Bruno	Mef2c labels a population of myonuclei at muscle tips during limb development
P56*	Groupe 2	DIOP	Guillaume	Identification of chemical factors modulating CTG repeat instability in Myotonic Dystrophy type 1
P75	Groupe 3	DUPONT	Olivier	Roles of the two STIM2 isoforms in human myotube formation and function

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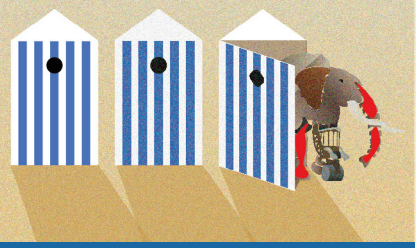

LISTE DES POSTERS

#	GROUPE	NOM	PRÉNOM	TITRE DE L'ABSTRACT
P20*	Groupe 2	EMERIT	Andréa	Muscle atrophy induced by chronic activation of ALK5/TGFbRI signaling in adult mouse skeletal muscle is associated with downregulation of polyamine biosynthesis pathway
P43	Groupe 1	EVANGELISTA	Teresinha	Suivi histologique et clinique à long terme de deux patients LOPD naïfs de traitement
P77	Groupe 3	FALCONE	Sestina	CaVđA and CaVđE embryonic isoforms in adult skeletal muscle, a Mbnl1 related-expression
P51*	Groupe 1	FERNANDEZ-EULATE	Gorka	Variabilité phénotypique et histoire naturelle de la myopathie avec excès d'autophagie liée à l'X (XMEA)
P22	Groupe 2	FESSARD	Aurélie	Kinetics of skeletal muscle alterations in a mouse model of sepsis
P95	Groupe 3	FORAND	Anne	Assessment of cardiac structure and function in a Dys-/-;Utr-/- mouse model of DMD treated with long term dystrophin replacement therapies.
P15*	Groupe 1	FOURGEAUD	Mélanie	Orai3 and its partner AHNAK2 regulate the activation of human skeletal muscle stem cells in vitro
P37*	Groupe 1	GALLAY	Laure	Myosite focale, approfondissement du cadre nosologique
P17*	Groupe 1	GARCIA	Pauline	H3K9 methyltransferase SETDB1 loss in post-mitotic myofibers perturbs muscle stem cell function during muscle regeneration
P19	Groupe 1	GICQUEL	Evelyne	Lipid metabolism is disrupted in mouse and human models of FKRP deficiency, and rescued after FKRP gene transfer
P97*	Groupe 3	GINESTE	Charlotte	Testing tamoxifen as a potential therapeutic approach for recessive RYR1-related myopathy
P39	Groupe 1	GITIAUX	Cyril	Myosites de chevauchement à début pédiatrique : description clinique et histopathologique d'une cohorte monocentrique
P24	Groupe 2	GODARD-BAUCHE	Stéphanie	Role of lamin A/C in the maintenance of AChR at the neuromuscular junction in Emery-Dreifuss muscular dystrophy
P26*	Groupe 2	GROSSI	Noëlla	Compensatory mechanisms involved in the pathophysiology of LGMD R2
P92	Groupe 4	GURIDI	Maitea	Integrated analyses of data from clinical trials of delandistrogene moxeparvovec in Duchenne muscular dystrophy
P94	Groupe 4	GURIDI	Maitea	EMBARK, a Phase 3 trial evaluating safety and efficacy of delandistrogene moxeparvovec in DMD: Study design and baseline characteristics

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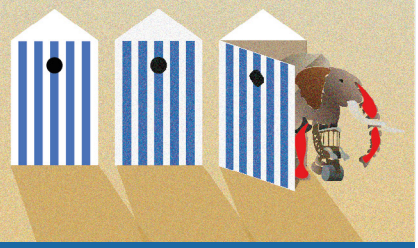

LISTE DES POSTERS

#	GROUPE	NOM	PRÉNOM	TITRE DE L'ABSTRACT
P79	Groupe 3	GYENGE	Melinda	Development of prediction model to identify DM1 individuals at higher risk of requiring non-invasive ventilation
P99	Groupe 3	HOCH	Lucile	Pathological modeling of Glycogen Storage Disease type III with CRISPR/Cas9 edited human pluripotent stem cells
P66	Groupe 4	HOGREL	Jean-Yves	Test-retest reliability and associations of some functional tests for the follow-up of patients with SMA
P68	Groupe 4	JAN-LAFAGE	Nicolas	Actualisation des données groupées de tolérance issues du programme de développement clinique de risdiplam dans l'amyotrophie spinale (SMA)
P21*	Groupe 1	JOMARD	Charline	Influence of sex / ovarian cycle on skeletal muscle regeneration in a mouse model of lengthening contraction-induced injury
P96	Groupe 4	KERTING	Catherine	ENVISION, a Phase 3, randomized trial evaluating the safety and efficacy of delandistrogene moxeparvovec in Duchenne muscular dystrophy: Study design
P98	Groupe 4	KERTING	Catherine	ENVOL, a Phase 2, open-label trial evaluating the safety and expression of delandistrogene moxeparvovec in Duchenne muscular dystrophy: Study design
P81	Groupe 3	KOENIG	Stéphane	Characterization of skeletal muscles from STIM1L KO mice
P45	Groupe 1	LAFORÊT	Pascal	104-week efficacy and safety of cipaglucosidase alfa plus miglustat in ambulatory patients with Pompe disease: a Phase III open-label extension study (ATB200-07)
P83*	Groupe 3	LAIR	Benjamin	Common mouse models of chronic kidney disease are not associated with cachexia
P28	Groupe 2	LAPORTE	Jocelyn	Differential impact of ubiquitous and muscle dynamin 2 isoforms in muscle physiology and centronuclear myopathy
P85*	Groupe 3	LAUBRY	Loann	STIM1 and STIM1L in skeletal muscle: central regulators of calcium circuitry.
P30*	Groupe 2	LECONTE	Marine	Dommages de l'ADN dans la dystrophie musculaire congénitale liée à LMNA
P47*	Groupe 1	LEFEUVRE	Claire	Les troubles de déglutition chez les patients adultes atteints de la maladie de Pompe : état des lieux du registre français
P23*	Groupe 1	LESSARD	Lola	Metabolic defects as a potential therapeutic target in Type I Myotonic Dystrophy

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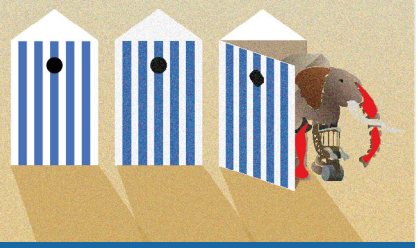

LISTE DES POSTERS

#	GROUPE	NOM	PRÉNOM	TITRE DE L'ABSTRACT
P53*	Groupe 1	LESSARD	Lola	The new missense G376V-TDP-43 variant induces late-onset distal myopathy but not ALS
P70*	Groupe 4	MANEL	Véronique	SUNFISH Parties 1 et 2 : efficacité et tolérance à 4 ans de risdiplam dans l'amyotrophie spinale (SMA) de types 2 et 3
P72	Groupe 4	MARCHADIER	Brice	RAINBOWFISH (NCT03779334) résultats préliminaires d'efficacité et tolérance du risdiplam dans une population pré-symptomatique de nouveaux nés atteints d'amyotrophie spinale (SMA)
P109	Groupe 3	MARQUIS	Mélanie	Impact de l'environnement matriciel 3D sur la biologie des cellules souches adultes humaines MuStem
P111	Groupe 3	MAYEUF-LOUCHART	Alicia	MuscleJ2: a rebuilding of MuscleJ with new features for high-content analysis of skeletal muscle immunofluorescence slides
P32	Groupe 2	MAZELIN	Laetitia	Chronic activation of ALK5/TGFbRI signaling in adult mouse skeletal muscle induces severe muscle wasting with concomitant impaired mitochondrial function
P55	Groupe 1	METAY	Corinne	FSHD1 atypique et duplication de CAV3 : quand un évènement moléculaire en cache un autre
P57*	Groupe 3	MILOT	Alicia	Arthrogryposis Multiplex Congenita in pediatric age: correlation between MUScular MRI and functional Evaluation (AMUSE), towards a biomechanical model
P46*	Groupe 2	MORETTA	Antonio	Proteomics Analysis of skeletal muscle Extracellular Matrix in dystrophic mice
P112	Groupe 3	MORIZUR	Lise	3D skeletal muscle constructs from human pluripotent stem cells for complex muscle disease modeling
P34	Groupe 2	NEFF	Laurence	Imaging of muscle perfusion of dystrophic mice in situ with laser-speckle contrast analysis
P36	Groupe 2	NICOLE	Sophie	Investigations of zebrafish lines with loss-of-function mutations in the genes encoding the skeletal muscle sodium channel Nav1.4 orthologs
P101*	Groupe 3	OSSENI	Alexis	Inhibition of HDAC6 improves muscle integrity in Duchenne Muscular Dystrophy mouse model
P103*	Groupe 3	OZTURK	Teoman	Restricting p38 MAPK activity in human MuSCs from their niche withdrawal to their ex vivo expansion is a key factor to preserve their therapeutic potential

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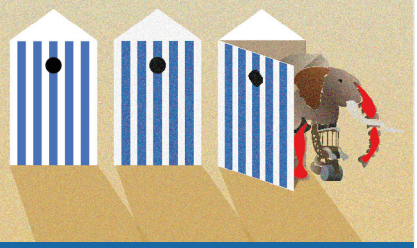

LISTE DES POSTERS

#	GROUPE	NOM	PRÉNOM	TITRE DE L'ABSTRACT
P113*	Groupe 3	PALMIERI	Laura	Generation of pro-fibrotic human engineered contractile MYOtissues suitable for muscle function analysis and gene therapy screening in Duchenne Muscular Dystrophy
P38*	Groupe 2	PILLER	Elsie	Study of paraspeckles status and role in ALS muscle cells
P49	Groupe 1	PION	Emmanuelle	Towards a pangenomic strategy in mitochondrial disorders: a French cohort of 397 patients carrying nuclear gene defects
P114	Groupe 4	QUIJANO ROY	Susana	Évaluation gastro-intestinale dans l'amyotrophie spinale (SMA) : l'expérience des professionnels de santé en France
P25*	Groupe 1	RAUSCH DE TRAUBENBERG	Anna	Delineating primary cilia-mediated signaling pathway in the muscle satellite cell
P105*	Groupe 3	ROTA GRAZIOSI	Emmanuelle	High dose localized skeletal muscle irradiation: hedgehog pathway as a new therapeutic target?
P84	Groupe 4	SACCONI	Sabrina	Rozanolixizumab responder and minimal symptom expression rates in generalised MG: Pooled Phase 3 and extension studies
P104	Groupe 4	SACCONI	Sabrina	L'Observatoire national français de la DMFSH, un hub de projets collaboratifs
P40*	Groupe 2	SALMAN	Badih	Is GEMIN5 a key player of flunarizine's neuroprotection in spinal muscular atrophy?
P106	Groupe 4	SALORT-CAMPANA	Emmanuelle	Recommendations of an expert group for cardiac assessment of non-dystrophic myotonic adult patients treated with mexiletine
P74	Groupe 4	SARRET	Catherine	Evaluation longitudinale des maladies neuromusculaires pédiatriques par les MyoTools en pratique courante sur un centre de référence neuromusculaire.
P29*	Groupe 1	SITOLLE	Julie	Exploring TGFα and BMP signaling interactions during muscle cell fusion
P86	Groupe 4	SOLÉ	Guilhem	Perceptions and expectations of patients with myasthenia gravis in France: The SPOON Study
P108	Groupe 4	TARD	Céline	RevEal the burdeN on daily life for myotonic dyStrophy patients due to myotoniA: the ENSA survey
P42*	Groupe 2	TOUREL	Amandine	The implication of RyR1 in muscle cell homeostasy

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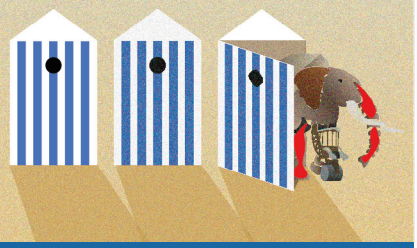

LISTE DES POSTERS

#	GROUPE	NOM	PRÉNOM	TITRE DE L'ABSTRACT
P76	Groupe 4	TRANCHAND	Audrey	FIREFISH Parties 1 et 2 : efficacité et tolérance à 4 ans de risdiplam dans l'amyotrophie spinale (SMA) de type 1
P44*	Groupe 2	TRAORÉ	Massiré	GDF5 as rejuvenating treatment for age-related neuromuscular failure
P100*	Groupe 4	VEREBI	Camille	Mosaïques germinales dans les Dystrophies Musculaires de Duchenne et Becker : étude de cohorte, synthèse de la littérature et conseil génétique associé
P31*	Groupe 1	VIRTANEN	Laura	Single-cell Spatio-Temporal profiling of striated muscle cell populations in Duchenne Muscular Dystrophy
P110	Groupe 4	WAHBI	Karim	Initiation and follow-up of mexiletine treatment in adult myotonic dystrophy patients: an expert opinion
P33	Groupe 1	WEISS-GAYET	Michèle	Restorative macrophage-derived RNAseT2 stimulates muscle stem cell fusion via an SLK/N-WASP/actin bundling dependent axis
P41*	Groupe 1	ZAIDAN	Louai	Reclassification de l'atteinte musculaire dans la sclérodermie systémique : Révélation de signatures histopathologiques uniques et de chevauchements avec les caractéristiques des myopathies inflammatoires

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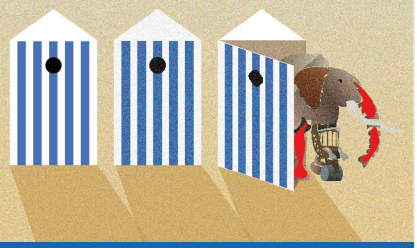


POSTER - P1 - GROUPE 1
Développement / Cellules souches / Régénération musculaire

Anne BIGOT
Mamchaoui K, Ohana J, Bensalah M, Negroni E, Butler-Browne G, Trollet C, Mouly V

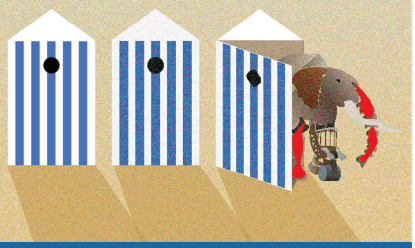
Sorbonne Université, Inserm, Institut de Myologie, Centre de Recherche en Myologie, Paris, France

Myogenic and non-myogenic cellular models to study neuromuscular diseases

The development of new therapeutic strategies to combat genetic diseases and the emergence of tailor-made therapies adapted to each mutation and each patient require the development of easy-to-use and suitable cellular models. Patient-derived muscle stem cells, also known as myoblasts, represent an ideal in vitro model that includes the genetic environment of each mutation. Human myoblasts can be isolated, but their use is restricted by their limited proliferative capacity, particularly in degenerative diseases. The Myoline platform of the Center of Research in Myology has developed a strategy to immortalize these human muscle cells.

Human muscle cells are immortalized by transduction of human telomerase (hTERT) and cyclin-dependent kinase 4 genes. These immortalized muscle cells retain their ability to differentiate and fuse into myotubes. We have generated more than 174 human immortalized myoblast lines including 36 neuromuscular diseases such as DMD, DM1, LGMDR2, OPMD, FSHD and control subjects. Whenever access to muscle biopsies is not possible, an alternative cellular model has been developed using human skin fibroblasts: the transduction with hTERT provides an extended proliferation, while the conditional expression of the myogenic factor MyoD drives the muscle conversion and differentiation into multinucleated myotubes. Several human fibroblast lines have thus been produced from controls and pathologies.

In recent years, Fibro-Adipogenic Progenitors (FAPs) have been described as key cell players during muscle homeostasis and in fibrotic conditions. To encourage research in this area, we are currently developing immortalized FAPs models isolated from muscles of patients with neuromuscular diseases. Our cellular models have the great advantage of being easy-to-use and allow rapid testing of therapeutic strategies. They are available to the academic international scientific community on a collaborative basis, and to private entities upon dedicated MTAs. The Myoline platform can also be solicited to set up new cellular models on request.



POSTER - P2* - GROUPE 2
Physiopathologie / Vieillissement

Candice BABARIT[1]
Sabrina Jagot[1], *Cindy Schleder*[1], *Johan Deniaud*[1], *Isabelle Leroux*[1], *Margarida Neunlist*[1], *Edoardo Malfatti*[2], *Pascal Laforêt*[3], *Karl Rouger*[1], *Marie-Anne Colle*[1]

1.Oniris, INRAE, UMR 703 PAnTher, 44307 Nantes, France
2. Université Paris Est Créteil, INSERM, U955 IMRB, APHP, Hôpital Henri-Mondor, Créteil, France
3. Service de Neurologie, CHU Raymond Poincaré, APHP, Garches, France; Université de Versailles Saint Quentin en Yvelines, Garches, France

Activation précoce de la voie de réparation/stabilisation du réseau membranaire dans la maladie de Pompe

La maladie de Pompe est due à un déficit en α-glucosidase acide (GAA), qui résulte en une accumulation de glycogène dans de nombreux tissus, en particulier le muscle squelettique. La pathogénie se caractérise par une accumulation de lysosomes, une dérégulation du flux autophagique et des anomalies mitochondriales à l'origine de dommages structuraux.

Afin de mieux comprendre les mécanismes physiopathologiques mis en jeu au cours de la maladie, nous avons réalisé une étude transcriptomique sur le muscle tibial antérieur de souris knock-out pour le gène de la GAA (Gaa-/-) âgées respectivement de 1.5, 4, 6 et 9 mois.

Nous montrons la présence d'une empreinte moléculaire précoce dès l'âge de 1.5 mois et peu évolutive au cours du temps chez les souris Gaa-/- : 414 gènes différentiellement exprimés ont été identifiés par rapport aux souris WT, dont seulement 42 montrent un changement de profil d'expression temporel. Un ensemble de gènes codant des protéines impliquées dans la voie de la réparation membranaire a notamment été identifié. Une surexpression de la dysferline, de l'annexine A2 et d'AHNAK2 a été démontrée en western blot dès l'âge de 1,5 mois chez les souris Gaa-/-. Une modification de leur localisation tissulaire est également observée. L'expression cytoplasmique de la dysferline semble refléter son implication dans la stabilisation du tubule-T face aux contraintes mécaniques causées par la surcharge en glycogène. La colocalisation de l'annexine A2 avec les lysosomes (LAMP1) souligne son rôle dans la stabilisation et la réparation de la membrane lysosomale. Quant à AHNAK2, sa colocalisation inattendue avec les autophagosomes (LC3) suggère un rôle dans le maintien de l'intégrité membranaire des autophagosomes, jusqu'alors jamais rapporté.

Ces résultats apportent de nouveaux éléments de compréhension sur la physiopathologie musculaire de la maladie de Pompe, en pointant notamment sur l'activation précoce du processus de réparation/stabilisation membranaire.

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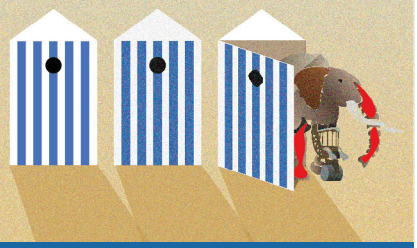

POSTER - P3* - GROUPE 1
Développement / Cellules souches / Régénération musculaire

Anaïs BLEUZEN
Ghislain Banos[1], Teoman Ozturk[1], Julien Mignot[1], Hélène Rouard[1,3], Frédéric Relaix[1,2,3] and Nathalie Didier[1]

1. Univ Paris Est Créteil, INSERM, EFS, IMRB, F-94010 Créteil, France
2. Ecole nationale vétérinaire d'Alfort, IMRB, F-94700 Maisons-Alfort, France
3. AP-HP, Hôpital Mondor, Service d'histologie, F-94010 Créteil, France

Human engineered skeletal muscles derived from iPSC for the modeling of neuromuscular disorders and the development of a high-throughput screening cellular platform

Rapid advances in gene therapy and drug discovery for the treatment of neuromuscular disorders have exacerbated the need to develop standardized and miniaturized cellular platforms reproducing the structural and functional characteristics of native skeletal muscle. Accordingly, important progress has been made in the field of skeletal muscle engineering, notably by moving from 2D models to more sophisticated 3D models, combining myogenic cells with biomaterials. For this purpose, human induced pluripotent stem cells (hiPSC) are of great interest, since they can be easily amplified, unlike muscle stem cells (MuSC), they give access to cells carrying various human disease genetic mutations and allow the engineering of isogenic models. However, to date, protocols for myogenic differentiation of hiPSC remain suboptimal, leading to poor enrichment of myogenic cells, and immature progenitor cells with reduced fusion capacity. Our lab has developed innovative hydrogels that greatly promote MuSC fusion and enable the engineering of 3D muscle constructs with highly mature and organized myofibers in vitro. Taking advantage of these hydrogels, we are now seeking to transfer this technology to the production of human 3D muscle from hiPSC. For this purpose, we successfully differentiated 3 hiPSC lines derived from 3 different cell types (Fibroblasts, PBMCs and myoblasts) into myogenic progenitors. In line with the literature, we obtained variable levels of myogenic cell purity, evidenced by the proportion of CD56, CD29, PAX7 and MYOD positive cells. Importantly, we observed that flow cytometric purification of CD56+ cells considerably enriched our cultures in myogenic progenitors, thus improving the fusion index. Lastly, we noticed that differentiation of hiPSC-derived myogenic progenitors on our hydrogels significantly improved their fusion efficiency and the maturation of the myofibers obtained. Given these encouraging results, our objective is to generate 3D human muscles to model neuromuscular disorders, such as Duchenne Muscular Dystrophy, and provide high-throughput screening platforms.

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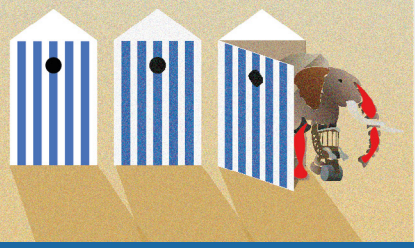

POSTER - P4* - GROUPE 2
Physiopathologie / Vieillissement

Edwige BELOTTI[1]

N. Lacoste[1], A. Iftikhar[2], T. Simonet[1], C. Papin[2], A. Osseni[1], N. Streichenberger[1], P-O. Mari[1], E. Girard[1], G. Giglia-Mari[1], S. Dimitrov[3], A. Hamiche[2], L. Schaeffer[1],

1. Institut NeuroMyoGène (INMG-PGNM), CNRS UMR5261, INSERM U1217, Faculté de Médecine Rockefeller, Université Claude Bernard Lyon I, 8 Avenue Rockefeller, 69373, Lyon Cedex 08, France
2. Institut de Génétique et Biologie Moléculaire et Cellulaire (IGBMC), CNRS, INSERM, Université de Strasbourg, 1 rue Laurent Fries, B.P. 10142, 67404 Illkirch Cedex, France
3. Institut for Advanced Biosciences (IAB), Inserm U1209, CNRS UMR 5309, Université Grenoble Alpes, 38042 Grenoble Cedex 9, France

The histone variant H2A.Z is required for DNA repair in muscle fibers and prevents premature aging

Skeletal muscle aging causes sarcopenia which is mainly characterized by muscle atrophy and neuromuscular junction dysfunction. It has recently been shown that histone variants gradually replace conventional histones during aging. However, the functional and physiological requirement of the replacement of conventional histones by histone variants during post-natal life remains poorly described. We have developed a conditional mouse model in which H2A.Z has been specifically invalidated in skeletal muscle fibers. We show that one-year-old H2A.Z mdKO muscles present all the features of premature aging. Investigation of the molecular mechanisms involved shows that H2A.Z is required to initiate DNA double-strand break repair by recruiting Ku80 at DNA lesions. This is achieved via specific interactions of Ku80 vWA domain with H2A.Z. Taken as a whole, our results demonstrate that H2A.Z containing nucleosomes act as a molecular platform to bring together the proteins required to initiate and process DNA double-strand break repair. H2A.Z is then essential to prevent the accumulation of DNA damage and mitochondrial dysfunction, thus preventing premature sarcopenia.

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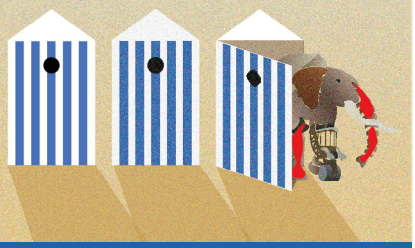

POSTER - P5* - GROUPE 1
Développement / Cellules souches / Régénération musculaire

Axelle BOUCHE
Diego Michel, Chloé Richard, Didier Hannouche, Thomas Laumonier

Cell Therapy & Musculoskeletal Disorders Lab, Department of Orthopedic Surgery, University Hospital and Faculty of Medicine, Geneva, Switzerland

Intracellular autofluorescence allows the isolation of functional human MuRC subpopulations with distinct stem cell states

Adult muscle stem cells (MuSC) are essential for skeletal muscle regeneration. The MuSC pool displays a continuum of cell states, with subpopulations more competent for self-renewal (Pax7-High) and others for proliferation and differentiation (Pax7-Low). We recently demonstrated that human muscle reserve cells (MuRC) are heterogenous for Pax7, with a Pax7-High subpopulation in a deeper quiescent state and a lower metabolic activity. These data suggest that Pax7-High MuRC may constitute an appropriate stem cell source for potential therapeutic applications in muscle diseases. Nevertheless, there is no tool to isolate viable human Pax7-High subpopulations.

In the present study, we evaluated if cellular autofluorescence (AF) can be used to isolate viable Pax7-High and Pax7-Low human MuRC. By flow cytometry, we observed that MuRC are highly autofluorescents as compared to proliferating myoblasts. MuRC were then sorted by flow cytometry based on their AF level (AF-High and AF-Low) and analyzed for Pax7 expression. We observed a significant increase in the proportion of Pax7-High cells in the MuRC-AF-High population (68% of Pax7-High) as compared to the MuRC-AF-Low population (35% of Pax7-High). Additionally, MuRC-AF-High significantly take a longer time to enter the cell cycle than do MuRC-AF-Low or myoblasts with respectively 5%, 31%, and 51% of EdU positive cells after 24h of reactivation. Moreover, MuRC-AF-High and MuRC-AF-Low displayed similar capacities to form myotubes after 48h in differentiation conditions as compared to myoblasts.

Together, these results demonstrate that cellular AF can be used to isolate viable MuRC subpopulations with distinct cell fates. In vivo experiments are currently underway to evaluate the therapeutic potential of MuRC-AFHigh and MuRC-AFLow subpopulations after transplantation in immunodeficient mice.

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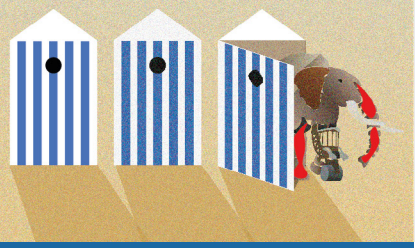


POSTER - P6 - GROUPE 2
Physiopathologie / Vieillissement

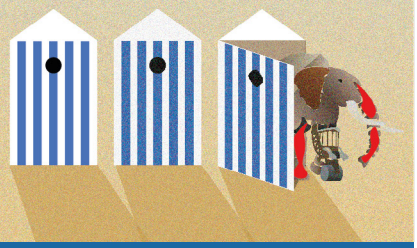
Johann BOHM[4]

Laura Vanden Brande[1,2], *Stéphanie Bauché*[1,3], *Laura Pérez-Guàrdia*[4], *Damien Sternberg*[5], *Roberto Silva-Rojas*[4], *Norma B. Romero*[1], *Jocelyn Laporte*[4], *Teresa Gidaro*[1,2]

1. Institut de Myologie, GHU La Pitié-Salpêtrière, Paris, France; (2) Assistance Publique Hôpitaux de Paris, Hôpital Armand Trousseau, Paris, France
3. Institut du Cerveau et de la Moelle épinière, ICM, Paris, France
4. Departement of Translational Medicine and Neurogenetics, IGBMC (Institut de Génétique et de Biologie Moléculaire et Cellulaire) Illkirch, France
5. Service de Biochimie Métabolique, Hôpital de la Pitié-Salpêtrière, Paris, France

DPAGT1 mutations in limb-girdle congenital myasthenic syndrome (LG-CMS) associated with tubular aggregates and ORAI1 hypoglycosylation

Limb-girdle congenital myasthenic syndrome (LG-CMS) is a genetically heterogeneous disorder characterized by muscle weakness and fatigability. The LG-CMS gene DPAGT1 codes for an essential enzyme of the glycosylation pathway, a posttranslational modification mechanism shaping the structure and function of proteins. In DPAGT1-related LG-CMS, reduced glycosylation of the acetylcholine receptor (AChR) restrains its localization at the neuromuscular junction (NMJ), and results in diminished neuromuscular transmission. LG-CMS patients also show tubular aggregates on muscle biopsies, but the origin and potential contribution of the aggregates to disease development are not understood.
Here we describe two unrelated LG-CMS patients with novel DPAGT1 mutations. Both presented with childhood-onset limb-girdle muscle weakness, abnormal electroneuromyogram (ENMG) findings with decremental response to repetitive nerve stimulations, and tubular aggregates on the muscle biopsies. Tubular aggregates can be seen in various muscle disorders and constitute the histopathological hallmark of tubular aggregate myopathy (TAM). TAM is caused by mutations in the Ca2+ buffer calsequestrin (CASQ1), the Ca2+ sensor STIM1, or the Ca2+ channel ORAI1, and involves skeletal muscle, bone, spleen, skin, and platelet anomalies. We illustrate that the tubular aggregates in our patients contain STIM1, calsequestrin, RyR1, and SERCA, and structurally conform to the aggregates observed in TAM. We also detected an abnormal ORAI1 glycosylation in the myofibers from our patients, establishing a physiopathological link between LG-CMS and TAM. Moreover, we treated our DPAGT1 patient with the acetylcholinesterase inhibitor pyridostigmine. We observed an amelioration of muscle force and function after an initial treatment period of 21 days and a stabilization of the condition after 6 months. Overall, we expand the mutation spectrum of LG-CMS, deliver insight into the formation of tubular aggregates in myasthenia, and provide quantitative data on the clinical effect of pyridostigmine on DPAGT1-related LG-CMS.



POSTER - P7* - GROUPE 1
Développement / Cellules souches / Régénération musculaire

Wilhelm BOUCHEREAU
Lola Lessard, Michèle Weiss-Gayet, Yseult Carbonara, Armelle Corpet, Patrick Lomonte, Bénédicte Chazaud

Institut Neuromyogène, Physiopathology and Genetics of the Neuron and Muscle

Dysregulation of myogenesis by chronic inflammation

After a muscle injury, inflammation regulates the regeneration process and eventually resolves itself. However inflammation can become chronic in myopathies. This impairs the regeneration process and eventually leads to progressive muscle loss. Dermatomyositis (DM) is an autoimmune disease characterised by muscle inflammation. In spite of the use of immunosuppressive drugs, a significant proportion of patients conserve muscle weakness. In addition, MuSC derived from DM muscle have an intrinsic proliferation and myogenesis impairment. This dysregulation seems to be linked to interferon (IFN) -signaling. Indeed, DM patients are characterised by a strong type I IFN signature. Inhibition of IFN-signaling through janus kinases inhibitors partially rescues the proliferation defect in vitro and improves the condition of DM patients.

It has been shown that IFN stimulation relocates the chaperone complex HIRA and its target histone 3 variant H3.3 to IFN-stimulated genes (ISG). In parallel, HIRA complex also accumulates in PML-nuclear bodies (PML-NB). In the mouse, deletion of HIRA during myogenesis in vitro and in vivo has been shown to inhibit the expression of muscle regulatory genes and impairs muscle regeneration.

Our hypothesis is that abnormal IFN stimulation of MuSC in DM patients induces loss of HIRA and H3.3 in myogenic genes and their relocalization to ISG. This would leads to persisting impairment of muscle regeneration and sustained inflammation. Investigation of the link between IFN, HIRA-H3.3 and myogenesis might uncover a novel epigenetic signalization that regulates muscle regeneration dysregulation in DM.

We are investigating the impact of IFN-stimulation on both MuSC derived from healthy controls and DM-patients. We analyse their proliferation, differentiation, the localization of HIRA in the nucleus, their transcriptome and the relocalization of H3.3 in the chromatin. We show that IFN stimulation impacts only weakly myogenesis, and that other pro-inflammatory signalizations might be the drivers of the defects observed in MuSC.

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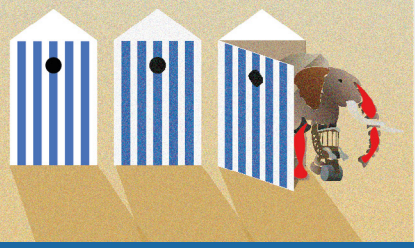

POSTER - P8* - GROUPE 2
Physiopathologie / Vieillissement

Émeline BON[1]
Delers P[1], Salman B[1], Sapaly D1, Adoux L[2], Letourneur F[2], Saintpierre B[2], Goulancourt R[3], De la Grange P[3], Lefebvre S[1]

1. UMRS_1124, T3S, UPCité, Paris, France
2. Plateforme Genom'ic, Institut Cochin, UPCité, Paris, France
3. GenoSplice technology, Paris Biotech Santé, Paris, France

Flunarizine influences transcriptome expression in spinal muscular atrophy

The Spinal Muscular Atrophy (SMA) is characterized by progressive loss of motor neurons and muscle atrophy. In SMA patients, Survival Motor Neuron 1 (SMN1) gene is mutated or deleted leading to a deficiency in the SMN protein. The SMN2 gene, a homologous gene of SMN1, produces low levels of SMN protein, and therefore partially compensate for the SMN1 mutations1.

Three innovative therapies increase SMN protein levels but improve patient motor symptoms to variable degrees2. A better understanding of disease mechanisms will help to better these therapies, especially for the low responder SMA patients. We have previously shown that flunarizine, known as a calcium channel blocker used in migraines and as a splicing modulator in cancer cells, improves survival and disease phenotype in the Taiwanese SMA mouse model3. To clarify the mode of action of flunarizine and find flunarizine-modulated cellular pathways, we performed mRNA- and micro-RNA-sequencing analyses in SMA patient fibroblasts and spinal cords of SMA mouse model. We are currently validating potential mRNA-microRNA pair(s) by RT-qPCR in spinal cord of flunarizine-treated control and SMA mice. Using murine NSC34 motor neuron-like cells to carry out microRNA-mimic transfections, RT-qPCR and immunodetection studies will allow us to understand their role in cellular functions link to cell survival and/or degeneration. Our study will uncover genes that can be tested in mouse models to modify SMA phenotype and identify new biomarkers in motor neuron diseases that are unmeet medical needs.

Références :
1 – Lefebvre S & al., Cell . 1995.
2 - Wirth B. & al., Annu Rev Genom Hum Genet 2020.
3 - Sapaly D & al., Sci. Rep. 2018.

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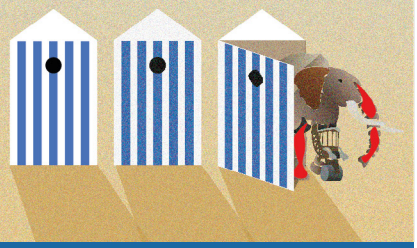

POSTER - P9* - GROUPE 1
Développement / Cellules souches / Régénération musculaire

Chloé CERVERA
Marco Valente, Laure Bobyk, Michel Gautier, Catherine Rousseau, Laure Barbier, Nathalie Guatto, Krisztina Nikovics, Anne-Laure Favier, François Sabine, Riccobono Diane

IRBA

Étude de l'évolution d'une lésion musculaire radio-combinée sur modèle de rat

Lors d'évènement radiologique, la situation peut engendrer des lésions associant une irradiation du corps entier à une blessure. Ces lésions radiocombinées sont connues pour leur impact sur la prise en charge des blessés en rendant les traitements de référence inadaptés.

Notre objectif est d'observer l'impact de l'irradiation sur le processus de régénération d'une lésion musculaire associée. Un modèle de lésion radio-combinée a été mis au point sur des rats Sprague-Dawley. L'étude a portée sur la comparaison de 4 groupes : contrôle, irradié (corps entier à 8 Gy équivalent à la dose létale 20), lésé (injection de 1 µg de notexine dans le muscle soléaire gauche) et lésé et irradié (radio-combiné). Des analyses moléculaires et histologiques de muscles soléaires congelé (isopentane) ont été réalisé à J7, J21 et J42.

L'étude macroscopique a montré des muscles plus fins et un poids plus faible pour les animaux radio-combinés, à respectivement 21 et 42 jours post-lésions par rapport à ceux du groupe lésé. Une analyse des coupes histologiques a montré des surfaces de section de fibre plus hétérogènes (marquage au WGA), un épaississement de la matrice extracellulaire (rouge sirius) et un infiltrat cellulaire au 42 ème jour (HPS). Le caractère inflammatoire de cet infiltrat a été confirmé par un immunomarquages des macrophages (CD68/CD206), qui montre une perturbation du processus inflammatoire dans le groupe radio-combiné. Ces observations sont également complétées par la variation de l'expression (RT-PCR) de marqueurs myogéniques (myogénine, MYOCHC) pour ce groupe par rapport au groupe lésé.

Ces données mettent en évidence une perturbation du processus myogénique par l'irradiation, avec des différences visibles à J21 et J42 entre les groupes lésé et radio-combiné. L'hypothèse d'un retard de régénération tissulaire sera approfondie par un suivi plus tardif ainsi que l'étude de la composante inflammatoire et des autres paramètres de la niche tissulaire.

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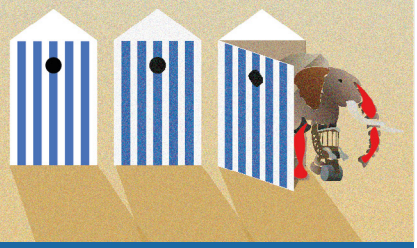

POSTER - P10* - GROUPE 2
Physiopathologie / Vieillissement

Dounia BOURAGBA
Mona Bensalah, Maria Kondili, Jessica Ohana, Alexis Boulinguiez, Elisa Negroni, Capucine Trollet, Anne Bigot and Vincent Mouly

Sorbonne Université, INSERM, Institut de Myologie, Centre de Recherche en Myologie, Paris, France

Human muscle cell in Dysferlinopathy

Limb Girdle Muscular Dystrophy R2 (LGMDR2) is an autosomal recessive muscular dystrophy caused by mutations in the DYSF gene leading to a loss or a severe reduction of dysferlin, a protein mainly known to be involved in muscle membrane repair. This leads to myofiber-necrosis, attenuated muscle regeneration and persistent inflammation with muscle loss and fat replacement. Moreover, literatures showed the involvement of dysferlin in vesicle trafficking.
Our lab has previously shown that human muscle cells isolated from control subjects release soluble secreted proteins through conventional secretory pathway but also packed into vesicles with, among others, dysferlin as a cargo. Taken together, we hypothesize that changes in the skeletal muscle secretome may contribute to the physiopathology observed in LGMDR2. Therefore, using a mass spectrometry-based label-free quantitative proteomic approach, we analyzed proteins secreted by immortalized myotubes from 6 healthy donors and 6 LGMDR2 patients. Results were analyzed using bio-informatic tools to highlight some specific pathways.
We focused on specific readouts that could explain the peculiar phenotype in LGMDR2, such as the massive fatty infiltration observed in this disease and underlined by our secretome and proteome analysis. We observed an accumulation of lipid droplets, the lipid storage organelles, in myotubes isolated from LGMDR2 patients. A Gene Set Enrichment Analysis of these proteomic data predicted a deregulation of mitochondrial-related pathways which are now under investigation.

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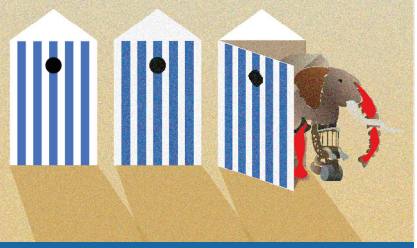

POSTER - P11* - GROUPE 1
Développement / Cellules souches / Régénération musculaire

Delia CICCIARELLO
Sandrine Mouradian, Agnes Duplany, Thomas Simonet, Laurent Schaeffer and Isabella Scionti

INMG-PGNM

PHF2 Demethylase controls muscle stem cell fate modulating lipid droplets turnover

Of date, one of the major questions regarding muscle stem cells metabolic status is to understand how metabolism can control muscle stem cell (MuSCs) fate transition from their quiescent to activated and differentiated state. MuSCs represent skeletal muscle resident stem cells required for muscle growth and regeneration upon injury. As all other cell type, MuSCs require energy to carry out all their specialized functions. However, energetic demands appear to be very different during MuSCs fate transition. Studies have shown that MuSCs fate transition is characterized by a shift in metabolic substrate utilization, a process that has been called metabolic reprogramming.

In this context, metabolites play a crucial role in the regulation of stem cell fates, serving not only as substrates for anabolic processes and for energy generation but also to directly influence epigenetic modifiers behavior, which control chromatin accessibility and downstream gene expression pattern. Recently, several studies have pointed out a link between lipid droplets (LDs) metabolism and stem cell function. Indeed, current evidences have demonstrated that lipid droplets abundance and turnover regulate muscle stem cells (MuSCs) fate choice. However, which are the upstream factors coordinating lipid droplet dynamics during MuSC fate are poorly investigated. Interestingly, epigenomic studies have shown that lipid accumulation results into severe changes in the methylation status of H3K9 and H3K4, highlighting a role for lysine demethylases in regulating lipid metabolism.

PHF2 is a demethylase functionally activated through a specific phosphorylation mediated by the protein kinase A (PKA), which is one of the metabolic sensor implicated into lipid metabolism. Indeed, studies have shown that PHF2 is implicated in the regulation of several cell differentiation programs, but there are no evidences on its involvement in MuSC fate choice. Here, we show that specific PHF2 ablation in MuSCs leads to lipid droplets accumulation in committed myocytes which impairs MuSCs regenerative capacity and self-renewal potential. Our results support the hypothesis that PHF2 might be crucial in regulating MuSCs fate, modulating the lipid droplet dynamics.

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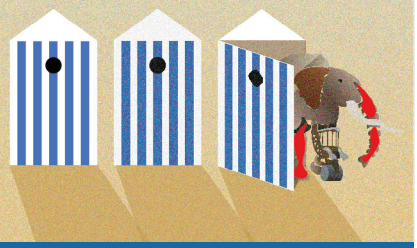

POSTER - P12* - GROUPE 2
Physiopathologie / Vieillissement

Léa CASTELLANO
Nathalie Couturier, Alireza Ghasemizadeh, Alexandre Janin, Rémi Mounier, Alexis Osseni, Jean-Luc Thomas, Stéphane Konig, Maud Freiden, Jessica Brunetti, Vincent Gache

NeuroMyoGène Institute - PGNM laboratory, CNRS UMR 5261 - INSERM U1315, Department of Basic Neurosciences, Geneva Medical Center

NuMA1 promotes microtubule organisation and controls myonuclear spreading and dynamics in skeletal muscle

Skeletal muscle consists in a bundle of thousands of post-mitotic multinucleated cells, called myofibres, in which myonuclei are evenly spaced and positioned at the periphery. This myonuclear positioning is driven by cytoskeleton and associated proteins and is required for proper myofibre function. In numbers of muscle diseases (i.e. myopathies), internalised and mispositioned myonuclei impair myofibre function, supporting the need to better understand the fundamental mechanisms that regulates myonuclei dynamics. We identified the microtubule-associated protein NuMA1 as an essential regulator of microtubule architecture and myonuclear spreading in the early phase of myotube formation.
Loss of NuMA1 alter myonuclear shape and positioning and we link this phenotype to a progressive accumulation of NuMA1 in the cytoplasmic compartment during muscle cell differentiation, that thus affect microtubule network orientation, especially at the vicinity of myonuclei, through the regulation of the nucleus-microtubule-organising center (nMTOC) integrity. NuMA1 is mainly localised inside myonuclei but it progressively accumulates in the cytoplasm during muscle cell differentiation. Finally, we investigate NuMA1 localisation in mdx muscles and prospect on the uses of NuMA1 as a marker of pathological myonuclei. Therefore, our results show that NuMA1 myonuclei content controls myonuclei motion through microtubule organisation and is a marker of pathological myonuclei inside myofibres. Altogether, our data identify a novel mechanism by which nuclear sequestration of a microtubule-associated protein allows to couple nuclear positioning and motion to muscle functionality.

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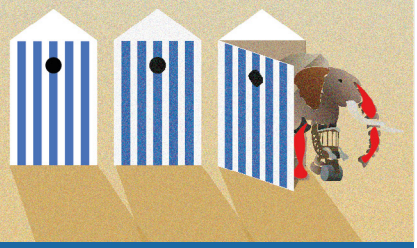

POSTER - P13* - GROUPE 1
Développement / Cellules souches / Régénération musculaire

Bruno DELLA GASPERA[1]
Cedrine Blavet[2], *Delphine Duprez*[2], *Frederic Charbonnier*[1] *and Christophe Chanoine*[1]

1. Faculté des Sciences Biomédicales et Fondamentales, Université de Paris-UMR INSERM 1124, Paris, France
2. Laboratoire de Biologie du Développement (LBD), CNRS-SU UMR 7622, INSERM ERL U1156, Institut Biologie Paris Seine (IBPS), Sorbonne Université (SU)

Mef2c labels a population of myonuclei at muscle tips during limb development.

In all vertebrate species, Mef2c transcripts have been detected in embryonic somites, albeit faintly in muscle cells, and strongly in the intersomitic region (della Gaspera et al, 2022, PMID: 35111756). Mef2c mRNA remains more specifically associated with cells between syndetome and myotome in chicken and mice. Mef2c transcripts have also been detected in cells at the edge of muscle masses in the head and hypaxial region in Xenopus, as well as in the hypaxial region of a cichlid fish, a teleost species. These expression data suggest that Mef2c is consistently transcribed in a specific cell population associated with muscle masses. RNA-sequencing datasets from chicken limb single-cells and mouse limb single-nuclei at developmental stages have identified Mef2C transcripts in muscle and also in dual-identity cells. These dual-identity cells, display a dual genetic program encompassing connective and skeletal muscle genes and preferentially fuse with myofibrils at muscle tips close to tendons, at the level of the future myotendinous junction (Esteves de Lima et al, 2021, PMID: 34158501). In chicken and mouse developmental limbs, Mef2c transcripts were enriched in myosin-positive myofibrils at muscle tips close to tendons, but also in associated-connective tissue fibroblasts. Mef2c protein was almost exclusively detected into myonuclei at muscle tips. Consequently, Mef2c protein is a promising nuclear marker of tip myonuclei. Functional experiments are underway to identify Mef2c involvement in myotendinous junction formation.

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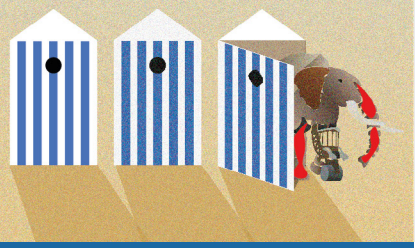

POSTER - P14* - GROUPE 2
Physiopathologie / Vieillissement

Linda CHENANE

J. Dal-Cin[1], C. Anquetil[1], D. Amelin[1], B. Tendrel[1], W. Bouchereau[3], A. Corpet[3], R. Mounier[3], P. Lomonte[3], B. Chazaud[3], Y.Allenbach[1,2], O. Benveniste[1,2]

1. Centre de Recherche en Myologie, UMRS 974, Institut National de la Santé et de la Recherche Médicale, Association Institut de Myologie, Sorbonne Université, Paris, France
2. Department of Internal Medicine and Clinical Immunology, Sorbonne Université, Pitié-Salpêtrière, Paris, France
3. Université Claude Bernard Lyon 1, CNRS UMR-5310, INSERM U-1217, Institut NeuroMyoGéne, Lyons, France

Deciphering the link between interferon stimulated genes and regeneration By spatial transcriptomics

Idiopathic inflammatory myopathies (IIM) are a group of rare, acquired myopathies. These diseases are classified using clinical, muscle pathology, and/or the presence of autoantibodies into: inclusion myositis (IMM), anti-synthetase syndrome (ASyS), immune-mediated necrotizing myopathy (IMNM), and dermatomyositis (DM). DMs are characterized by progressive symmetrical proximal myopathy, and skin manifestations. Interferon-stimulated genes (ISGs) are among the most up-regulated genes in DM, therefore, the interferon (IFN) signature is emerging as a diagnostic tool. Despite immunosuppressive treatments to extinguish the autoimmune reaction, most IIM patients sustain muscle atrophy and fat replacement of muscle tissue, leading to loss of muscle strength and handicap. Still, histological analysis shows that DM muscles exhibit continuous attempts of regeneration. It is widely admitted that inflammation is necessary during the first steps of regeneration. However, the link between inflammation and attempts of regeneration in DM muscles are not well understood. Using spatial transcriptomics on healthy and DM biopsies, we found an upregulation of both ISGs and genes related to regeneration/myogenesis in DM samples and, interestingly, an anticorrelated expression of these two groups of genes at tissular domains. These data suggest a potential negative effect of ISGs during regeneration.

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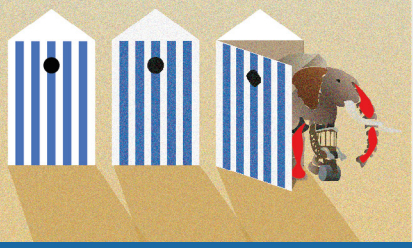

POSTER - P15* - GROUPE 1
Développement / Cellules souches / Régénération musculaire

Mélanie FOURGEAUD
Axel Tollance, Emma Sandoz, Stéphane Koenig, Maud Frieden

Department of Cell Physiology and Metabolism, University of Geneva

Orai3 and its partner AHNAK2 regulate the activation of human skeletal muscle stem cells in vitro

Skeletal muscle repair and maintenance rely primarily on the activation of quiescent muscle stem cells (MuSC). Upon activation, the skeletal MuSC re-enter the cell cycle and proliferate as myoblasts, which subsequently either differentiate and fuse to form new fibers, or return to quiescence to replenish the MuSC pool. Mechanisms underlying human MuSC activation and self-renewal remain poorly understood, largely due to the difficulty of monitoring these processes in humans. In our work, we used an in vitro model of human primary muscle cells where we can study the activation of stem cell-like cells called reserve cells (RC). We demonstrated that the activation of RC is promoted by the Ca2+ channel Orai3, but surprisingly, in a Ca2+-independent manner. Indeed, Orai3 downregulation decreased the ability of RC to activate in response to serum stimulation, while an Orai3 mutant protein not permeable to Ca2+ rescued RC activation. Moreover, Orai3 depletion was associated with a reduced RC population and an increased myotube differentiation after 48h. Proximity-dependent biotin identification (BioID) revealed a large scaffold protein, AHNAK2, as a new potential partner of Orai3. When downregulated, AHNAK2 demonstrated similar effects on RC activation and myotube differentiation than Orai3 knockdown. The downregulation of both Orai3 and AHNAK2 did not potentiate the effects suggesting a role in the same signaling pathway. Furthermore, we postulate that Orai3 and AHNAK2 may act either early during differentiation by promoting commitment to myotubes or play a role in the maintenance of RC quiescent state at later stages. These studies on Orai3 and AHNAK2 shall provide new insights into the molecular process that underlies human RC activation and quiescence. In addition, we found that dystrophin downregulation increases the expression of Orai3 and AHNAK2 suggesting that these proteins may be involved in the pathological mechanisms of Duchenne muscular dystrophy (DMD). Thus, our work shall open up a new understanding of MuSC dysregulation during the process of DMD.

*Éligible pour le prix du meilleur Poster

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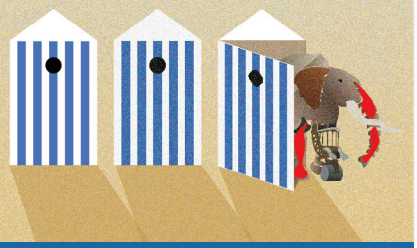
JOURNÉES DE LA SOCIÉTÉ FRANÇAISE DE MYOLOGIE
15 - 17 Novembre 2023 • Palais des Congrès - Atlantia



POSTER - P16* - GROUPE 2
Physiopathologie / Vieillissement

Zoé CLERC[1]
Laure Weill[1], *Sabrina Bendris*[1], *Perrine Delers*[1], *Delphine Sapaly*[1], *Bruno Della-Gaspera*[1], *Frédéric Charbonnier*[1], *Olivier Biondi*[2]

1. Laboratoire Environmental Toxicity, Therapeutic Targets, Cellular Signaling and Biomarkers, UMRS1124-T3S, Université Paris Cité, Faculté Des Sciences Fondamentales Et Biomédicales, Paris, France
2. Laboratoire de Biologie de l'Exercice pour la Performance et la Santé (LBEPS), UMR, Université d'Evry, IRBA, Université de Paris Saclay - Evry-Courcouronnes, France

Development of molecular tools for fast-motorneuron-specific RNA isolation

Amyotrophic Lateral Sclerosis (ALS) and Spinal Muscular Atrophy (SMA), are two different neurodegenerative diseases characterized by progressive muscle denervation, that can be fatal due to respiratory failure. In ALS, fast motorneuron (fMN) are mainly impaired, while in SMA both fast and slow MN (sMN) degenerate.

Submitting adult mouse models of ALS and SMA to a high-intensity swimming exercise, known to activate fMN, induces their specific neuroprotection in both diseases. Molecular mechanisms responsible for these cross pathological neuroprotective effects remain to be elucidated.
In this context we decided to develop two complementary approaches devoted to isolate mRNA specifically from the sensitive fMN.

The first consist on a cre recombinase dependant-serotype 9 Adeno associated virus (AAV9)-based expression of a tagged Poly-A Binding Protein (PABP) under the control of the Calcitonin related Polypeptide Alpha (Calca), a fMN marker. This adapted ctag-PAPERCLIP technique allows to immunoprecipitate mRNA from fMN in generated heterozygous Calca-cre ALS and SMA mouse models. We produced the pAAV-LSL-PABP3Flag and tested its cre-dependent expression in vitro and in vivo after encapsidation. However, tagged PABP expression was observed in non cre-expressing cells in both conditions leading us to design cre-specificity enhancing plasmids to improve the specificity of expression.

The second involves microdissection of the exercise-recruited MN by retrograde labelling. We investigated whether intramuscular injection of an activity-dependent trans-synaptic retrograde tracer, the nontoxic C-fragment of Tetanus toxin (TTC), could preferentially label viable fMN in animals subjected to our swimming protocol. However, the TTC failed in specifically labelling fMN subpopulation in swimming protocol subjected mice when compared to non-trained mice. Moreover TTC did not allow us to exclude degenerating MN when compared to Fluorogold, a retrograde, pan-motoneuronal, non-activity-dependent retrograde tracer in ALS mice.
Developing such molecular tools allowing specific and non-disrupting selection of fMN RNA could contribute to decipher molecular basis of the cross-pathological neuroprotective effect of exercise, a prerequisite for the development of new therapies.

Mots clés : Motor neuron disease, physical exercice, transcriptomic, retrograde tracer, adeno-associated virus.

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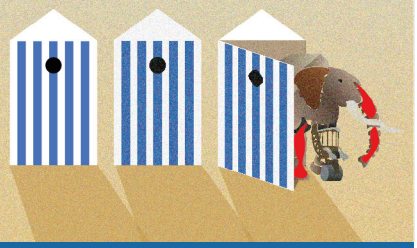

POSTER - P17* - GROUPE 1
Développement / Cellules souches / Régénération musculaire

Pauline GARCIA
Fany Agostini, Jade Ravent, Sidy Fall, Fabien Le Grand

Institut NeuroMyoGene (INMG-PGNM), CNRS/UCBL1 UMR5261 - Inserm U1315, Lyon, France

H3K9 methyltransferase SETDB1 loss in post-mitotic myofibers perturbs muscle stem cell function during muscle regeneration

Skeletal muscle's ability to regenerate is possible thanks to muscle stem cells (MuSCs) that will activate, proliferate and differentiate in order to form myofibers de novo. This regeneration process depends on intrinsic factors of MuSCs in addition to external cues derived from the cells in the skeletal muscle environment. However, the signaling interactions between the muscle fiber and its stem cell niche during regeneration is poorly understood. We decided to study the role of histone lysine methyltransferase (KMT) SETDB1 in this interdependent signaling during regeneration.

To address this, we generated a conditional mouse model that allows us to delete SETDB1, specifically in myofibers through the Acta1 promoter. Afterwards, we looked how MuSCs behaved during muscle regeneration in this model.

At first, ex vivo experiments using isolated myofibers cultured for 72 hours demonstrated an increase of MuSCs proliferation and a decrease of differentiation, suggesting a dysregulation of the MuSCs niche in absence of SETDB1 in myofibers. To confirm these data, in vivo experiments using partial Cardiotoxin injury in Tibialis Anterior (TA) show an increase of the number of MuSCs at 7 days post injury (dpi), along with a reduction of myofiber area in the regenerative part, suggesting a defect of regeneration in the absence of SETDB1 in myofibers. This higher number of MuSCs is also found at 14dpi, followed this time by an increase of myofiber area in the uninjured part of the TA. At 28dpi, cryosections show a complete regeneration but uninjured myofiber still display a bigger cross-sectional area compared to the control, demonstrating again that the loss of SETDB1 in myofibers will perturb the regenerative process.

In conclusion, our data show that the loss of SETDB1 in myofibers affects the muscle stem cell niche for effective regeneration, suggesting a perturbed signaling between MuSCs and myofibers during muscle regeneration.

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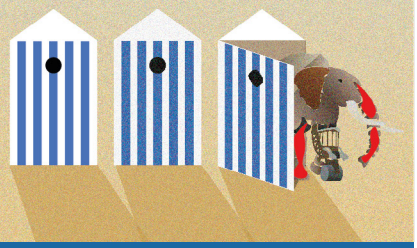

POSTER - P18* - GROUPE 2
Physiopathologie / Vieillissement

Barbara CRISOL
Julia Orio, Ludovic Gaut-Serey, Jessica Ohana, Maria Kondili, Nathalia Pinzon, Gillian Butler-Browne, Vincent Mouly, Anne Bigot, Capucine Trollet

Sorbonne Université, Inserm, Institut de Myologie, Centre de Recherche en Myologie, Paris, France

Effects of aging and sex-difference on the muscle secretome.

Aging is a gradual decline in physiological well-being, resulting in diminished tissue functionality. During aging, skeletal muscle strength and mass decrease and this is accompanied by a decrease in regenerative capacity. Muscle is a secretory organ capable of regulating its own function and/or influencing the activity of other tissues via myokines. In this context, how muscle secretion is modified during aging and how this affects muscle regeneration and homeostasis is still not known. Here, combining bioinformatic analysis and in vitro experiments we have identified alterations in the secretome of human muscle cells during aging. We have analyzed the medium of differentiated muscle cells isolated from muscles of young and old human subjects by proteomic approaches and we have identified 100 proteins differentially secreted between the young and old samples. Bioinformatic analysis using Nichenet from the proteome and secretome of these cells, allowed us to identified receptor-ligand interactions, as autocrine effects (on muscle cells) and potential paracrine effects involved in the cell communication. In parallel, it is known that male and female respond differently to muscle aging and present different DNA methylation and gene expression profiles. Here we also identified that the secreted proteins were also affected by the sex-bias, especially in the young donors samples. Using in silico transcriptome analyses from male and female using the Genotype-Tissue Expression study of young adults (12 females and 30 males) and older adults (6 females and 12 males) we observed that besides age, sex acts as a major source of variation in the muscle transcriptome. Altogether, these results suggest that aging and sex difference have major effects in the muscle secretome and now we aim to identify specific targets to reduce the effects of muscle aging in the elderly, by testing in vitro the proteins of interest identified in the muscle secretome.

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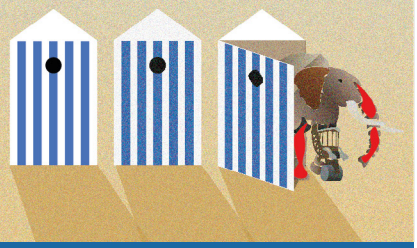


POSTER - P19 - GROUPE 1
Développement / Cellules souches / Régénération musculaire

Evelyne GICQUEL
Marine Faivre, Quentin Miagoux, Manon Benabidès, Abbass Jaber, David Israeli, Xavier Nissan, Isabelle Richard

Université Paris-Saclay, Univ Evry, Inserm, Généthon, Integrare research unit UMR_S951, 91000, Evry-Courcouronnes, France
CECS, INSERM U861, I-STEM, AFM, Institut des cellules Souches pour le Traitement et l'Etude des maladies Monogéniques, 28 Rue Henri Desbruères, 91100, Corbeil-Essonnes, France

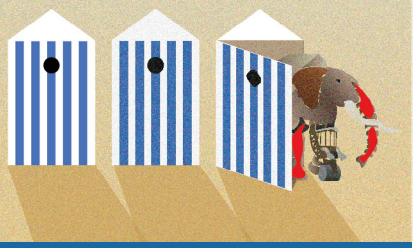
Lipid metabolism is disrupted in mouse and human models of FKRP deficiency, and rescued after FKRP gene transfer

Background: Among Limb Girdle Muscular Dystrophies (LGMDs), LGMD-R9 is due to mutations in the FKRP gene, encoding Fukutin related protein (FKRP). In muscle fibers, FKRP participates to the maturation process of alpha-dystroglycan (aDG), a highly glycosylated protein, part of the dystrophin-glycoprotein complex in the sarcolemma. The long glycosylation chains of aDG allow the binding to extracellular matrix (ECM) proteins as laminin, agrin and perlecan, and by this way anchor the muscle fiber in the ECM, protecting it from damages during contractions. LGMD-R9 patients suffer of progressive muscle weakness affecting predominantly the proximal muscles. FKRP knock-in mouse models carrying human mutations are very mildly affected, while total knock-out of the protein leads to lethality due to the role of FKRP in the central nervous system during development.

Methods: We generated a mouse model in which FKRP is specifically deleted in mature muscle fibers, through the action of the cre recombinase under the control of the human αskeletal actin promoter. The new model displayed muscle dystrophy characteristics, with aDG glycosylation defect, skeletal muscle histological damages, and muscle weakness. Global analyses as RNA sequencing and lipidomics were used to explore in depth muscle disruption. A comparison was done with patient iPS cells. FKRP gene transfer studies were conducted in the aim to restore the phenotype.

Results: A disruption in cholesterol metabolism was brought to light, occurring both in FKRP-deficient mouse muscle fibers and in patient iPS cells. FKRP gene transfer using Adeno-Associated Vector (AAV) proved to be efficient in restoring aDG glycosylation and muscle function. The defects observed in cholesterol metabolism returned to normal condition. A dose effect analysis yielded 5E12 vg/kg for efficient dose.

Conclusions: This study highlights for the first time a decrease in cholesterol metabolism in FKRP-deficient muscle cells, possibly playing a role in LGMD-R9 dystrophic process. The new mouse model for FKRP deficiencies also allowed to define the efficient dose of AAV for FKRP gene transfer, data of importance for future clinical trials.



POSTER - P20* - GROUPE 2
Physiopathologie / Vieillissement

Andréa EMERIT
Thomas Simonet, Laurent Schaeffer, Laetitia Mazelin**

Institut NeuroMyoGene (INMG-PGNM), Université Lyon 1, CNRS UMR 5261, INSERM U 1315, Lyon, France

Muscle atrophy induced by chronic activation of ALK5/TGFβRI signaling in adult mouse skeletal muscle is associated with downregulation of polyamine biosynthesis pathway

Background: Transforming Growth Factor β (TGFβ) pathway is a major negative regulator of skeletal muscle mass. Dysregulation of TGFβ signaling is implicated in muscle wasting of chronic diseases (myopathies, cancer…) and aging sarcopenia. It has been shown that polyamines levels, especially spermidine, decrease during muscle aging concomitant with autophagy defects appearance. Polyamines are polycations involved in many cellular processes, such as translation, post-translational modification, protein acetylation and autophagy induction.

Methods: We have generated a conditional mouse model to activate TGFβ signaling in adult myofibers through the muscle-specific and inducible expression of a constitutively active ALK5/TGFβRI receptor (RCA mice). Transcriptomics, Metabolomics and lipidomics analysis have been performed on atrophied and control muscle. Polyamines pathway and autophagy process are investigated upon TGFβ signaling activation in skeletal muscle fibers. Impact of spermidine supplementation on muscle phenotype is analyzed.

Results: Our previous work showed activation of Smad2/3 signaling leading to severe muscle wasting due to ubiquitin-proteasome system activation in RCA mice. In addition, RCA muscles developed progressive impairment of autophagy and accumulation of dysfunctional mitochondria. RNA sequencing and metabolomic analysis revealed immediate downregulation of polyamine biosynthesis pathway and decrease in muscle spermidine content.
Then, we characterized rapid and strong dropped expression of the key enzymes of polyamine biosynthesis, Amd1 and Smox, leading to lowered spermidine muscle levels both in males and females. Even if, Amd1 and Smox expressions are regulated by Androgen Receptor (AR) signaling, AR protein level and other AR target genes expression were not affected in RCA muscle. Besides, decreased spermidine level is not sufficient to affect eiF5a hypusination.
Finally, as spermidine has an important role as inducer of autophagy process (inhibiting function of histone acetyltransferase EP300) we investigate the potential benefice of treating RCA mice with spermidine.

Conclusions: Our study highlight an impact of TGFβ-mediated muscle atrophy on polyamines pathway regulation. Supplementation of RCA mice with spermidine might restore autophagy and mitochondrial defects, improving muscle phenotype. Our results will give additional input in spermidine therapeutic approach for muscle pathologies including sarcopenia.

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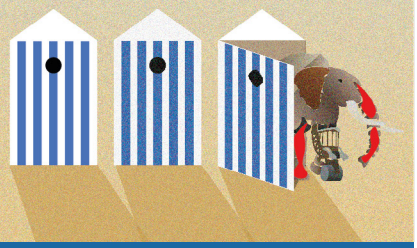

POSTER - P21* - GROUPE 1
Développement / Cellules souches / Régénération musculaire

Charline JOMARD
Bénédicte Chazaud, Julien Gondin

Institut NeuroMyoGene (INMG), Physiopathologie et Génétique du Neurone et du Muscle (PGNM), CNRS 5261, INSERM U1315, UCBL1

Influence of sex / ovarian cycle on skeletal muscle regeneration in a mouse model of lengthening contraction-induced injury

After injury, skeletal muscle regenerates thanks to a dynamic interplay between satellite cells (SCs) and inflammatory cells. Ovarian hormones, and more particularly a greater estrogen production, could confer a physiological advantage to females via their role in SC fate and the modulation of the inflammatory response. Estrogen levels naturally fluctuate during the ovarian cycle. However, little is known about the influence of estrogen cycling on muscle regeneration, notably due to the absence of standardized EIMD protocols, leading to extremely heterogenous functional alterations and, above all, the lack of control of the ovarian cycle.

We assessed the impact of sex/cycle on skeletal muscle regeneration in adult male and female C57Bl6/J mice using a standardized model of muscle injury (Bernard C., 2023 PMID: 37534948). The ovarian cycle, usually divided in four phases (i.e., proestrus, estrus, metestrus, diestrus) was controlled by smear analysis. Female mouse muscles were injured either in proestrus or estrus so that muscle regeneration takes place during the decrease or increase of circulating estrogen concentration, respectively. Muscle injury was also performed in males. Despite more severe histological alterations for females, maximal force recovered faster in estrus females than in males and proestrus females between 3 to 14 days post-injury. Estrus females also showed a greater activation, proliferation and differentiation of SCs in-situ compared to males and proestrus females and both female types showed a lower macrophage infiltration compared to males. Uninjured estrus female SC had a greater ability to proliferate as compared with male SCs while no difference was observed for the later steps of myogenesis. We demonstrated an impact of sex/ovarian cycle on force recovery and muscle regeneration after injury. Further analyses are now required to investigate the specific role of estrogens in this process.

Key words: skeletal muscle, force, regeneration, estrogen, ovarian cycle

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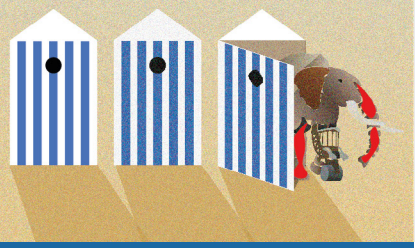


Aurélie FESSARD
Julien Gondin

Institut NeuroMyoGène - Laboratoire Physiopathologie et Génétique du Neurone et du Muscle UMR CNRS 5261 - INSERM U1315 - Université Claude Bernard Lyon 1 Faculté de Médecine - 8 Avenue Rockefeller - 69008 Lyon, France

Kinetics of skeletal muscle alterations in a mouse model of sepsis

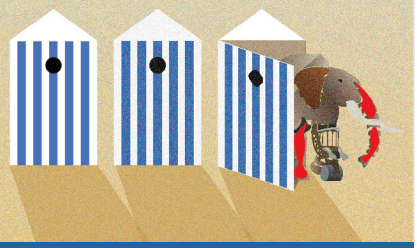
Muscle atrophy in critical illness neuromyopathy (CINM) patients exceeds that seen in normal hospitalized or bed-ridden persons so that this clinical condition is considered as inducing the fastest rate of muscle atrophy. CINM is associated with long lasting muscle weakness while sepsis is the major risk factor of CINM. Evidence is emerging that sepsis-induced reduction of contractile activity severely disturbs muscle stem cells (MuSC) homeostasis and its environment. However, the kinetics of changes in muscle force, mass and the number of mononuclear cells has been poorly described in relation to sepsis.

Sepsis was induced by cecal ligation and puncture in 12 weeks-old C57Bl6/J male mice (Rittirsch et al, 2008). Sham C57BL6/J mice were subjected to the same surgical procedure except that the cecum was neither tied nor punctured. Body weight and force production were daily monitored until day 8 post-surgery. Gastrocnemius muscle was harvested at ethical endpoint to analyze the content of mononuclear cells by immunostaining.

Septic mice lose up to 18% of their body weight at day 8. We also identified an early muscle weakness occurring at days 1-2 in septic mice that persisted until day 8. Interestingly, early muscle weakness was not related to a decrease in muscle mass, the latter occurring in the late phase of sepsis. Histological analyses were therefore performed at early (days 1-2) and late (day 8) phases of sepsis. While the number and/status of MuSC were not affected in septic mice, we found an early infiltration of macrophages that persists in the late phase of sepsis. Interestingly, the number of fibro-adipogenic precursors was also increased in the late phase of sepsis.

Overall, our findings show an early alteration of the MuSC niche in septic mice that take places before the occurrence of muscle wasting but concomitantly to muscle weakness.

Rittirsch, et al, Immunodesign of experimental sepsis by cecal ligation and puncture, Nat Protoc, 2009, 31-36, doi:10.1038/nprot.2008.214



POSTER - P23* - GROUPE 1
Développement / Cellules souches / Régénération musculaire

Lola LESSARD[2]

Julia Zibold[1]†, Lola E.R. Lessard[2,3]†, Flavien Picard[2]†, Lara Gruijs da Silva[4,5], Nathalie Streichenberger[2,6], Elisabeth Errazuriz-Cerda[7], Laurence Michel-Calemard[2,8] , Rita Menassa[2,8], Edwige Belotti[2], Laurent Coudert[2] , Alexis Osseni[2], Manuela Wiessner[1], Rolf Stucka[1], Thomas Klopstock[1,9,10], Francesca Simonetti[4,5,9], Takashi Nonaka[11], Masato Hasegawa[11], Tim M. Strom[12], Emilien Bernard[2,3], Elisabeth Ollagnon[13], Andoni Urtizberea[14], Dorothee Dormann[4,10,15], Philippe Petiot[16] , Laurent Schaeffer[2]#, Jan Senderek[1]††#, Pascal Leblanc[2]††#

1. Friedrich-Baur Institute at the Department of Neurology, University Hospital, LMU Munich, Munich, Germany
2. Institut NeuroMyoGène-PGNM, Faculté de Médecine Rockefeller, Université Claude Bernard Lyon, Lyon, France
3. Service d'Electroneuromyographie et de pathologies neuromusculaires, Hôpital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, France
4. Johannes Gutenberg University (JGU), Biocenter, Institute of Molecular Physiology, Mainz, Germany
5. Graduate School of Systemic Neurosciences (GSN), Planegg-Martinsried, Germany
6. Département d'Anatomo-Pathologie, Groupement Hospitalier Est, Hospices Civils de Lyon, Lyon, France
7. Plateforme d'imagerie CIQLE, Lyon, France
8. Service Biochimie et Biologie Moléculaire, Centre de biologie et pathologie Est, Hospices civils de Lyon, Lyon, France
9. German Center for Neurodegenerative Diseases (DZNE), Munich, Germany
10. Munich Cluster for Systems Neurology (SyNergy), Munich, Germany
11. Dementia Research Project, Tokyo Metropolitan Institute of Medical Science, 2-1-6 Kamikitazawa, Setagaya-ku, Tokyo 156-8506, Japan
12. Institute of Human Genetics, Klinikum rechts der Isar, Technical University Munich, Munich, Germany
13. Service de Génétique, Neurogénétique et Médecine Prédictive, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, France
14. Centre de Référence Neuromusculaire, Hôpital Marin - APHP, Hendaye, France
15. Institute of Molecular Biology (IMB), Mainz, Germany
16. Centre de santé Medicina Rockefeller, Lyon, France

Metabolic defects as a potential therapeutic target in Type I Myotonic Dystrophy

Introduction: Type I Myotonic Dystrophy (DM1) is a hereditary multi-systemic disorder caused by a CTG expansion in the 3'UTR of the DMPK transcript leading to alternative splicing dysregulation. AMPK signaling is one of the dysregulated pathways in DM1 and plays a crucial role in muscle metabolism and energy production necessary for proper myogenesis.

Objectives: The objectives of the study were to characterize the metabolic defects of DM1 muscle cells and explore the potential therapeutic role of AMPK signaling in rescuing myogenic defects in DM1.
Results: The immortalized DM1 muscle cell line had impaired differentiation and fusion capacities, which were partially rescued using the AMPK allosteric activator 991. AMPK activation capacity was assessed through Western Blot and FRET imaging. We assessed energy production using innovative techniques like the Scenith technique and the metabolic biosensor iATPs for cytoplasmic ATP. DM1 cells suffered from basal ATP deprivation and lacked the ability to increase oxidative metabolism in galactose medium, indicating a deficiency in energy production flexibility. DM1 cells exhibited a decrease in mitochondrial membrane potential and an increase in mitochondrial fragmentation after 3D reconstruction, suggesting structural and functional defects in mitochondria.

Conclusion: DM1 muscle cells have metabolic flexibility defects which could potentially be targeted by AMPK activators. By improving energy production and mitochondrial function in DM1, it may be possible to mitigate the myogenic defects associated with this disorder. Further research in this area could lead to novel treatment approaches in DM1.

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20ÈME ÉDITION
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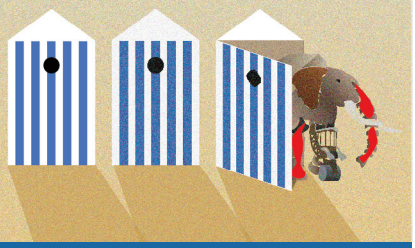


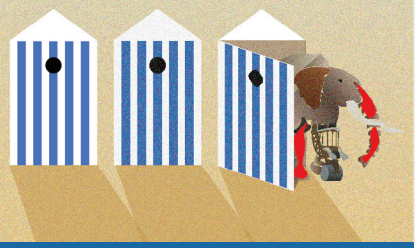
POSTER - P24 - GROUPE 2
Physiopathologie / Vieillissement

Stéphanie GODARD-BAUCHE[1]
Jérôme Nasr[1], *Morgane Euchparmakian*[1], *Mégane Lemaitre*[2], *Cécile Peccate*[1], *Antoine Muchir*[1]

1. Center of Research in Myology, UMRS 974, Hôpital de la Pitiè-Salpetrière, Paris, France
2. Centre d'Expérimentation Fonctionnelle - UMS 28 -Faculté de médecine - Sorbonne-Université, Hôpital de la Pitiè-Salpetrière, Paris, France

Role of lamin A/C in the maintenance of AChR at the neuromuscular junction in Emery-Dreifuss muscular dystrophy

Lamin A/C, encoded by LMNA gene, are proteins beneath the inner membrane of the nuclear envelope, which are involved in nuclear mechanical maintenance and gene expression regulation. LMNA mutations are responsible for Emery-Dreifuss Muscular Dystrophy (EDMD), characterized by muscle weakness associated with dilated cardiomyopathy. To date, the pathophysiological mechanisms involving the nuclear envelope proteins responsible for muscle defects in EDMD are not well understood. Furthermore, studies have reported that lamin A/C-mediated defects in the neuromuscular junction (NMJ) could contribute to EDMD. These studies raise the question of the possible role of nuclear envelope proteins in the maintenance of this peripheral synapse.
In order to better understand the role of nuclear envelope proteins in the NMJ maintenance, we used a mouse model of laminopathies (Lmnap.H222P/p. H222P) and revealed functional and structural abnormalities of NMJs in limb and diaphragm muscles manifested by neurotransmission defects associated with pre- and postsynaptic abnormalities at an early stage of the pathology .These NMJ abnormalities are confirmed from a molecular point of view, with a significant increase in the gene expression coding for RACh subunits (CHRNA1, CHRND, CHRNG), as well as a decrease in the expression of the gene coding for rapsyne associated with a decrease in the protein expression of the α subunit of RACh and rapsyne, defects characteristic of a functional denervation/reinnervation process.
This study emphasizes the important role of lamin A/C in the maintenance of NMJ, while also highlighting the involvement of rapsyne in the pathophysiological mechanisms of AChR stability beneath the nerve terminal when inner nuclear envelope proteins are deficient. Further studies to identify the signalling pathways underlying the NMJ defects in this laminopathy mouse model would shed light on gene expression mechanisms in sub-synaptic nuclei that are still poorly understood.



POSTER - P25* - GROUPE 1
Développement / Cellules souches / Régénération musculaire

Anna RAUSCH DE TRAUBENBERG
Marion J. Bouvet, Caroline E. Brun

Institut NeuroMyoGène - Physiopathologie et génétique du neurone et du muscle (INMG-PGNM), CNRS UMR5261, Inserm U1315, Université Claude Bernard Lyon 1, Lyon, France

Delineating primary cilia-mediated signaling pathway in the muscle satellite cell

Background: The primary cilium is a microtubule-based organelle acting as a signaling hub in a variety of cells including adult muscle stem cells (MuSCs). MuSCs are responsible for skeletal muscle regeneration, a process where normally quiescent MuSCs activate, enter the cell cycle and proliferate to give rise to i) lineage-committed myocytes or ii) self-renewing MuSCs. The primary cilium is dynamically regulated and actively participate to the lineage progression, at least by controlling the canonical Hedgehog signaling. Interestingly, Hedgehog-related factors differentially localize in the primary cilium as MuSCs progress into the myogenic lineage, leading to the hypothesis that cilia protein content may vary as well during this process. Whether the cilia proteome and signaling associated proteins, other than Hedgehog signaling, can influence MuSC quiescence and fate remains to determine.

Objectives: Our project aims to profile the protein content of primary cilia using proximity labelling tools in order to identify cilia-mediated signaling receptors and effectors at each stage of the myogenic lineage (i.e. quiescence, proliferation, self-renewal).

Methods: To do this, we used a cilia-targeted biotinylation approach, originally designed by Mick et al. 2015, to address the Ascorbate Peroxidase (APEX) enzyme in primary cilia of transfected C2C12 muscle cell line. The APEX biotinylates neighboring proteins upon H2O2 treatment, allowing for precise and rapid labelling of 40nm-surrounding proteins.

Results: We first generated the C2C12 stable cell lines expressing cilia-targeted APEX or not and tested multiple experimental conditions to biotinylate specifically the ciliary proteins. The optimal condition was determined by fluorescence using fluorophore-conjugated streptavidin, analyzing the ratio of specific signal versus background.

Conclusion & perspectives: We are currently optimizing the streptavidin-based purification for future analysis of C2C12 ciliary proteome by mass spectrometry. We will then adapt our system to MuSC-derived myoblasts, which will allow to determine the ciliary proteome in physiological and diseased models.

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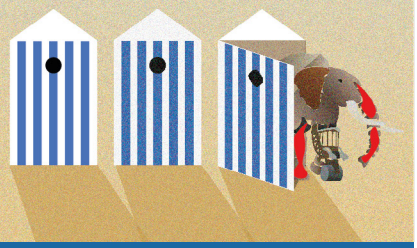

Noëlla GROSSI
Céline Bruge, Emilie Pellier, Gorka Fernandez, Tanya Stojkovic, Teresinha Evangelista And Xavier Nissan

CECS, INSERM U861, I-STEM, AFM, Institute for Stem Cell Therapy and Exploration of Monogenic Diseases, 28 Rue Henri Desbruères, 91100, Corbeil-Essonnes, France.
Institute of myology, Hôpital Pitié-Salpêtrière, Bâtiment Babinski, 47-83 Boulevard de l'Hôpital, 75013, Paris, France.

Compensatory mechanisms involved in the pathophysiology of LGMD R2

Limb Girdle muscular dystrophies are a heterogeneous group of genetic diseases leading to progressive loss of the limb girdle muscles. Caused by mutations in the gene encoding dysferlin, limb girdle myopathy type R2 (or LGMDR2, formerly known as LGMD2B) is a rare disease affecting less than 1 in 100,000 people for which there is no treatment. The particularity of this dystrophy is the variability in the clinic and the age of onset of symptoms between patients. Because this difference is not correlated to patient's genotypes, recent in vitro findings suggest that the overexpression of some genes probably participate in compensatory mechanism against increased proteolysis. To identify these compensatory mechanisms, we have compared gene expression profiles of muscular biopsies obtained from late onset and early onset patients. Several pathways have been identified including autophagy, a lysosomal degradation pathway, which seems to play an important role in the disease, especially in the ability to preserve fibers from stress and damage. These compensatory mechanisms will be now functionally evaluated in several in vitro models and stimulated to develop therapeutic procedures.

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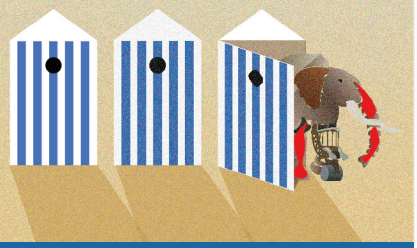

POSTER - P27 - GROUPE 1
Développement / Cellules souches / Régénération musculaire

Gaëlle BONCOMPAIN[2]
Delphine Desigaud[1], *Vincent Gache*[2], *Franck Perez*[1]

1. Institut Curie, CNRS UMR144, Paris, France
2. Institut NeuroMyoGene, PGNM, UCBL CNRS UMR5261, INSERM U1315, Lyon France

Adaptability of the Golgi-dependent protein secretory routes

Secretory protein transport is necessary to fulfil essential cellular functions. At the centre of the secretory pathway, the Golgi apparatus has to handle the diversity of the cargos to be transported. It is now clear that diversity in the Golgi-dependent secretory routes does exist and that multiple trafficking mechanisms are at work. However, if general regulators of secretory transport have been identified, specific regulators of the trafficking of cargos transported by a given specialized cell type are still unknown. Differentiated cells from tissues show distinct secretory needs related to their function.
In this study, we explore the adaptability of the secretory routes to fit specific secretion needs using human induced pluripotent stem (iPS) cells.
iPS cells are differentiated into chondrocytes and cardiomyocytes. Chondrocytes abundantly secrete components of the articular cartilage and thus have to sustain efficient transport of large and heavily glycosylated proteins which are the articular collagens. Cardiomyocytes secrete small proteins or peptides called 'cardiokines' or 'cardiomyokines' involved in maintenance of the viability of cardiomyocytes and acting as autocrine/paracrine hormones.
The organization of the Golgi apparatus is analysed using confocal microscopy by comparing iPS cells in their undifferentiated state and differentiated into chondrocytes and cardiomyocytes. A Golgi-targeted TurboID probe has been developed to determine the Golgi proteome by proximity biotinylation followed by quantitative mass spectrometry.
The secretory function of the Golgi apparatus in iPS cells-based models is monitored using the RUSH (Retention Using Selective Hooks) assay. The synchronized transport of reporter proteins as well as newly developed cell-type specific cargo is assessed by real-time imaging.
Altogether our study aims to get a better understanding of the adaptive capacity of the Golgi apparatus while specific secretion needs are required and will explore specialization of cellular functions upon cell differentiation.

20ÈME ÉDITION
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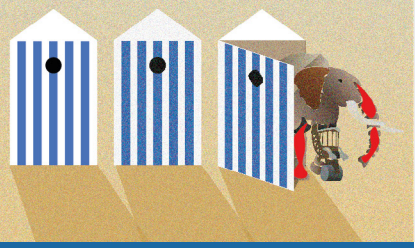


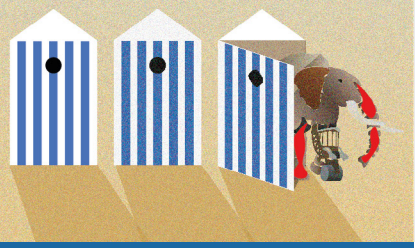
POSTER - P28 - GROUPE 2
Physiopathologie / Vieillissement

Jocelyn LAPORTE[1]
Raquel Gómez-Oca[1,2], *Evelina Edelweiss*[1], *Belinda S. Cowling*[2]

1. IGBMC, CNRS UMR 7104, Inserm U 1258, Illkirch, France
2. Dynacure, Illkirch, France

Differential impact of ubiquitous and muscle dynamin 2 isoforms in muscle physiology and centronuclear myopathy

The Dynamin 2 mechanoenzyme is a key regulator of membrane remodeling, and dominant mutations in its gene cause centronuclear myopathies. Here, we investigate the functions of dynamin 2 isoforms and their associated phenotypes and, specifically, the ubiquitous (Ub-DNM2) and muscle-specific dynamin 2 (M-DNM2) isoforms expressed in skeletal muscle. Using in vitro and cell-based assays, we found M-DNM2 forms larger oligomers that sequester BIN1, a membrane remodeling protein implicated in T-tubule structure. We also found that a centronuclear myopathy-related mutation in the ubiquitous but not the muscle-specific dynamin 2 isoform causes increased membrane fission. In vivo, overexpressing the ubiquitous dynamin 2 isoform correlates with severe forms of centronuclear myopathy, while overexpressing the muscle-specific isoform leads to hallmarks seen in milder cases of the disease. Previous mouse studies suggested that reduction of the total dynamin 2 pool could be therapeutic for centronuclear myopathies. Here, dynamin 2 splice switching from M-DNM2 to Ub-DNM2 aggravated the phenotype of a severe X-linked form of centronuclear myopathy caused by loss-of-function of the MTM1 phosphatase, supporting the importance of targeting the ubiquitous isoform for efficient therapy in muscle. Our results highlight that, unexpectedly, the ubiquitous and not the muscle-specific dynamin 2 isoform is the main modifier contributing to centronuclear myopathy pathology.



POSTER - P29* - GROUPE 1
Développement / Cellules souches / Régénération musculaire

Julie SITOLLE
Jade Ravent, Fabien Le Grand

Institut NeuroMyoGène, CNRS UMR 5261 -INSERM U1315, Université Claude Bernard Lyon 1, France

Exploring TGFβ and BMP signaling interactions during muscle cell fusion

Skeletal muscle possesses an outstanding ability to regenerate. As such, the muscle tissue can grow back after acute injury. This process is mediated by Muscle Stem Cells (MuSCs) which are present in a quiescent state in resting muscle. Following injury to the myofibers, MuSCs activate, proliferate, differentiate and fuse together to form new multinucleated functional myofibers. Research in our team recently highlighted that Transforming Growth Factor beta (TGFβ) acts as an inhibitor of fusion in adult mice muscles (Girardi et al. 2021). Our lab showed that TGFβ treatment impaired myoblast fusion both in vitro and in vivo. We thus wanted to further investigate the pathways downstream TGFβ signaling and characterise TGFβ target genes.

To this aim, we performed a transcriptome analysis of MuSCs treated by TGFβ1 in both proliferating and differentiating conditions. We performed differential gene expression analysis to decipher the changes in MuSCs transcriptome following TGFβ1 stimulation as well as upstream regulator analysis. We found that TGFβ signaling increase the expression of genes related to extra-cellular matrix remodelling in both contexts. Interestingly, in proliferating MuSCs, TGFβ1 treatment stimulated the expression of genes involved in BMP signaling, another pathway belonging to the TGFβ superfamily. Investigation of the transcriptome of BMP4-stimulated MuSCs revealed that BMP signaling, likewise, induced the expression of TGFβ1 transcripts.

We are now currently investigating the redundancy of these two branches of TGFβ superfamily in MuSCs, and their functional consequences in blocking MuSC differentiation. In parallel, we are using single cell RNA-Sequencing to investigate the hypothetical synexpression between these pathways' target genes during muscle tissue repair. Our work will provide insights into TGFβ/BMP-driven mechanisms that control MuSC biology.

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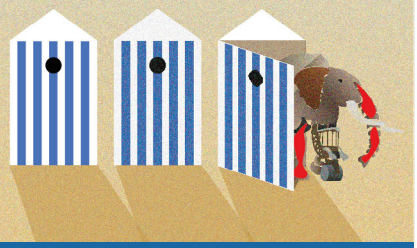

POSTER - P30* - GROUPE 2
Physiopathologie / Vieillissement

Marine LECONTE
Zoheir Guesmia, Gisèle Bonne et Anne T. Bertrand

Sorbonne Université, Inserm, Institut de Myologie, Centre de Recherche en Myologie, UMR974, 75014, Paris, France.

Dommages de l'ADN dans la dystrophie musculaire congénitale liée à LMNA

La réparation des cassures double-brins de l'ADN via la jonction des extrémités non-homologues (NHEJ) implique plusieurs modifications d'histones, notamment la phosphorylation de H2AX (γH2AX), suivi d'ubiquitylation, déacétylation et méthylation d'histones, nécessaires au recrutement de 53BP1 via ses domaines BRCT, UDR et Tudor. Des études récentes montrent une accumulation de cassures de l'ADN dans un groupe de pathologies neuromusculaires lié à des mutations du gène LMNA, et plus particulièrement dans sa forme la plus sévère, la dystrophie musculaire congénitale liée à LMNA (L-CMD). Le gène LMNA code pour les lamines A/C, protéines organisées en réseau sous la membrane nucléaire appelé lamina nucléaire notamment impliqué dans la résistance des noyaux aux contraintes mécaniques. Les lamines A/C interagissent avec de nombreuses protéines dont différentes histone-acétylases et –désacétylases, ainsi que 53BP1 via son domaine Tudor, le protégeant de la dégradation dans les cellules intactes et facilitant son recrutement au niveau des sites de cassures. Nous émettons l'hypothèse que l'augmentation des cassures de l'ADN dans les L-CMD serait liée à des défauts d'interaction des lamines A/C mutées avec leurs partenaires protéiques.
Nos données préliminaires confirment que les myoblastes primaires de patients L-CMD différenciés en myotubes présentent un plus grand nombre de cassures, marqués γH2AX, que les contrôles. L'induction de cassures double-brins par traitement à l'étoposide phosphate (EP), suivi de 2h sans traitement, montre une augmentation du marquage γH2AX pendant le traitement EP suivi d'une diminution pendant les 2h sans EP signant la réparation de l'ADN dans les contrôles. Le traitement EP entraine une plus forte augmentation des cassures dans les myotubes L-CMD, suivi d'une mort cellulaire. Dans ces mêmes conditions, contrairement aux myotubes contrôles, les myotubes L-CMD sont incapables de former des foyers 53BP1. Cela pourrait être dû à la plus forte interaction de 53BP1 avec les lamines A/C mutées observée par Proximity Ligation Assay.

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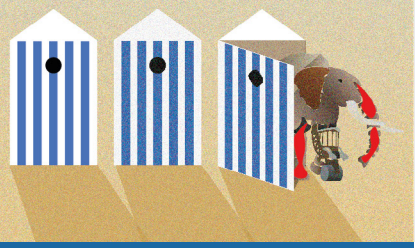

POSTER - P31* - GROUPE 1
Développement / Cellules souches / Régénération musculaire

Laura VIRTANEN[1]

Peccate Cécile[1], *D'Ercole Chiara*[2], *Karunanithy Vaarany*[3], *Bertholon Cindy*[3], *Izac Birgitte*[4], *Saintpierre Benjamin*[4], *Andrieu Muriel*[3], *Letourneur Franck*[4], *Madaro Luca*[2], *Giordani Lorenzo*[1]

1. Sorbonne Université, INSERM UMRS974, Association Institut de Myologie, Centre de Recherche en Myologie, 75013, Paris, France
2. Department of Anatomy, Histology, Forensic Medicine and Orthopedics, University of Rome ,«la Sapienza», Rome, Italy
3. Cybio Platform, Institut Cochin, INSERM U1016, CNRS UMR8014, F-75014 Paris, France
4. GenomIC Platform, Institut Cochin, INSERM U1016, CNRS UMR8014, F-75014 Paris, France

Single-cell Spatio-Temporal profiling of striated muscle cell populations in Duchenne Muscular Dystrophy

Duchenne Muscular Dystrophy (DMD) is a severe pediatric myopathy characterized by progressive muscle degeneration. DMD is caused by mutations in the dystrophin gene, which leads to the loss of functional protein, myofiber fragility, and constant degeneration/regeneration cycles. Over time, muscle regenerative potential is exhausted, and necrosis prevails, leading to fat and fibrotic infiltration. Currently, the mechanisms triggering the functional exhaustion of muscle regeneration are poorly understood. To identify these mechanisms, we have performed single-nuclei RNA/ATAC sequencing and Spatial Transcriptomics on dystrophin-deficient mice (mdx) over time. The goal is to identify defective signaling pathways responsible for the exhaustion of regenerative potential in DMD muscle. We have identified several potential targets that are more expressed in satellite cells of older mdx mice compared to young ones. In primary mdx mouse myoblasts undergoing differentiation, the silencing of these candidates led to a substantial enhancement in myotube formation, suggesting their involvement in impeding the typical myotube formation. This project has uncovered critical missing knowledge of how different cell populations evolve and interact during the progression of DMD, with the ultimate goal of identifying targets for therapeutic intervention to halt muscle degeneration and enhance regeneration.

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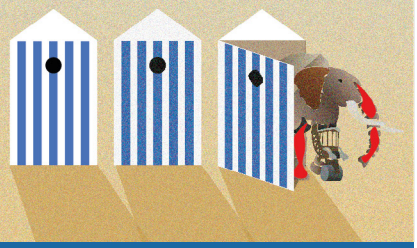


POSTER - P32 - GROUPE 2
Physiopathologie / Vieillissement

Laetitia MAZELIN

Andréa Emerit[*1], Véronique Chauvet*[*1], Lola Lessard[1], Damien Roussel[3], Caroline Romestaing[3], Thomas Simonet[1], Julien Gondin[1], Osseni Alexis[1], Belotti Edwige[1], Girard Emmanuelle[1], Yann-Gael Gangloff[1], Laurent Bartholin[2], Laurent Schaeffer[1#]*

1. Institut NeuroMyoGene (INMG-PGNM), Université Lyon 1, CNRS UMR 5261, INSERM U 1315, Lyon, France
2. Université de Lyon, Université Claude Bernard Lyon 1, Centre de Recherche en Cancérologie de Lyon (CRCL) INSERM 1052, CNRS 5286, Centre Léon Bérard, Centre de Recherche en Cancérologie de Lyon (CRCL), Lyon 69008, France
3. Laboratoire d'Ecologie des Hydrosystèmes Naturels et Anthropisés, UMR 5023, Université de Lyon, Université Lyon1, CNRS, 69622, Villeurbanne, France.
** Both authors contributed equally to this work*

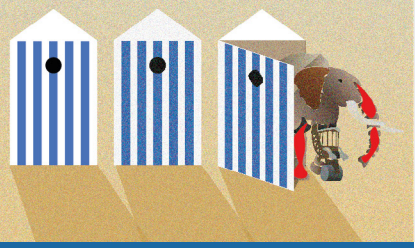
Chronic activation of ALK5/TGFβRI signaling in adult mouse skeletal muscle induces severe muscle wasting with concomitant impaired mitochondrial function

Background: Transforming Growth Factor β (TGFβ) pathway is a major negative regulator of skeletal muscle mass. Dysregulation of TGFβ signaling is increasingly being implicated in muscle wasting in chronic diseases (myopathies, cancer…) and aging sarcopenia. However, the impact of chronic TGFβ activation restricted to skeletal muscle has not yet been examined.

Methods: We have generated a new conditional mouse model to activate TGFβ signaling in adult myofibers through the muscle-specific and inducible expression of a constitutively active ALK5/TGFβRI receptor, also called TGFβRI-CA (RCA). The pathophysiology of dysregulated TGFβ signaling in skeletal muscle was investigated.

Results: We observed that expression of a constitutively active ALK5 receptor in adult myofibers promoted activation of Smad2/3 signaling leading to severe muscle wasting, fiber type shift and progressive reduction in muscle force. Myofiber atrophy resulted from decreased protein synthesis and upregulation of Ubiquitin-Proteasome-System catabolic pathways involving sequential activation of atrogenes. Interestingly, our results identified that chronic activation of ALK5 signaling leads to progressive alteration of autophagy flux and mitochondrial dysfunction impairing muscle homeostasis overtime.

Conclusions: Our study provides the first transgenic mouse model to investigate the impact of cell-autonomous, inducible and chronic activation of TGFβ signaling in skeletal muscle. Altogether, our data show that chronic activation of ALK5 signaling in adult muscle fibers leads to concomitant myofiber atrophy and metabolic defects.



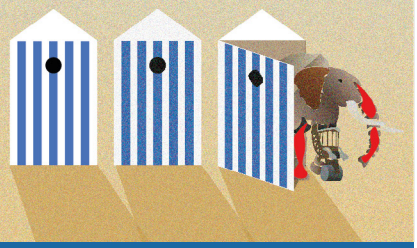
POSTER - P33 - GROUPE 1
Développement / Cellules souches / Régénération musculaire

Michèle WEISS-GAYET
Gaëtan Juban, Bénédicte Chazaud

Institut NeuroMyoGène - Laboratoire Physiopathologie et Génétique du Neurone et du Muscle. UMR CNRS 5261 - INSERM U1315 - Université Claude Bernard Lyon 1 Faculté de Médecine - 8 Avenue Rockefeller - 69008 Lyon - France

Restorative macrophage-derived RNAseT2 stimulates muscle stem cell fusion via an SLK/N-WASP/actin bundling dependent axis

During skeletal muscle regeneration, macrophages provide signals that coordinate myogenesis. Recovery macrophages support the final stages of myogenesis, which are differentiation and fusion. Using a screening approach, we identified ribonuclease T2 (RNAseT2) as secreted by anti-inflammatory macrophages. RNAseT2 is a highly conserved secreted factor with a variety of biological properties. RNAseT2 did not impact the differentiation of myogenic cells, but specifically stimulated their fusion. Gain and loss of function in human macrophages, tested in coculture with myogenic cells, confirmed the specificity of RNAseT2 action on cell fusion. We showed that RNAseT2 enters myogenic cells via the mannose receptor, which is required for myogenic cell fusion.
Actin cytoskeleton remodeling is required for myogenic cell fusion. Our results showed an increase in actin stress bundle formation in myoblasts treated with recRNAseT2.
In vivo gain-of-function experiments, using plasmid electroporation, validated the profusogenic effect of RNAseT2 during skeletal muscle regeneration, assessed by an increase in the number of myonuclei in regenerating myofibers.
Immunoprecipitation and mass spectrometry experiments identified Ste20-like protein kinase (SLK) as a partner of RNAseT2. SLK triggered the phosphorylation, and therefore the activation of N-WASP, which is necessary for actin remodeling at the time of MuSC fusion. In the absence of SLK, the effect of recRNAseT2 on fusion was abolished in vitro. Furthermore, Proximity Ligation Assay (PLA) experiments showed colocalization of SLK with recRNAseT2 in myoblasts.
In conclusion, our study reveals a new molecular mechanism by which restorative macrophages support MuSC fusion at the time of muscle regeneration and provides a new function for the highly conserved RNAseT2.



Laurence NEFF
Leonardo Scapozza, Olivier M. Dorchies

Biochimie Pharmaceutique, Institut des Sciences Pharmaceutiques de Suisse Occidentale, Université de Genève, Genève, Suisse

Imaging of muscle perfusion of dystrophic mice in situ with laser-speckle contrast analysis

Duchenne muscular dystrophy (DMD) is a rare genetic disease characterized by progressive muscle wasting in affected boys. Death occurs usually before 30 due to cardiac and respiratory failure. Understanding pathogenesis is key to the development of an effective cure for DMD.
In normal muscle, dystrophin binds a muscle-specific isoform of nitric oxide synthase (μNOS). Upon muscle contraction, μNOS converts arginine to citrulline and nitric oxide radicals (NO*) next to the sarcolemma. NO* diffuses out of the myofibres and triggers vasodilation of the surrounding capillaries, allowing to adjust oxygen supply to increased energy demand. In DMD, the absence of dystrophin leads to mislocation of NOS, resulting in impaired contraction-perfusion coupling. This causes functional ischemia: insufficient oxygen supply would lead to massive drop in ATP production and contribute to global loss of muscle homeostasis. However, the contribution of NOS isoforms to DMD and the therapeutic potential of NO* donors have been debated for decades.
Here, using LASCA (laser-speckle contrast analysis), an imaging technology developed by Perimed, we show blood perfusion of muscles in situ, in sedated mice. Perfusion was examined at rest and in response to electrically-evoked tetanic contractions. We found striking alteration in the perfusion pattern of adult dystrophic mice (mdx5Cv) compared to their normal counterparts (C57BL/6J): the peak amplitude, the time for half-decay, and the area under the curve were all diminished in dystrophic versus wildtype muscles. Treatment with tamoxifen rescued normal perfusion at least in part.
We believe that LASCA will be useful to explore the roles of NOS isoforms in DMD and correlate the efficacy of gene therapies to AAV-microDys products that either lack or retain the μNOS binding site. LASCA may also be used to establish the actual contribution to muscle perfusion of drugs currently considered for clinical trials for their expected actions at stimulating NOS activity via AMPK (metformin) or acting as NO* donors (arginine, citrulline). LASCA may also be helpful to understand why drugs previously assessed to prolong vasodilation via inhibition of phosphodiesterases finally failed in clinical trials (e.g., pentoxifylline, sildenafil, tadalafil).

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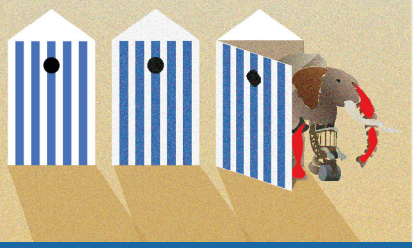


POSTER - P35 - GROUPE 1
Myopathie inflammatoire (et autre myopathie acquise)

François-Jérôme AUTHIER[1,2]
Mehdi Aoun Sebaiti[1], *Edoardo Malafatti*[1,2], *Sarah Souvannanorath*[1,2], *Emmanuel Itti*[2], *Gianmarco Severa*[1,2*]

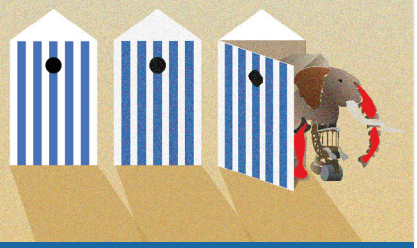
1. Université Paris Est-Créteil, INSERM U955-Eq. Relaix
2. AP-HP, HU Henri Mondor, Centre Expert de Pathologie Neuromusculaire
** Auteur Principal*

Myological evaluation of patients with post-acute COVID-19 syndrome

Post-acute COVID-19 syndrome (PACS) is a highly multifaceted condition, mimicking myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in patients with the most prolonged evolution. Due to the frequency of muscle pain and exertion intolerance, these patients are often suspected of having a muscular disease. Here we present the results of the neuromuscular evaluation of patients with a clinically defined PACS.

Twenty-two consecutive PACS patients (17F, 5M; median age 47 yrs) were included. All had at least one Covid-infection, confirmed by PCR, with mild respiratory symptoms, only one having required hospitalization and transfer to intensive care unit at acute stage. After a variable period between weeks to few months, patients developed chronic fatigue (duration > 6 months; n=22, 100%), post-exertional malaise (n=22, 100%), cognitive impairment including short-term memory loss or "brain fog" (n=22, 100%), muscle pain (n=18, 82%). No specific neuromuscular clinical signs have been found. 100% of patients satisfied diagnostic criteria for ME/CSF: CDC1994/Fukuda, International Consensus Criteria 2011, US Institute of Medicine 2015, UK National Institute for health and Care Excellence, 2021. Nineteen (86%) didn't show any recovery period after the onset of symptoms. ENMG examination was normal, without myogenic pattern; CK levels were normal; and muscle MRI available in five patients did not present any changes including fibro-fatty replacement. Brain 18FDG -PET/MRI showed a pattern of hypometabolism compatible with ME/CSF in half of patients. Muscle biopsy was performed in 3 patients and disclosed mild myopathic features in 2/3.

In conclusion, our long-lasting PACS patients with muscular symptoms fulfilled criteria for ME/CSF and no clear change was found in myological evaluation.



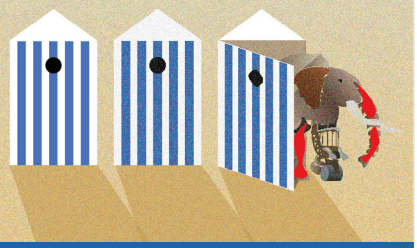
POSTER - P36 - GROUPE 2
Physiopathologie / Vieillissement

Sophie NICOLE
C. Bronstein, Y. Issa, A. Mkadmi, A. Lesage, P. Lory, S. Nicole

Institut de Génomique Fonctionnelle (IGF), Univ Montpellier, CNRS, INSERM, LabEx ,ÄòIon Channel Science and Therapeutics' (ICST) Montpellier, France

Investigations of zebrafish lines with loss-of-function mutations in the genes encoding the skeletal muscle sodium channel Nav1.4 orthologs

The force developed by one skeletal muscle depends on the ability of its myofibers to sustain repetitive action potentials (APs) in response to motor nerve firing with a direct correlation between the AP frequency and the developed muscle tension: the higher the AP frequency is, the greater the force developed is (up to tetanus). One major regulator in this process is the voltage-gated Na+ channel Nav1.4, whose activation generates AP and inactivation would regulate myofiber excitability. Hypomorphic loss-of-function (LoF) mutations in the gene encoding the pore-forming subunit of Nav1.4 result in congenital muscle weakness that we name Sodium Channel Weakness (SCW) in human, ranging from periodic paralysis in adult to fetal arthrogryposis with possible dosage effect: the less functional Nav1.4 is, the more severe the muscle weakness would be (Nicole and Lory, Front Pharmacol, 2021). It is therefore tempting to postulate that enhancing residual Nav1.4 activity would improve muscle force in SCW for which no therapy exists. We aim to determine the ability of Nav activators to improve skeletal muscle weakness resulting from hypomorphic mutations of Nav1.4 channels. With this objective in mind, we have established and investigated the phenotypes of zebrafish mutant lines from the Zebrafish Mutation Project (Welcome Sanger Institute) with hypomorph and amorph mutations in the two Nav1.4 paralogs (Scn4aa and Scn4ab) expressed in skeletal muscles of zebrafish. We will report the investigations of two "double" (Scn4aa and Scn4ab) mutant lines and will discuss their status as preclinical animal models for SCW.



POSTER - P37* - GROUPE 1
Myopathie inflammatoire (et autre myopathie acquise)

Laure GALLAY[1]
Nathalie Streichenberger, Clara Baverez, Lola Lessard, Yves Allenbach, Arnaud Hot

Service d'anatomopathologie GHE Hospices civils de Lyon, Service de Médecine interne Hospices Civils de Lyon, Service de Médecine interne Pitié Salpétriere Paris

Myosite focale, approfondissement du cadre nosologique

Les myosites focales sont des atteintes musculaires focales rares appartenant au groupe des myopathies inflammatoires idiopathiques. Dans le cadre de plusieurs travaux, notre équipe a travailler à la meilleure définition du cadre nosologique des myosites focales. Initialement, une série de cas a été analysé, identifiant la forte prévalence de cas avec des pathologies associées. La réalisation de 2 travaux complémentaires prenant en compte ces associations pathologiques, permet de mieux définir des entités clinico-histologiques particulières. D'une part, la mise en évidence d'un pattern de myosite focale s'intégrant dans les tableaux cliniques de patients souffrant de maladie de Behcet (n=10), et d'autre part la présence d'une association de myosite focale survenant dans un contexte néoplasique (n=14). Pour ces 2 sous-groupes de patients, l'analyse approfondies des données cliniques et histologiques identifie des pattern spécifiques, permettant ainsi d'attirer l'attention du clinicien et de l'anatomopathologiste prenant en charge de tel patients.

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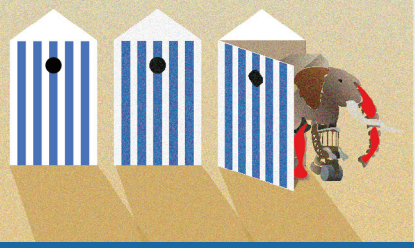

POSTER - P38* - GROUPE 2
Physiopathologie / Vieillissement

Elsie PILLER
Sabrina Bendris, Olivier Biondi, Frédéric Charbonnier, Laure Weill

T3S UMR S1124 team 4 et LBEPS Université Evry Paris Saclay

Study of paraspeckles status and role in ALS muscle cells

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by motor neuron degeneration and progressive muscular atrophy. 90% of cases are sporadic and over 50 causative gene mutations have been identified but no curative treatment exists.
Among the proteins mutated in ALS, several like FUS and TDP43 are involved in the formation of membraneless subnuclear bodies called paraspeckles. They are formed by the long noncoding RNA NEAT1_2 and RNA-binding proteins. Paraspeckles are involved in many pathways altered in ALS including mitochondrial homeostasis and myogenesis and are upregulated in ALS motor neurons. However, their status in the ALS muscle is unknown.
Despite ALS being known as the Motor Neuron Disease, a lot of alterations occur in the muscle including RNA processing and mitochondrial homeostasis, pathways in which paraspeckles play a somewhat important role. Therefore we wonder whether paraspeckles could be involved in the development of ALS and degeneration of the motor unit especially at the level of muscle cells.

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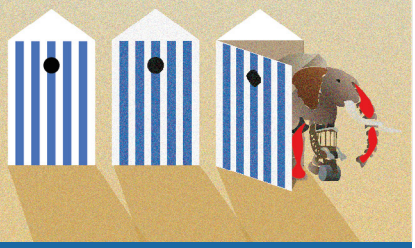


POSTER - P39 - GROUPE 1
Myopathie inflammatoire (et autre myopathie acquise)

Cyril GITIAUX[2]
Laurye Anne Eveillard[1], *Christine Bodemer*[3], *François-Jérôme Authier*[4,5], *Brigitte Bader-Meunier*[1]

1. *Service d'Immunologie et Rhumatologie Pédiatrique ; Centre de Référence national des Maladies Rhumatologiques et Inflammatoires Pédiatriques (RAISE)*
2. *Unité de neurophysiologie clinique pédiatrique; Centre de Référence des Maladies Neuro-Musculaires Nord-Est-Ile de France (NEIDF)*
3. *Service de dermatologie; Centre de Référence MAGEC*
4. *UF Centre Expert de Pathologie Neuromusculaire/Histologie, Centre de Référence des Maladies Neuro-Musculaires (NEIDF), HU Henri Mondor, APHP*
5. *UMR INSERM/UPEC U955-Eq. Relaix, Faculté de Santé, Université Paris Est-Créteil.*

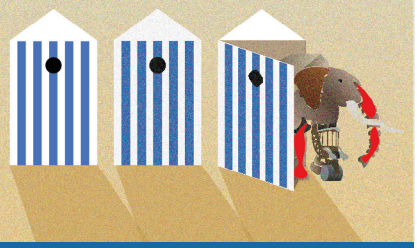
Myosites de chevauchement à début pédiatrique : Description clinique et histopathologique d'une cohorte monocentrique

Objectifs : Les myosites de chevauchement (JOM) sont des pathologies rares et hétérogènes. L'objectif de ce travail est de rapporter une série monocentrique de JOM afin d'améliorer leur description et leur classification.

Méthodes : Étude rétrospective de patients suivis à l'hôpital Necker-Enfants Malades entre janvier 2008 et août 2023, présentant une JOM définie par les critères diagnostiques de « Troyanov ». Les dossiers complets comportant les données cliniques initiales, évolutives et une biopsie musculaire ont été inclus.

Résultats : 16 patients ont été inclus. L'âge médian est de 9,8 ans [7,8-13 ans], la durée médiane de suivi est de 5.7 ans [2,5-9,7 ans]. Au diagnostic une myosite est présente chez 14/16 patients et 15/16 patients avaient un taux de CPK élevé. 7/16 présentent des signes de chevauchement avec la sclérodermie (JOM-SS), 7/16 avec le lupus (JOM-LES) et 2/16 des autoanticorps associés aux connectivites sans signes de chevauchement cliniques évident. On retrouve la présence d'un ou plusieurs anticorps chez tous les patients : FAN 16/16, anticorps de chevauchements 14/16, anti-DNA natifs 5/16, DOT myosite positif 4/16, des anti-SSc classiques 2/16 et des anti-synthétases 1/16. Le traitement initial a comporté une corticothérapie (16/16) seule (1/16) ou en association avec hydroxychloroquine (9/16), mycophénolate mofetil (10/16), méthotrexate (7/16), des immunoglobulines intraveineuses (4/16), ou autres. Un patient est décédé (JOM-SS). 11/16 patients sont actuellement en rémission complète dont 4/16 sans traitement. 13/16 sont en rémission complète sur le plan musculaire. Le profil histopathologique était pour les JOM-LES celui d'une dermatomyosite (2/7) et MNAI (5/7); pour les JOM-SS, celui d'une myopathie fibrosante (1/7) et scléromyosite (6/7) et pour les non classés (n=2) une myopathie dysimmunitaire avec pathologie périmysiale.

Conclusion : Les myosites de chevauchement à début pédiatrique sont des pathologies hétérogènes pour lesquelles la rémission de l'atteinte musculaire est fréquente. Les JOM-SS semblent plus sévères.



POSTER - P40* - GROUPE 2
Physiopathologie / Vieillissement

Badih SALMAN
Perrine Deleres, Steve Cottin, Emeline Bon, Delphine Sapaly, Suzie Lefebvre.

INSERM UMR 1124, Toxicité Environnementale, Cibles Thérapeutiques, Signalisation Cellulaire et Biomarqueurs, Campus Saint-Germain-des-Prés, Université de Paris, Paris, France

Is GEMIN5 a key player of flunarizine's neuroprotection in spinal muscular atrophy?

Spinal muscular atrophy (SMA) is an inherited neuromuscular disease characterized by the degeneration of alpha motor neurons and progressive skeletal muscle atrophy. SMA is caused by mutations or deletions of the "Survival Motor Neuron 1" (SMN1) gene, leading to lower SMN protein levels, produced solely by an almost identical gene (SMN2). Innovative therapies have been developed to increase SMN protein levels that have remarkably improved clinical outcomes. However, some heterogeneity is found amongst patient responses. Therefore, further research is required to decipher disease mechanisms and to find adjuvant treatments. SMN forms a protein complex with Gemins2-8 and Unrip, involved in RNA metabolism. It also plays a role in axon outgrowth where it's highly associated with the RNA-binding protein GEMIN5. Our research team previously found flunarizine to restore SMN protein's localization in nuclear Cajal bodies of motor neurons, to protect them and prolong lifespan of SMA model mice. What remains unclear is how flunarizine achieves its neuroprotective effects without modulating SMN protein levels. Treating murine NSC34 motor neuron-like cells for increasing periods of treatment, we show that flunarizine induces a gradual increase in the number of Cajal bodies early on after treatment. Additionally, a time-course expression analysis shows that flunarizine exerts a transient impact on SMN complex components RNA and protein levels, notably GEMIN5. Moreover, we identify new GEMIN5 RNA targets that are modulated by flunarizine and implicated in motor neuron diversification. In addition, using genetic tools we show that GEMIN5 regulates the RNA levels of these targets similarly to flunarizine. Finally, we show that GEMIN5 co-immunoprecipitates a target of flunarizine as well as a known RNA-binding protein associated with amyotrophic lateral sclerosis. Therefore, our research suggests that Gemin5 is a potential key player in the mode of action of flunarizine in neuronal cells and a promising therapeutic target in SMA and beyond.

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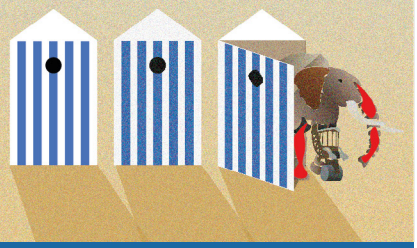

POSTER - P41* - GROUPE 1
Myopathie inflammatoire (et autre myopathie acquise)

Louai ZAIDAN[1]
Noémie Le Gouellec[2], *Nadia Oubaya*[3], *Baptiste Periou*[4], *Matthew Borok*[5], *Frederic Relaix*[6], *Éric Hachulla*[7], *François-Jérôme Authier*[8]

1. Univ Paris Est Creteil, INSERM, IMRB, F-94010 Creteil, France
2. Reference Center for Neuromuscular Diseases, Henri Mondor Hospital, France
3. Department of Internal Medicine and Nephrology, Centre Hospitalier de Valenciennes, France.
4. Service de Médecine Interne et Immunologie Clinique, CeRAINO, \CHU Lille, U1286 INFINITE, France
5. Department of Internal Medicine, National Reference Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, France
6. Ecole nationale vétérinaire d'Alfort, IMRB, F-94700 Maisons-Alfort, France
7. EFS, IMRB, F-94010 Creteil, France
8. AP-HP, Hopital Mondor, Service d'histologie, F-94010 Creteil, France

Reclassification de l'atteinte musculaire dans la sclérodermie systémique : Révélation de signatures histopathologiques uniques et de chevauchements avec les caractéristiques des myopathies inflammatoires

La myopathie associée à la sclérodermie systémique (SScM) est une condition fréquente, cependant, sa pathologie, sa classification et ses implications cliniques restent ambiguës. Une caractéristique pathologique notable est la microangiopathie, et il a été suggéré que les cas de myopathie fibrosante pourraient être associés à un pronostic plus sévère.
Dans le cadre d'une cohorte nationale multicentrique, nous avons réalisé une évaluation histopathologique, clinique et transcriptomique portant sur 83 patients atteints de SScM, que nous avons classés en sous-types fibrosants (FM, n=42), inflammatoires (IM, n=25) ou nécrosants (NAM, n=16) selon les critères du ENMC.
Les résultats ont révélé une augmentation significative de la fibrose chez les patients atteints de SScM par rapport aux témoins ($p<0,0001$). L'analyse morphométrique des fibres musculaires a révélé une diminution de leur nombre chez les patients atteints de SScM, ainsi qu'un score d'atrophie de type II élevé. De plus, les échantillons de SScM ont présenté une microangiopathie caractérisée par une réduction du nombre de microvaisseaux ($p=0,02$), une augmentation de la surface des microvaisseaux ($p=0,0021$) et une distance accrue entre les microvaisseaux et les fibres musculaires ($p=0,017$).
Sur le plan clinique, la durée médiane de suivi a été de 7,9 ans, avec 21 décès principalement dus à des maladies cardiaques et des infections. Les taux de survie à 10 ans ainsi que l'incidence de la rechute musculaire étaient similaires entre les sous-types de SScM, mais le groupe IM présentait un risque moindre d'événements pulmonaires.
L'analyse transcriptomique a révélé des caractéristiques pathologiques communes à tous les sous-types de SScM, notamment une surexpression de gènes associés à l'inflammation, à l'interféron, à la fibrose et à la microvascularisation. Cette surexpression augmentait progressivement de FM à IM à NAM.
En conclusion, la SScM présente des altérations musculaires communes, indépendamment du sous-type, soulignant l'unicité de la maladie. Cette étude remet en question la classification actuelle des sous-types de SScM et suggère l'utilisation de marqueurs quantifiables pour un diagnostic et une thérapie plus précis.

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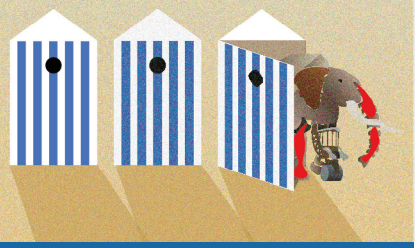

POSTER - P42* - GROUPE 2
Physiopathologie / Vieillissement

Amandine TOUREL[1]
A. Petiot[1], *J. Brocard*[1], *J. Brocard*[2], *I. Marty*[1]

1. Grenoble institut des Neurosciences, INSERM U1216 GRENOBLE, « Cellular Myology and Pathologies » 38700, Grenoble, France
2. Ecole normale supérieure de Lyon, INSERM LYON, 69342, Lyon, France

The implication of RyR1 in muscle cell homeostasy

Muscle contraction is induced by the release of calcium into the sarcoplasm via a multiprotein complex called the "calcium release complex". The type 1 ryanodine receptor (RyR1) calcium channel is a key component of this complex. Mutations in the gene encoding the RyR1 protein cause "RyR1-related myopathies" characterized by a decrease in the quantity and/or functionality of the protein, leading to a decrease in the release of calcium into the sarcoplasm, associated with muscle weakness. These myopathies cause many symptoms (ranging from muscle pain to perinatal death) and there is currently no treatment.

The laboratory has developed an inducible and muscle-specific transgenic mouse model (RyR1-Rec), which shows a reduction of approximately 50% of the muscle RyR1 protein. This is a model of RyR1-related myopathies, characterized by body and muscle weight loss, associated with muscle weakness. Interestingly, the biochemical analysis of the RyR1-Rec mice muscles revealed a perturbation of both the kinase mTOR, and the autophagy pathway, which are modulators of muscle mass, by regulating the anabolic/catabolic balance, and which could account for the muscle weight loss.
In order to understand the role of RyR1 quantity in the homeostasy of the muscle cells, we developed primary myotubes cultures from RyR1-Rec mice muscles. We first investigated the effect of RyR1 reduction on the morphology and functionality of this RyR1-Rec primary myotubes using fluorescence and calcium imaging. We then investigated the effect of the reduction of RyR1 on the mTOR pathway activity in the RyR1-Rec primary myotube cultures using western blot, to see if they showed a perturbation similar to the one seen in the muscles of the RyR1-Rec mice. Finally, we investigated the effect of activation and inhibition of RyR1 calcium channel activity on the mTOR pathway.

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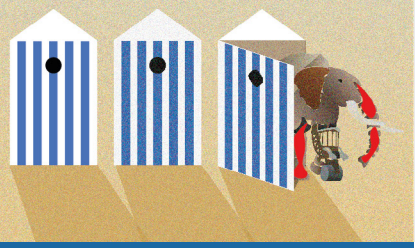


POSTER - P43 - GROUPE 1
Myopathie métabolique

Teresinha EVANGELISTA[1,3,4]
Claire Lefeuvre[2]*, Anaïs Chanut3; Emmanuelle Lacene1, 3; Guy Brochier1, 3; Clémence Labasse3; Pascal Laforêt2, Gorka Fernández-Eulate*[1*]

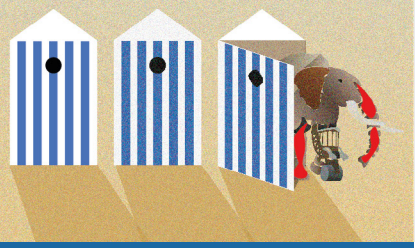
1. Nord/Est/Ile-de-France Neuromuscular Diseases Reference Center, Institut de Myologie, Pitié-Salpêtrière Hospital, APHP, Paris
2. Service de Neurologie CHU Raymond Poincaré, APHP, Université de Versailles Saint Quentin en Yvelines Garches France
3.Unité de Morphologie Neuromusculaire, Institut de myologie, Pitié-Salpêtrière Hospital, APHP, Paris
4.Functional Unit of Neuromuscular Pathology, Department of Neuropathology, GHU Pitié-Salpêtrière, Paris, France
** Auteur Principal*

Suivi histologique et clinique à long terme de deux patients LOPD naïfs de traitement

Objectif et méthodes: Décrire l'évolution histopathologique et clinique de deux patients naïfs de traitement atteints de LOPD. Les patients ont subi deux biopsies musculaires (BM) à un intervalle de temps de 24 ans pour le patient 1 et de 31,5 ans pour le patient 2. Nous avons revu la clinique et la BM.

Résultats: Patiente 1, femme de 70 ans explorée pour la première fois à l'âge de 48 ans pour une légère faiblesse de la ceinture pelvienne. La BM présentait des anomalies mineures avec des fibres vacuolisées et une légère augmentation de la teneur en glycogène. L'activité de l'alpha-glucosidase-acide (GAA) leucocytaire était diminuée et le test génétique a révélé le variant c.-32-13T>G/del dans l'exon 18 du gène GAA à l'état homozygote. Au cours des 15 années de suivi, elle a perdu 60mètres au 6MWT et 18 % à la MFM-D1. La deuxième BM montre une légère augmentation du contenu en glycogène. La microscopie électronique (ME) des deux biopsies montre des altérations équivalentes.
Patient 2, homme de 34 ans, découvert fortuite d'un taux de CK élevé à l'âge de 13 mois. La BM à l'âge de 19 mois montre une myopathie vacuolaire avec une quantité augmentée de glycogène. L'activité GAA leucocytaire était diminuée et le patient porte deux variantes dans le gène GAA: c.-32-13T>G ; c.655G>A. Trente ans après le diagnostic le patient est asymptomatique. Les examens complémentaires montrent une légère détérioration. La deuxième BM retrouve des altérations moins marqués et non spécifiques. La ME montre également une moindre accumulation de glycogène et de désorganisation myofibrillaire.

Discussion : Ces cas soulèvent la question de quand commencer l'ERT chez les patients LOPD. Question pertinent dans le cadre du dépistage néonatal.
Malgré les connaissances actuelles sur la LOPD qui suggèrent une accumulation progressive de glycogène et remplacement graisseuse du muscle, nous pouvons demander si, dans certains cas légers, le dépôt musculaire de glycogène peut s'améliorer spontanément avec le temps.
Enfin, la quasi-normalité des BM réalisées dans le même muscle années après le diagnostic déconseille la quantification du glycogène musculaire comme critère d'évaluation dans les essais thérapeutiques.



POSTER - P44* - GROUPE 2
Physiopathologie / Vieillissement

Massiré TRAORÉ[1]

Noviello Chiara[1], *Vergnol Amélie*[1], *Saillard Lucile*[1], *Gentil Christel*[1], *Halliez Marius*[1], *Julien Mésséant*[1], *Strochlic Laure*[1], *Lemaitre Mégane*[2], *Guesmia Zoheir*[1], *Cadot Bruno*[1], *Caldas Eriky*[3], *Marty Benjamin*[3], *Ariane Jolly*[4], *De la Grange Pierre*[4], *Jean-Yves Hogrel*[5], *Piétri-Rouxel France*[1]* and *Falcone Sestina*[1]*

1. Sorbonne Université, INSERM, Institut de Myologie, Centre de Recherche en Myologie, F-75013 Paris, France
2. Sorbonne Université, INSERM UMS28, Phénotypage du Petit Animal, Paris 75013, France
3. Institut de Myologie, CEA, Laboratoire d'imagerie et de spectroscopie par RMN, F-75013 Paris, France
4. GenoSplice, Paris Biotech Santé, Paris, France
5. Institut de Myologie, Laboratoire de physiologie et d'évaluation neuromusculaire, Paris, F-75013 France

GDF5 as rejuvenating treatment for age-related neuromuscular failure

Sarcopenia is a disease defined as progressive age-related loss of muscle strength, function and mass leading to increased mortality. Several mechanisms have been proposed to explain the onset and progression of sarcopenia, but some pathophysiological aspects are still not well understood and no cure has yet been established. Our previous work demonstrated that GDF5/BMP14 (Growth Differentiation Factor 5/Bone Morphogenetic Protein 14) overexpression in old mouse prevented muscle mass decline, however, a deeper report on the mechanisms and consequences on aged muscle is lacking.

Here, we demonstrate that GDF5 overexpression induces muscle mass gain, improves nerve/muscle connectivity and neuromuscular junction (NMJ) morphology in old muscle. In addition, we performed a genome-wide transcriptomic analysis in whole muscle showing a "rejuvenating signature" induced by GDF5 overexpression. Based on this proof of concept, we defined a cutting-edge therapeutic approach describing how the treatment with the recombinant GDF5 protein (rGDF5) is able to counteract the age-related skeletal muscle wasting in mice and might have a strong curative potential on humans.

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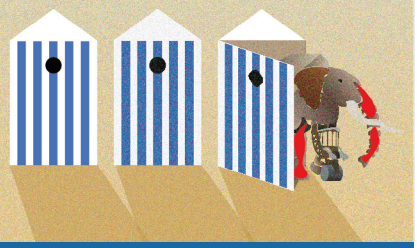

POSTER - P45 - GROUPE 1
Myopathie métabolique

Pascal LAFORÊT

D. Bratkovic[2], B.J. Byrne[3], K.G. Claeys[4], J. Díaz-Manera[5], P.S. Kishnani[6], T. Mozaffar[7], M. Roberts[8], A. Toscano[9], A.T. van der Ploeg[10], J. Castelli[11], M. Goldman[11], H. Jiang[11], S. Sitaraman Das[11], Y. Wasfi[11], B. Schoser[12], on behalf of the ATB200-07 Study Group

1. Neurology Department, Nord/Est/Île-de-France Neuromuscular Reference Center, FHU PHENIX, Raymond-Poincaré Hospital, AP-HP, Garches, France
2. PARC Research Clinic, Royal Adelaide Hospital, Adelaide, SA, Australia
3. University of Florida, Gainesville, FL, USA
4. Department of Neurology, University Hospitals Leuven, and Laboratory for Muscle Diseases and Neuropathies, Department of Neurosciences, KU Leuven, Leuven, Belgium
5. John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle upon Tyne, UK
6. Duke University Medical Center, Durham, NC, USA
7. Department of Neurology, University of California, Irvine, CA, USA
8. Salford Royal NHS Foundation Trust, Salford, UK
9. ERN-NMD Center for Neuromuscular Disorders of Messina, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
10. Erasmus MC University Medical Center, Rotterdam, Netherlands
11. Amicus Therapeutics, Inc., Philadelphia, PA, USA
12. Friedrich-Baur-Institute at the Department of Neurology, LMU University Hospital, LMU Munich, Munich, Germany

104-week efficacy and safety of cipaglucosidase alfa plus miglustat in ambulatory patients with Pompe disease: a Phase III open-label extension study (ATB200-07)

The Phase III double-blind PROPEL study (NCT03729362) compared the novel two-component therapy cipaglucosidase alfa+miglustat (cipa+mig) with alglucosidase alfa+placebo (alg+pbo) in adults with late-onset Pompe disease (LOPD) over 52 weeks. The ongoing open-label extension (OLE) of PROPEL (NCT04138277) evaluates long-term safety and efficacy of cipa+mig. Outcomes include 6 minute walk distance (6MWD), forced vital capacity (FVC), creatine kinase (CK), and hexose tetrasaccharide (Hex4) levels and safety. Data are reported as change from the PROPEL baseline to OLE week 52 (104 weeks after the PROPEL baseline). In the OLE (N=119; 91 enzyme replacement therapy [ERT] experienced and 28 ERT naïve), 82/85 (96.5%) patients previously treated with cipa+mig continued cipa+mig and 37/38 (97.4%) switched from alg+pbo to cipa+mig; 90.8% of patients remained in the OLE through week 52. Mean change in % predicted 6MWD was +3.1(8.07 standard deviation) for cipa+mig-cipa+mig and −0.5(7.76) for alg+pbo-cipa+mig in ERT-experienced patients and +8.6(8.57) for cipa+mig-cipa+mig and +8.9(11.65) for alg+pbo-cipa+mig in ERT-naïve patients. Mean change in % predicted FVC was −0.6(7.50) for cipa+mig-cipa+mig and −3.8(6.23) for alg+pbo-cipa+mig in ERT-experienced patients and −4.8(6.48) and −3.1(6.66) in ERT-naïve patients. Mean reduction in CK (U/L) for ERT-experienced and ERT-naïve patients was −132.1(215.74) and −216.9(243.66) for cipa+mig-cipa+mig and −161.0(269.52) and −218.6(316.47) for alg+pbo-cipa+mig, respectively. Mean reduction in Hex4 (mmol/mol) for ERT-experienced and ERT-naïve patients was −1.9(3.22) and −2.9(2.45) for cipa+mig-cipa+mig and −2.6(3.75) and −2.9(2.22) for alg+pbo-cipa+mig, respectively. During PROPEL through week 52 of the OLE, treatment-emergent adverse events occurred in 84 (98.8%) cipa+mig-cipa+mig and 36 (97.3%) alg+pbo-cipa+mig patients. During the OLE, three patients discontinued because of infusion-associated reactions (urticaria, urticaria and hypotension, and anaphylaxis) and no new safety signals were identified. Data demonstrate treatment with cipa+mig to 104 weeks was associated with a durable effect and was well tolerated, supporting long-term benefits of treatment for patients with LOPD.
Funded by Amicus Therapeutics, Inc.

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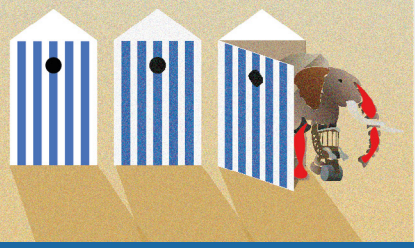

POSTER - P46* - GROUPE 2
Génétique / Omique

Antonio MORETTA[1]
Mélissa Dussoyer[2], *Catherine Moali*[2], *Frédéric Delolme*[2], *Bénédicte Chazaud*[1]

1. *Institut NeuroMyoGène - Physiopathology and Genetics of Neuron and Muscle, Université Claude Bernard Lyon 1, CNRS 5261, Inserm 1315, Univ Lyon, Lyon, France*
2. *University of Lyon, CNRS, Tissue Biology and Therapeutic Engineering Laboratory, LBTI, UMR5305, F-69367 Lyon, France*

Proteomics Analysis of skeletal muscle Extracellular Matrix in dystrophic mice

Adult healthy skeletal muscle has a powerful capacity to completely regenerate after an injury. On the opposite, muscular dystrophies are devastating diseases where the regenerative capacities of the muscle are overwhelmed and the muscle fibers are progressively replaced by fibrosis, leading to muscle loss of function and, finally to death, due to respiratory and cardiac failures. Fibrosis is the final outcome of excessive production of specific molecules in between the cells of the tissue, which constitute the Extracellular Matrix (ECM).

Degenerative myopathies are a heterogeneous group of rare genetic disorders that lead to the progressive loss of muscle integrity. Particularly, mutations in the dystrophin gene cause the Duchenne Muscular Dystrophy (DMD). DMD patient muscles show variable degrees of atrophy, hypertrophy, necrosis, regeneration, and fibrosis. Although fibrosis is recognized as a bad outcome in patients, a few evidence are related to the ECM.

In order to identify the proteins involved in the skeletal muscle extracellular matrix remodeling and their potential alterations in the context of the DMD, gastrocnemius muscle from WT and mdx mice has been used. Different decellularization protocols were exploited in order to extract ECM proteins. Dussoyer et al. protocol has been selected as the best one based on the histological analysis by hematoxylin/eosin staining, DNA quantification from decellularized muscles compared to not decellularized one, and amount of ECM proteins identified by expression proteomics and Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS).

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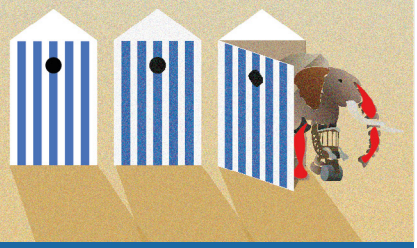

POSTER - P47* - GROUPE 1
Myopathie métabolique

Claire LEFEUVRE[1,2]

Marie De Antonio[3], *Françoise Bouhour*[4], *Celine Tard*[2,5], *Emmanuelle Salort-Campana*[6,7], *Sharam Attarian*[6,7], *Emmeline Lagrange*[8], *Anthony Béhin*[2,9], *Guilhem Solé*[10], *Jean-Baptiste Noury*[11], *Sabrina Sacconi*[12], *Armelle Magot*[13], *Aleksandra Nadaj Pakleza*[2,14], *David Orlikowski*[1,15], *Stéphane Beltran*[16], *Marco Spinazzi*[17], *Pascal Cintas*[18], *Maxime Fournier*[19], *Fatma Bouibede*[20], *Nadjib Taouagh*[1,2], *Taissir El Guizani*[1,2], *Azzeddine Arrassi*[2,9], *Dalil Hamroun*[21], *Pascal Laforêt*[1,2,22], *Emilie Retailleau*[1]*

1. Neurology Department, Raymond Poincaré University Hospital, Garches, APHP, France
2. Nord-Est-Ile-de-France Neuromuscular Reference Center, FHU PHENIX, France
3. Biostatistics Unit (DRCI), Clermont-Ferrand University Hospital, 63000 Clermont-Ferrand, France
4. Service d'Electroneuromyographie et Pathologies Neuromusculaires, Hospices Civils de Lyon, Lyon, France
5. Inserm, Lille University Hospital Center, U1172, Lille Neuroscience & Cognition, University of Lille, Lille, France
6. Centre de Référence des Maladies Neuromusculaires, Hôpital Timone Adultes, Assistance Publique Hôpitaux de Marseille, Marseille, France
7. PACA Réunion Rhône Alpes Reference Center for Neuromuscular Diseases, FILNEMUS, France
8. Department of neurology, Grenoble University Hospital, Grenoble, France
9. APHP, Service de Neuromyologie, Institut de Myologie, GH Pitié Salpêtrière, Paris, France
10. Neuromuscular Reference Center, Bordeaux University Hospital (Pellegrin), University of Bordeaux, Place Amélie Raba-Léon, 33000, Bordeaux, France
11. Neurology Department, Neuromuscular Center, CHRU Cavale Blanche, Brest, F-29609, France
12. Peripheral Nervous System and Muscle Department, Université Cote d'Azur, CHU de Nice, France
13. Centre de Référence des Maladies Neuromusculaires AOC, CHU Hôtel Dieu, Nantes, France
14. Department of Neurology, University Hospital, Strasbourg, France
15. Inserm, CIC 1429 GHU Paris Saclay, AP-HP, 92380 Garches, France
16. ALS Center, Francois-Rabelais University, Tours, Centre-Val de Loire, France
17. Neuromuscular Reference Center, Department of Neurology, University Hospital, Angers, France
18. CHU Toulouse, Hôpital Purpan, Département de Neurologie, F-31300 Toulouse, France
19. Department of Neurology, CHU Caen, Normandie. France
20. CHR d'Orléans, Internal Medicine Department, Orléans, France
21. Centre Hospitalo-universitaire de Montpellier, Hôpital Arnaud-de-Villeneuve, 371, avenue du Doyen-Gaston-Giraud, 34295 Montpellier cedex 5, France
22. U 1179 INSERM, Université Versailles Saint Quentin en Yvelines, Paris-Saclay, France
** Auteur Principal*

Les troubles de déglutition chez les patients adultes atteints de la maladie de Pompe: État des lieux du registre français

Introduction: La maladie de Pompe est une maladie neuromusculaire rare d'origine génétique liée à un déficit lysosomal en maltase acide. La présence possible d'une macroglossie a été rapportée dans la littérature, mais la fréquence des troubles de la déglutition avec ou sans macroglossie est mal connue et probablement sous-estimée. Elle peut pourtant impacter fortement la qualité de vie des patients.
Matériel et méthode : Dans le registre français des patients adultes atteints de la maladie de Pompe, un examen standardisé a été réalisé afin d'évaluer la fonction de déglutition. Le score de Salassa a classé la sévérité de la dysphagie et les auto-questionnaires de McHorney et le Sydney Swallow Questionnaire ont évalué le retentissement sur la qualité de vie.
Résultats : Parmi les 92 patients adultes étudiés, 55 femmes et 37 hommes avec un âge médian de 56.7 ans, 29% des patients présentaient des troubles de déglutition, le plus souvent modérés mais pouvant aussi être sévères jusqu'à la gastrostomie, impactant alors considérablement la qualité de vie. La dysphagie quotidienne et les fausses routes étaient rapportées respectivement chez 17% et 15% des patients, 23% des patients rapportent des temps de repas très allongés et 6% ayant dû arrêter de manger hors de leur domicile. Une macroglossie a été rapportée pour 18% des patients et une atrophie linguale dans 11% des cas. Le temps nécessaire pour boire 80mL était allongé chez 38% des patients. Les troubles de la déglutition semblent associés à la présence d'une macroglossie, une longue durée d'évolution de la maladie et un âge avancé.
Conclusion : Les troubles de la déglutition des formes tardives de la maladie de Pompe sont présents chez un tiers des patients. La recherche systématique de ces symptômes permettra de les orienter vers une prise en charge multidisciplinaire adaptée comprenant un nutritionniste, un ORL et un orthophoniste.

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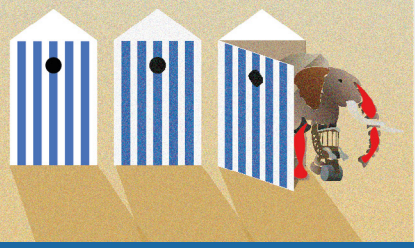

POSTER - P48* - GROUPE 2
Génétique / Omique

Louise BENARROCH[1]
Julia Madsen-Østerbye[2,$], *Mohamed Abdelhalim*[2], *Kamel Mamchaoui1,3*, *Jessica Ohana*[1,3], *Anne Bigot*[1,3], *Vincent Mouli*[1,3], *Anne Bertrand*[1], *Philippe Collas*[2,4], *Gisèle Bonne*[1]

1. Sorbonne Université, Inserm, Institut de Myologie, Centre de Recherche en Myologie, Paris, France
2. Department of Molecular Medicine, Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo, 0372 Oslo, Norway
3. MyoLine Immortalization Platform, Sorbonne Université-UMRS974-Inserm-Institut de Myologie, Paris, France
4. Department of Immunology and Transfusion Medicine, Oslo University Hospital, 0372 Oslo, Norway
$ Equally contributed

Cellular and genomic features of myo-converted fibroblasts, an alternative cellular model to myoblasts

The ability to recapitulate muscle differentiation in vitro enables the exploration of mechanisms underlying myogenesis and muscle diseases. However, obtaining myoblasts from patients with neuromuscular diseases or from healthy subjects poses ethical and procedural challenges that limit such investigations. An alternative consists in converting skin fibroblasts into myogenic cells by forcing the expression of the myogenic regulator MYOD. Here, we directly compared cellular phenotype, transcriptome, and nuclear lamina-associated domains (LADs) in myo-converted human fibroblasts and myotubes differentiated from myoblasts. We used isogenic cells from a 16-year-old donor, ruling out, for the first time to our knowledge, genetic factors as a source of variations between the two myogenic models. To validate this model, we immortalized fibroblast (containing MyoD vector) and myoblast cells from 1 control. We differentiated myotubes from myoblasts and myo-converted fibroblasts from fibroblasts for five days. By performing RNA-seq and ChIP-seq, we showed that myo-conversion of fibroblasts upregulates genes controlling myogenic pathways leading to multinucleated cells expressing muscle cell markers. However, myotubes are more advanced in myogenesis than myo-converted fibroblasts at the phenotypic and transcriptomic levels. Moreover, while most LADs are shared between the two cell types, each also displays unique domains of lamin A/C interactions. Our data globally favor a view of myogenic conversion of human skin fibroblasts as an alternative system to myoblast differentiation and allow us to investigate some aspects of chromatin organization and genome regulation in muscle cells. Our results also point to differences in phenotype, higher-order genome organization, and gene expression between myo-converted fibroblasts and myotubes, the latter not being directly linked to LAD differences.

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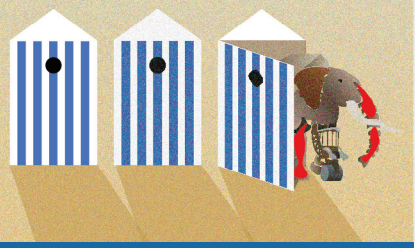

POSTER - P49 - GROUPE 1
Myopathie métabolique

Emmanuelle PION[1]
Cécile Rouzier[2]*,Mitodiag Réseau, Annabelle Chaussenot*[3]*, Mireille Cossée*[4]*, Shahram Attarian*[5]*, Jean-Paul Bonnefont*[6]*, Véronique Paquis-Flucklinger*[7]*, Vincent Procaccio*[8]

1. *Filnemus, laboratoire de génétique moléculaire, CHU Montpellier*
2. *Service de génétique médicale, Centre de référence des maladies mitochondriales, CHU Nice, Université Cote d'Azur, CNRS, INSERM, IRCAN, Nice*
3. *Service de génétique, CHU de Nice, Hôpital l'Archet 2, Nice*
4. *Laboratoire de Génétique Moléculaire, CHU Montpellier, PhyMedExp, Université de Montpellier, INSERM, CNRS, Montpellier*
5. *Service de Neurologie, FILNEMUS, Hôpital La Timone, CHU Marseille*
6. *Fédération de génétique médicale, Service de génétique moléculaire du GH Necker-enfants malades, Hôpital Necker-Enfants Malades, Paris*
7. *Service de génétique médicale, Centre de référence des maladies mitochondriales, CHU Nice, Centre de référence CALISSON, Université Cote d'Azur, CNRS, INSERM, IRCAN, Nice*
8. *Service de génétique, Institut de Biologie en santé, Centre National de référence Maladies Neurodégénératives et Mitochondriales, CHU Angers.*

Towards a pangenomic strategy in mitochondrial disorders: A French cohort of 397 patients carrying nuclear gene defects

Mitochondrial diseases (MD) are characterized by a huge heterogeneity which poses significant diagnostic challenges for clinicians and around 50% of patients are still undiagnosed. Since 2000, the French Network of Mitochondrial Diseases Diagnostic Laboratories, called MITODIAG, has been created and works in close collaboration with the two National Reference Centers, CARAMMEL and CALISSON, and the Neuromuscular rare disease network FILNEMUS, in order to improve the diagnosis and health care for patients with MD.

We describe here the organization of the MITODIAG network, the evolution of genetic diagnosis in MD in France these last years and the interactions with national platforms of genome core sequencing facilities named AURAGEN and SEQOIA. We also report the first clinical and genetic description of a cohort of 397 patients tested by NGS, in whom a diagnosis could be confirmed by the identification of pathogenic variants in nuclearly encoded genes. Among the 397 patients (294 children and 103 adults), 322 had primary MD and 75 had non-mitochondrial disorders. A total of 170 different genes were implicated and we reported 253 novel variants. We described a large clinical and genetic heterogeneity with a high prevalence of pathogenic variants in genes involved in mitochondrial translation and OXPHOS function in children and in genes involved in mtDNA metabolism in adults. Patients with Leigh syndrome and chronic progressive external ophtalmoplegia (CPEO) were highly suggestive of primary MD, whereas in patients with possible MD (MDC score 2-4), more than half carried pathogenic variants in non-mitochondrial genes.

We reported the French largest cohort of patients suspected of MD. We confirmed that WES/WGS, instead of panel approach, was clearly more valuable to identify the genetic basis in patients with possible MD (MDC score 2-4) and we provided a genetic testing flowchart to guide physicians in their diagnostic strategy.

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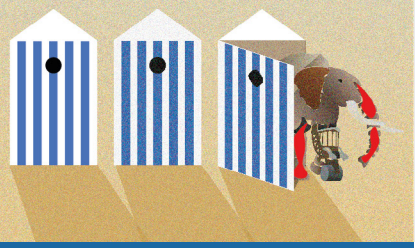

POSTER - P50* - GROUPE 2
Génétique / Omique

Yvan DE FERAUDY[1]
Marie Vandroux[1], *Norma Beatriz Romero*[2], *Valérie Biancalana*[1,3], *Johann Böhm*[1], *Jocelyn Laporte*[1]

1. IGBMC, Inserm U1258, Cnrs UMR7104, Université de Strasbourg, Illkirch, France
2. Myology Institute, Neuromuscular Morphology Unit, Sorbonne Université, INSERM, GHU Pitié-Salpêtrière, Paris, France
3. Laboratory of genetic diagnosis, Strasbourg University Hospital, Strasbourg, France

Myocapture: exome sequencing in undiagnosed congenital myopathies reveals new genes and expand the clinical phenotypes associated with known myopathy genes

Congenital myopathies (CM) define very severe muscle diseases that affect the quality of life and survival of patients. Genetic identification remains the gold standard for diagnosis. It allows genetic counselling and inclusion of diagnosed patients in appropriate therapeutic protocols. Unfortunately, the mutated gene remains unknown for a large number of patients. Our objective was to enhance the diagnostic process using Myocapture, an exome sequencing project, in an international cohort of 310 families with CM, excluded for the main known genes. If available, clinical information and histological data from muscle biopsies were collected for each patient.

Families were included from 2009 to 2018. We successfully identified disease-causing genes in 51% of CM cases, with 41% resulting in a definite genetic diagnosis. Interestingly, only 36% of the diagnoses corresponded to the combination of a known gene with a previously reported phenotype. Mutations in RYR1, NEB and TTN were prevalent in our CM cohort. In 44% of diagnosed cases, the phenotype was nonconventional, expanding the range of disease presentations within 24 known genes. These genes included genes associated with other forms of myopathy (n=17), with congenital myasthenia syndromes (n=3), and with other syndromes (n=4). These results highlight a larger than expected genetic and phenotypic heterogeneity for congenital myopathies. For the remaining 20% of diagnosed families, we identified mutations in 14 new genes, revealing novel disease mechanisms and potential therapeutic targets.

Overall, this “all genes” approach facilitates the diagnostic of CM, improved health care for several patients, and opened novel perspectives for either repurposing of existing molecules or development of novel treatments. Our study also confirms the advantages of using non-targeted NGS sequencing for undiagnosed CM cases with diverse genetic and phenotypic conditions.

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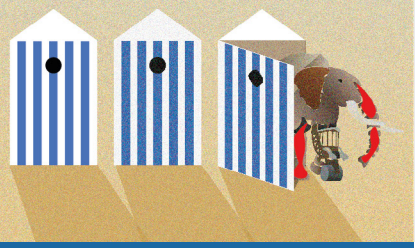

POSTER - P51* - GROUPE 1
Autre myopathie héréditaire (mito, myofibrillaire…)

Gorka FERNANDEZ-EULATE[1]

Girolamo Alfieri[1,2], *Gorka Fernandez-Eulate*[1], *Isabelle Ackermann-Bonan*[3], *Florence Caillon*[4], *Fanny Duval*[5], *Guilhem Solé*[5], *Armelle Magot*[6], *Antoine Pegat*[7], *Emmanuelle Salort-Campana*[8], *Marco Spinazzi*[9], *Teresinha Evangelista*[10], *Anthony Behin*[1], *Corine Metay*[11], *Tanya Stojkovic*[1]

1. Nord/Est/Ile-de-France Neuromuscular Diseases Reference Center, Institut de Myologie, Pitié-Salpêtrière Hospital, APHP, Paris
2. Azienda Ospedaliera Universitaria Sant'Andrea, Rome
3. Nuclear Magnetic Resonance Laboratory, Institut de Myologie, Paris
4. Radiology department, CHU de Nantes, Nantes
5. Neuromusuclar Diseases Reference Center ,«AOC», Nerve-Muscle Unit, Pellegrin Hospital, CHU Bordeaux, Bordeaux
6. Neuromuscular Diseases Reference Center, CHU Nantes, Nantes
7. Electroneuromyography and Neuromuscular Diseases Unit, Pierre Wertheimer Hospital, Hospices Civils de Lyon, Lyon
8. Neuromuscular Diseases and ALS Reference Center, CHU La Timone, APHM, Marseille
9. Neuromuscular Diseases Reference Center, CHU Angers, Angers
10. Muscle pathology unit, Institut de Myologie, Nord/Est/Ile-de-France Neuromuscular Diseases Reference Center, Pitié-Salpêtrière Hospital, APHP, Paris 5Cardiomyogenetics and Molecular and Cellular Myogenetics unit, Institut de Myologie, Pitié-Salpêtrière Hospital, APHP, Paris

Variabilité phénotypique et histoire naturelle de la myopathie avec exces d'autophagie liée À L'X (XMEA)

La myopathie avec excès d'autophagie liée à l'X (XMEA) est causée par des variants pathogéniques du gène VMA21 entraînant une vacuolisation et une atrophie progressives des muscles squelettiques. Seules quelques familles ont été répertoriées, les séries faisant défaut. Nous présentons une description complète de la maladie et de son histoire naturelle à travers d'une étude rétrospective rassemblant les données cliniques, génétiques, neurophysiologiques, histopathologiques et d'imagerie musculaire des patients VMA21 suivis en France, ainsi que d'une revue de la littérature à la recherche des cas additionnels. Dix-huit patients masculins français et 8 patients de la littérature ont été recensés (n=26). L'âge moyen d'apparition des symptômes était de 10,2 ±12,8 ans (intervalle 1-55) avec une majorité de patients (77%) présentant le premier symptôme durant l'enfance (<15 ans), bien que 3 patients aient un début très tardif (>40 ans). Les patients présent une faiblesse de la loge antérieure des cuisses, des rétractions distales fréquentes (43,5%), une élévation modérée de CPKs (1440,7 ±977,4 U/l) et des vacuoles autophagiques avec un immunomarquage positif pour les protéines sarcolemmales en histopathologie. L'IRM musculaire réalisé chez 10 patients montraient invariablement une atrophie graisseuse des membres inférieurs de topographie spécifique. Concernant le handicap à long terme, 8 patients (30,8%) avaient besoin d'une aide à la marche après une médiane de 15 ans d'évolution (intervalle 2-29) et 4 (15,4%) avaient perdu la marche après une médiane de 36 ans (intervalle 19-47). L'insuffisance respiratoire (42,9%) était modérée et l'atteinte cardiaque rare (9,1%). Les variants d'épissage du gène VMA21 sont fréquentes (80,8%) et le variant c.164-7T>G est associé a un debut plus tardif et une progression plus lente de l'handicap. La XMEA relié au gène VMA21 a un âge d'apparition variable mais la présentation clinique, histopathologique et l'imagerie musculaire sont caractéristiques permettant d'orienter le diagnostic. L'évolution du handicap moteur est lente, la majorité des patients restant ambulatoires sans insuffisance cardiorespiratoire importante.

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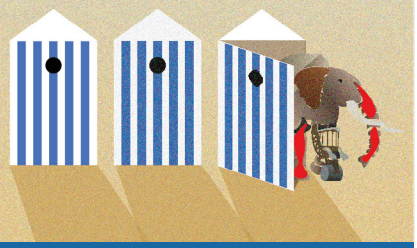

POSTER - P52* - GROUPE 2
Génétique / Omique

Laure DE PONTUAL[1]
François-Xavier Lejeune[2], *Christopher Smith*[3], *Vincent Dion*[3], *Geneviève Gourdon*[1] *and Stéphanie Tomé*[1]

1. Sorbonne Université, Institut du Cerveau - Paris Brain Institute - ICM (Data and Analysis Core), CNRS, Inserm, F-75013, Paris, France
2. UK Dementia Research Institute at Cardiff University, Cardiff
3. Sorbonne Université, INSERM, Institut de Myologie, Centre de Recherche en Myologie, F-75013 Paris, France

Deciphering the mechanisms of CTG repeat contractions induced by an inhibitor of histone deacetylase in myotonic dystrophy type 1

Myotonic dystrophy type 1 (DM1) is caused by the abnormal expansion of an unstable CTG repeat (>50 CTG) that usually increases across generations and over time in somatic tissues. Larger expansions are associated with more severe symptoms and a decreasing age of onset from one generation to the next. Consequently, the development of innovative therapeutic strategies aimed at decreasing the length of CTG repeat (contractions), and thus halting or reversing disease progression, is essential to improve the quality of life of DM1 individuals.

Recently, a selective inhibitor of histone deacetylase 3 (HDAC3), RGFP966, was shown to suppress CAG repeat expansions in models of Huntington's disease, suggesting that this molecule protects against triplet repeat expansions. We therefore investigated the role and mechanisms of action of RGFP966 on CTG repeat instability using DM1 cell models.

Using single-molecule long-read sequencing, we showed that RGFP966 decreases the frequency of CTG repeat expansions while increasing the frequency of CTG repeat contractions in DM1 murine fibroblasts carrying 700 CTG. To better understand the mechanisms of RGFP966-induced contractions, we first performed RNA-seq analysis in DM1 cells treated with this molecule. We identified dysregulated genes involved in DNA repair and in replication, two processes known to modify the dynamics of repeat instability. By RT-qPCR, we also showed that sense and antisense transcription of DMPK is decreased twofold in RGFP966 treated cells, which could directly affect CTG repeat instability. In parallel, HDAC3 KO cells containing CTG repeats were generated to confirm that the main action of RGFP966 on CTG repeat instability is directly linked to its inhibition of HDAC3.

The direct perspective of this work is to identify mechanisms promoting CTG repeat contractions, thus offering new therapeutic perspectives for DM1 and other trinucleotide repeat disorders.

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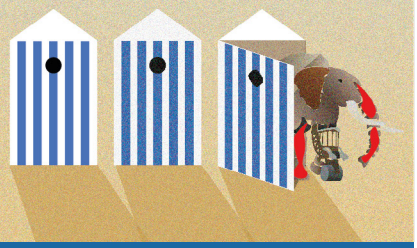

POSTER - P53* - GROUPE 1
Autre myopathie héréditaire (mito, myofibrillaire…)

Lola LESSARD[2,3]

Julia Zibold[1]†, Flavien Picard[2]†, Lara Gruijs da Silva[4,5], Nathalie Streichenberger[2,6], Elisabeth Errazuriz-Cerda[7], Laurence Michel-Calemard[2,8] , Rita Menassa[2,8], Edwige Belotti[2], Laurent Coudert[2] , Alexis Osseni[2], Manuela Wiessner[1], Rolf Stucka[1], Thomas Klopstock[1,9,10], Francesca Simonetti[4,5,9], Takashi Nonaka[11], Masato Hasegawa[11], Tim M. Strom[12], Emilien Bernard[2,3], Elisabeth Ollagnon[13], Andoni Urtizberea[14], Dorothee Dormann[4,10,15], Philippe Petiot[16] , Laurent Schaeffer[2]#, Jan Senderek[1]††#, Pascal Leblanc[2]††#

1. Friedrich-Baur Institute at the Department of Neurology, University Hospital, LMU Munich, Munich, Germany
2. Institut NeuroMyoGène-PGNM, Faculté de Médecine Rockefeller, Université Claude Bernard Lyon, Lyon, France
3. Service d'Electroneuromyographie et de pathologies neuromusculaires, Hôpital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, France
4. Johannes Gutenberg University (JGU), Biocenter, Institute of Molecular Physiology, Mainz, Germany
5. Graduate School of Systemic Neurosciences (GSN), Planegg-Martinsried, Germany
6. Département d'Anatomo-Pathologie, Groupement Hospitalier Est, Hospices Civils de Lyon, Lyon, France
7. Plateforme d'imagerie CIQLE, Lyon, France
8. Service Biochimie et Biologie Moléculaire, Centre de biologie et pathologie Est, Hospices civils de Lyon, Lyon, France
9. German Center for Neurodegenerative Diseases (DZNE), Munich, Germany
10. Munich Cluster for Systems Neurology (SyNergy), Munich, Germany
11. Dementia Research Project, Tokyo Metropolitan Institute of Medical Science, 2-1-6 Kamikitazawa, Setagaya-ku, Tokyo 156-8506, JapaN
12. Institute of Human Genetics, Klinikum rechts der Isar, Technical University Munich, Munich, Germany
13. Service de Génétique, Neurogénétique et Médecine Prédictive, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, France
14. Centre de Référence Neuromusculaire, Hôpital Marin - APHP, Hendaye, France
15. Institute of Molecular Biology (IMB), Mainz, Germany 16 Centre de santé Medicina Rockefeller, Lyon, France

The new missense G376V-TDP-43 variant induces late-onset distal myopathy but not ALS

TDP-43-positive inclusions in neurons are a hallmark of several neurodegenerative diseases, including familial amyotrophic lateral sclerosis (fALS) as well as sporadic ALS (sALS). Here we report a G376V missense variant in the TARDBP gene, affecting the C-terminal prion-like domain of the protein TDP-43 in two French families presenting with late-onset autosomal dominant distal myopathy without ALS. Patients from both families presented with progressive weakness and atrophy of distal muscles, starting in their 5th-7th decade. Muscle biopsies revealed a degenerative myopathy characterized by an accumulation of rimmed vacuoles, a disruption of sarcomere integrity and severe myofibrillar disorganization. The G376V variant altered a highly conserved amino acid residue and was absent in databases on human genome variation. Variant pathogenicity was supported by in silico analyses and functional studies. The G376V mutant increased the formation of cytoplasmic TDP-43 inclusions in cell culture models, promoted assembly into high molecular weight oligomers in vitro and altered morphology of TDP-43 condensates arising from liquid-liquid phase separation.
The identification of individuals with TDP-43-related myopathy but not ALS implies that TARDBP missense variants may have more pleiotropic effects than previously anticipated and support a primary role for TDP-43 in skeletal muscle pathophysiology.

We propose to include TARDBP screening in the genetic work-up of patients with late-onset distal myopathy. Further research is warranted to examine the precise pathogenic mechanisms of TARDBP variants causing either a neurodegenerative or myopathic phenotype.

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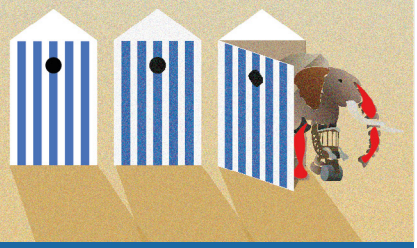

POSTER - P54* - GROUPE 2
Génétique / Omique

Nagi DEBBAH
Antoine Frenoy, Mandy Leger, Isabelle Marty, Vincent Jacquemond, Krzysztof Jagla, Julien Faure, Aline Thomas, John Rendu

CNRS Alpes - TIMC, INSERM - Grenoble Institut Neurosciences, INSERM - Grenoble Institut Neurosciences, CNRS-Institut Neuromyogène, INSERM - IGRED

Classifying RyR1 Variants

Mutations in the human protein RyR1 are responsible for a wide range of neuromuscular disorders, including severe conditions ranging from fetal akinesia to susceptibility to perianesthetic malignant hyperthermia. More than 2850 variants of this gene have been identified, many with unknown clinical significance, leading to diagnostic challenges. A reliable classification of RYR1 variants of unknown significance is therefore needed. The objective of our project is to create an efficient classification pipeline to aid in the medical diagnosis of RyR1-related myopathies.

To achieve this goal, we combine structural modeling, computational biology with an AI approach, fundamental biology, and molecular genetics.

In this poster presentation, we showcase our results, outlining the various steps of our work:

Building a structural model for the Human RyR1 protein, using a standard homology modeling strategy, both in its closed and open conformations. The molecular models are based on the closely related rabbit RYR1 structure that was solved with high resolution.

Identifying and preparing the physico-chemical descriptors derived from our predicted RyR1 Human Structure. To do so, 886 variants containing pathogenic and benign mutations have been modeled. From these models, we have derived structural and physico-chemical descriptors.

Using these descriptors, we have developed several Machine Learning models, which we present here, such as Logistic Regression, Gradient Boosting, Random Forest, and Deep Learning Networks.

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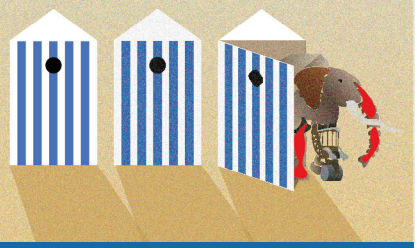
20ÈME ÉDITION
JOURNÉES DE LA SOCIÉTÉ FRANÇAISE DE MYOLOGIE
15 - 17 Novembre 2023 • Palais des Congrès - Atlantia



POSTER - P55 - GROUPE 1
Autre myopathie héréditaire (mito, myofibrillaire…)

Corinne METAY[1]

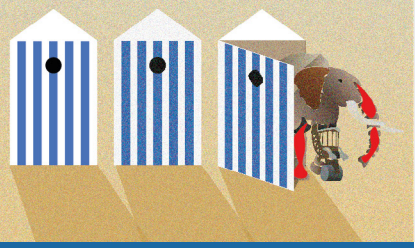
*C. Verebi[2], J. Nectoux2, F. Leturcq[2], G. Severa[3], A. Chaouch[4], I. Baatout[1], B. Keren[5], P. Richard[1], S. Souvannanorath[*3], E. Malfatti A[*3], Edoardo Malfatti[3#], [*]co-last authors*

1 AP-HP, Centre de Génétique Moléculaire et Chromosomique, Unité Fonctionnelle de Cardiogénétique et Myogénétique moléculaire et cellulaire et INSERM UMRS 974, Institut de Myologie. GH Pitié-Salpêtrière, Sorbonne Université, 75013 Paris, France
2. AP-HP, Service de Médecine Génomique, Maladies de Système et d'Organe - Fédération de Génétique et de Médecine Génomique, DMU BioPhyGen, Centre-Université Paris Cité - Hôpital Cochin, 75014 Paris, France
3. AP-HP, Université Paris Est, U955, IMRB, INSERM, Centre de Référence de Pathologie Neuromusculaire Nord-Est-Ile-de-France, Filnemus, Henri Mondor Hospital, 94000 Creteil, France
4. AP-HP, Service de Cardiologie, Hôpital Henri Mondor, 94000 Créteil, France
5. AP-HP, Centre de Génétique Moléculaire et Chromosomique, UF Génétique du Développement, GH Pitié-Salpêtrière, Sorbonne Université, 75013 Paris, France
[*]co-last authors
[#] Auteur Principal

FSHD1 atypique et duplication de CAV3: Quand un évènement moléculaire en cache un autre

Un homme a consulté devant des troubles de la marche d'installation progressive depuis l'âge de 71 ans. L'examen neurologique montre une camptocormie, une atteinte scapulo-péronière avec une scapula alata asymétrique, une atrophie des creux susclaviculaires et des plis pectoraux, sans atteinte de la musculature faciale. Il rapporte des troubles de la déglutition. Il souffre de fibrillation atriale. Les CPK sont normales. L'EMG s'avère myogène. La biopsie musculaire montre des internalisations nucléaires et une atrophie des fibres de type 2 sans anomalies de protéines membranaires. L'IRM musculaire montre une atteinte symétrique des muscles paraspinaux et une atteinte asymétrique des gastrocnémiens médiaux. Le père du patient aurait eu une camptocormie à un âge avancé. L'analyse génétique de FSHD1 détecte un allèle contracté de la région D4Z4 du chromosome 4 de taille estimée à 5(+/-1) unités répétées. Le panel NGS de gènes des myopathies montre la présence d'une duplication hétérozygote de l'exon 1 du gène CAV3, confirmée par CGHa. L'expression protéique de la cavéoline s'avère très diminuée en WB sur la biopsie musculaire.

La présence de l'allèle contracté de la région D4Z4 est cohérente avec l'atteinte musculaire scapulopéronière, les troubles de la déglutition et l'IRM d'une FSHD1 atypique à début tardif (OMIM#158900). La duplication hétérozygote de l'exon 1 de CAV3 est associée à une diminution de l'expression protéique de la cavéoline dans le muscle. Des duplications dans CAV3 n'ont jamais été rapportées (LOVD, HGMD-Pro, Database of Genomic variants). Le gène CAV3 est impliqué dans la « Rippling muscle disease » et des atteintes cardiaques de type cardiomyopathie hypertrophique ou troubles du rythme. Chez notre patient, la diminution de la cavéoline en Western Blot pourrait être corrélée à l'atteinte cardiaque.



POSTER - P56* - GROUPE 2
Génétique / Omique

Guillaume DIOP[1]
Laure de Pontual[1], *François-Xavier Lejeune*[2], *Antoine Mangin*[1,5], *Sonia Lameiras*[3], *Tina Alaeitabar*[3], *Ismail Jamail*[3,4], *Nicolas Servant*[4], *Sylvain Baulande*[3], *Vincent Dion*[5], *Geneviève Gourdon*[1], *Stéphanie Tomé*[1]

1. Sorbonne Université, INSERM, Institut de Myologie, Centre de Recherche en Myologie, F-75013 Paris, France
2. Sorbonne Université, Institut du Cerveau - Paris Brain Institute - ICM (Data and Analysis Core), CNRS, Inserm, F-75013, Paris, France
3. ICGex Next-Generation Sequencing Platform, Institut Curie, PSL Research University, Paris, France
4. Institut Curie, INSERM U900, Mines Paris Tech, PSL University
5. UK Dementia Research Institute at Cardiff University, Cardiff

Identification of chemical factors modulating CTG repeat instability in Myotonic Dystrophy type 1

Myotonic Dystrophy type 1 (DM1) is a neuromuscular disease caused by an abnormal CTG repeat expansion within the DMPK gene. In patients, the number of CTG repeats varies from 50 to thousands and usually increases over generations and over time in tissues. Longer CTG repeat expansions are often associated with worsening symptoms and an earlier age of onset. Stabilizing or decreasing the number of CTG repeats may lead to reversal of disease progression in DM1 patients. Our project consists in identifying pharmacologically relevant chemical modulators of instability to develop new therapeutic strategies aimed at reducing the number of CTG repeats.

First, we performed a large-scale screen using the Prestwick Library (>1200 FDA-approved drugs) and taking advantage of a chromosomal GFP reporter assay that can accurately measure expansions and contractions in the same population of HEK293 cells. We identified 39 molecules that modify GFP expression, suggesting that these compounds may also impact CTG repeat instability. Using long read sequencing (Pacific Biosciences), we estimated the direct effect of six pre-selected molecules on the dynamics of CTG repeat instability in murine fibroblasts carrying the human DMPK gene with 700 unstable CTG repeats over a three-month cell culture period. Our preliminary data indicate that two molecules alter the pattern of CTG repeat instability in DM1 fibroblasts by mechanisms that require further studies.

The identification of these molecules could help us better understand the mechanisms behind triplet repeat expansions and identify new therapeutic targets to reduce CTG instability in DM1 patients.

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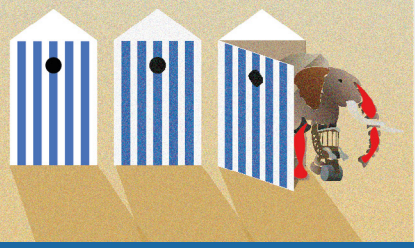

POSTER - P57* - GROUPE 3
Imagerie musculaire

Alicia MILOT[1,2,3]
Klaus Dieterich[1,3]

1 - Univ. Grenoble Alpes, Inserm U1209, IAB, CHU Grenoble Alpes, Medical Genetics, France
2 - Pediatric Physical Medicine and Rehabilitation, CHU Grenoble Alpes, France
3 - National Reference Center for Developmental Anomalies, Multidisciplinary AMC Clinic

Arthrogryposis Multiplex Congenita in pediatric age: correlation between MUScular MRI and functional Evaluation (AMUSE), towards a biomechanical model

Introduction: Arthrogryposis Multiplex Congenita (AMC) is a group of diseases with joint limitations at two or more distinct joint levels at birth. Joint limitations are not progressive, but the functional consequences (motor function, ambulatory status, autonomy in daily life and participation in social life) have a lifelong impact on patients. The management of these conditions is therefore demanding, necessarily multidisciplinary and is a long-term process. The aim of our study was to evaluate the correlation between muscle fat infiltration and activity deficits and limitations in children with AMC.

Material and methods : We conducted a monocentric retrospective observational study including patients under 18 years of age and/or over 18 years of age with exclusive pediatric follow-up evaluated at the AMC Reference Centre (RC) of the University Hospital of Grenoble Alpes between 2010 and 2022. These children underwent a multidisciplinary assessment including whole body MRI. Muscle fat infiltration was quantified using the MERCURI score.

Results : We included 97 patients (57% girls), of whom 50% had Amyoplasia, 38% had Distal Arthrogryposis (DA) and 12% from group 3 “other”. Median age at first evaluation was 36 months. We showed that the Mercuri score was significantly correlated with PROM in the upper and lower limbs in Amyoplasia and in DA and for lower limbs in group 3 “other”, and also with muscular weakness in lower limbs. Furthermore, in Amyoplasia and in DA, the Mercuri score was also correlated with reaching ability.

Conclusion : Our study is one of the first in a pediatric population to investigate the link between muscle imaging and functional aspects of AMC. Muscle MRI is a recognized and recommended tool for diagnosis, but it is also a suitable non-invasive tool to assess and assist in the functional prognosis of patients.

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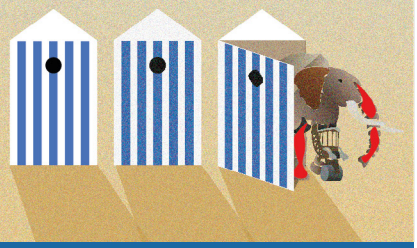


POSTER - P58 - GROUPE 4
Pathologie du nerf et motoneurone

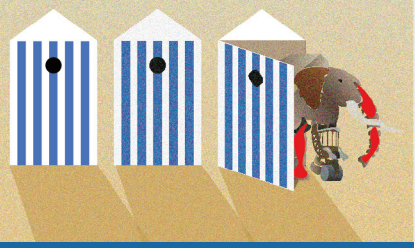
Claude CANCÈS[3]
Claudio Bruno[2], *Tina Duong*[4], *Dirk Fischer*[5], *Janbernd Kirschner* [6], *Mariacristina Scoto*[7], *Eugenio Mercuri*[8], *Marianne Gerber*[9], *Ksenija Gorni*[10], *Heidemarie Kletzl*[11], *Imogen Carruthers*[12], *Carmen Martin*[12], *Teresa Gidaro*[13], *Francesco Muntoni*[7], *au nom du groupe d'étude JEWELFISH, Claudia A Chiriboga*[1,3]*

1. *Department of Neurology, Columbia Irving Medical Center, New York, NY, États-Unis*
2. *Translat/Experimental Myology, Istituto Giannina Gaslini, Gênes, Italie*
3. *CHU de Toulouse, Service de Pédiatrie, neurologie et infectiologie, Toulouse, France*
4. *Department of Neurology, Stanford University, Palo Alto, CA, États-Unis*
5. *Division of Neuropediatrics, University Children's Hospital, Bâle, Suisse*
6. *Neuropedi/Muscle Disorders, University of Freiburg, Freiburg, Allemagne*
7. *Dubowitz Neuromuscular Centre, University College London, Londres, Royaume-Uni*
8. *Pediatric Neurology Institute, Catholic University, Rome, Italie*
9. *Pharma Development, Safety, F. Hoffmann-La Roche Ltd, Bâle, Suisse*
10. *PDMA Neuro/Rare Disease, F. Hoffmann-La Roche Ltd, Bâle, Suisse*
11. *Research and Early Development, Roche Innovation Center Basel, Bâle, Suisse*
12. *Roche Products Ltd, Welwyn Garden City, Royaume-Uni*
13. *Pharma Development, Neurology, F. Hoffmann-La Roche Ltd, Bâle, Suisse.*

* *Auteur Principal*

JEWELFISH : Tolérance, pharmacodynamie et données d'efficacité exploratoires dans une population de patients atteints d'amyotrophie spinale (SMA) déjà traitée, recevant risdiplam - analyse à 24 mois

Risdiplam (EVRYSDI®) est un modificateur d'épissage du pré-ARNm du gène SMN2, à distribution centrale et périphérique, administré per os, autorisé dans plus de 90 pays.
JEWELFISH (NCT03032172) est une étude ouverte, multicentrique évaluant risdiplam en administration quotidienne chez des patients atteints de SMA (âgés de 6 mois à 60 ans à l'inclusion), ayant participé à l'étude MONNFISH (évaluant RG7800) ou déjà traités par nusinersen, olesoxime ou onasemnogene abeparvovec-xioi.
La population de l'étude (N=174) présentait une diversité en termes d'âge (1-60 ans), de type de SMA (1 à 3), de nombre de copies du gène SMN2 (1-4) et de statut ambulatoire (non-sitter/sitter/ambulant). Sur 174 patients inclus, 13 avaient participé à l'étude MOONFISH (dont 3 naifs de traitement car ayant reçu le placebo et n'ayant pas été passés à RG7800), 76 avaient été traités avec nusinersen, 70 avec olesoxime et 14 avec onasemnogene abeparvovec. Un patient avait quitté l'étude à l'inclusion. Sur 4 semaines, le niveau de protéine SMN a plus que doublé sous risdiplam comparé aux niveaux de référence, quel que soit le traitement reçu précédemment. Aucun effet indésirable lié au traitement n'a conduit un patient à quitter l'étude. Le profil de tolérance était comparable à celui de patients naïfs de traitement traités avec risdiplam dans les études FIREFISH (NCT02913482) et SUNFISH (NCT02908685). D'après l'analyse exploratoire de l'efficacité, la fonction motrice était stabilisée après 24 mois de traitement par risdiplam selon l'évaluation par les échelles 32-item Motor Function Measure et Revised Upper Limb Module (cut-off 31/01/2022).
L'étude JEWELFISH se poursuit en Europe et aux États-Unis, produisant des données importantes de tolérance, pharmacodynamie, et efficacité de risdiplam dans une population large de patients déjà traités atteints de SMA.



POSTER - P59* - GROUPE 3
Physiologie / Fonction musculaire / Biomécanique / Métabolisme

Ricardo J. ANDRADE[1]
Ha-Hien-Phuong Ngo[2], *Javier Brum*[3], *Nicolas Benech*[3], *Simon Chatelin*[4], *Aude Loumeaud*[4], *Thomas Frappart*[5], *Christophe Fraschini*[5], *Armelle Magot*[6], *Yann Péréon*[6], *Antoine Nordez*[1], *Jean-Luc Gennisson*[2]

1. Nantes Université, Movement - Interactions - Performance, MIP, UR 4334, F-44000 Nantes, France
2. BioMaps, Université Paris Saclay, CEA, CNRS, Inserm, Orsay, France
3. Laboratorio de Acústica Ultrasonora, Instituto de Física, Facultad de Ciencias, Universidad de la República, Montevideo, Uruguay
4. ICube, CNRS UMR 7357, University of Strasbourg, Strasbourg, France
5. Hologic - Supersonic Imagine, Aix-en-Provence, France
6. CHU Nantes, Centre de référence pour les maladies neuromusculaires AOC, Filnemus, Euro-NMD, Hôtel-Dieu, 1 Pl. Alexis-Ricordeau, 44000 Nantes, France

Noninvasive quantification of elastic anisotropy factor by steered ultrasound pushing beams: towards a novel imaging biomarker of muscle health

Muscular diseases such as Duchenne muscular dystrophy (DMD) lack reliable biomarkers for disease progression and response to therapies. Tissue mechanical properties are vital for the structure and function of human physiological systems, and often reflect pathophysiological conditions. Ultrasound shear wave elastography (SWE) is an approach that uses focused pushing beams to generate shear waves and employs ultrafast ultrasound imaging to visualize and quantify shear wave propagation in biological soft tissues. In isotropic tissues like the liver, shear wave propagation is governed by tissue elasticity such that wave speed provides an accurate estimate of the shear modulus and, by extension, the Young's modulus – the most relevant measure of stiffness of a material. However, muscles exhibit significant anisotropy across multiple scales, with muscle fibers typically displaying a pennation angle. Collectively these factors influence wave propagation and the accurate muscle elasticity quantification, rendering its clinical applicability challenging. Here, we introduce an application of SWE that employs a novel steered pushing beam method in conjunction with ultrafast imaging beamformed along the steered pushing beams. We integrated this innovative approach into a commercial ultrasound scanner, making it possible to quantify new biomechanical markers such as in-plane muscle shear modulus and the elastic anisotropy factor – a promising indicator of muscle structural integrity. We first demonstrated the feasibility and validation of this approach using in vitro phantoms and ex vivo fusiform beef muscles. Further ex vivo validation was performed using tensile mechanical testing in pig fusiform muscles. We then applied this technique in vivo to assess, for the first time, the in-plane muscle shear modulus of pennate muscles and their anisotropy factor under different tensile muscle (active and passive) states in healthy humans. Finally, we performed preliminary tests on patients with DMD. This study highlights a translational proof of concept for a novel SWE approach, offering real-time quantification of new noninvasive mechanical variables with potential for monitoring neuromuscular diseases affecting tissue biomechanics. Further research is required to investigate the clinical value of these biophysical parameters.

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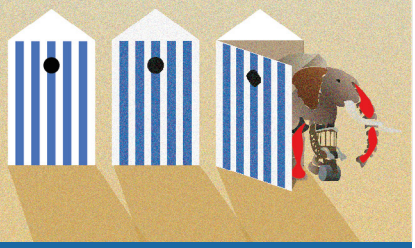

POSTER - P60* - GROUPE 4
Pathologie du nerf et motoneurone

Yvan DE FERAUDY[1]
Marie-Pierre Reboul[2], *Nadège Calmels*[3], *Amandine Vaidie*[4], *Caroline Stalens*[5], *Valérie Biancalana*[3], *Virginie Raclet*[2], *Marie de Castelmur*[6], *Virginie Haushalter*[3], *Sarah Romain*[7], *Carole André*[5], *Hervé Nabarette*[5], *Christian Cottet*[5], *Caroline Espil-Taris*[8], *Vincent Laugel* [1], *Didier Lacombe*[9,10], *pour le consortium DEPISMA*

1 Unité de neuropédiatrie, Hôpitaux Universitaires de Strasbourg, France
2 Laboratoire de génétique biologique, CHU de Bordeaux, France
3 Laboratoire de diagnostic génétique, Hôpitaux Universitaires de Strasbourg, France
4 Direction de la recherche clinique et de l'innovation, Hôpitaux Universitaires de Strasbourg, France
5 AFM-Téléthon, Evry, France
6 Département de recherche clinique, CHU de Bordeaux, France
7 Centre régional de dépistage néonatal, Hôpitaux Universitaires de Strasbourg, France
8 Service de neuropédiatrie, CHU de Bordeaux, France
9 Centre régional de dépistage néonatal, CHU de Bordeaux, France
10 Service de génétique médicale, CHU de Bordeaux, France

Projet préfigurateur DEPISMA : Étude de faisabilité du dépistage néonatal de l'amyotrophie spinale infantile en France

L'amyotrophie spinale infantile (ASI) est une maladie génétique sévère affectant les motoneurones périphériques. Elle concerne 1/7000 nouveau-nés et est principalement causée par une délétion homozygote de SMN1. Son pronostic varie en fonction du nombre de copies de SMN2, avec 60% de décès avant 18 mois pour la forme majoritaire (ASI type 1). Actuellement, 3 traitements peuvent être prescrits, dont l'efficacité diminue avec le stade d'avancée de la maladie lors de l'initiation. Un consensus scientifique existe pour le dépistage et le traitement pré-symptomatique de cette maladie. Plusieurs pays ont déjà initié un programme de dépistage néonatal moléculaire de l'ASI.

L'objectif du projet DEPISMA est de démontrer la faisabilité du dépistage néonatal systématique de l'ASI en France via la réalisation d'un test génétique ciblé, pour tous les nouveau-nés des régions Grand-Est et Nouvelle-Aquitaine, pendant 2 ans. Les critères de jugement principaux sont l'exhaustivité du dépistage et le délai naissance - discussion en RCP thérapeutique pour les cas positifs.

Le projet a débuté en décembre 2022. La totalité des maternités des deux régions a donné son accord pour participer au projet DEPISMA (n=81) : 79% recrutent, assurant une couverture des naissances de 85%. L'exhaustivité du dépistage est de 92% pour l'ensemble des maternités recrutantes. 26 873 nouveau-nés ont été dépistés : 2 nouveau-nés présentaient un test positif. Tous les deux étaient asymptomatiques lors de la consultation d'annonce. Le premier présentait 3 copies SMN2, a été discuté en RCP thérapeutique à J10 et a reçu une thérapie génique par onasemnogene abeparvovec à J27. Le second présentait 4 copies SMN2 et a été discuté en RCP thérapeutique à J17. Une abstention thérapeutique avec surveillance clinique et électromyographique a été préconisée.

Le projet DEPISMA est un pré-requis pour la généralisation du dépistage néonatal de l'ASI en France et ouvre la perspective de dépister de nouvelles pathologies.

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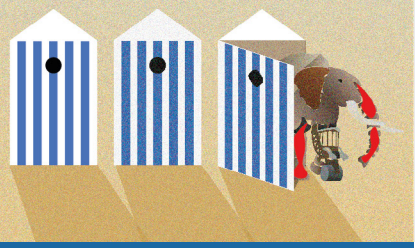

POSTER - P61* - GROUPE 3
Physiologie / Fonction musculaire / Biomécanique / Métabolisme

Marion BENOIST
Aghate Frank, Kevin Millet, Jeanne L'aîné, Norma Romero, Catherine Coirault, Marc Bitoun, Stéphane Vassilopoulos

Sorbonne université, INSERM, Institut de Myologie, Centre de Recherche en Myologie, UMRS-974, Paris, France.

Mechanosensitive clathrine platforms regulate YAP/TAZ signaling.

Long-lived clathrine plaques containing integrin beta 5 have been associated with sites of strong adhesion suggesting that they could also play a role in force transduction. Here we analyzed how clathrin plaques respond to mechanical cues in differentiated skeletal muscle myotubes. We show that branched actin networks surrounding clathrin plaques that are directly regulated by Dynamin 2 (DNM2), sequester YAP/TAZ mechanotransducers at the plasma membrane. Clathrin and Dynamin 2 are both required for basal YAP/TAZ nucleo/cytoplasmic distribution and endocytosis is required for an efficient nuclear translocation in response to mechanical stimuli. We show that DNM2 mutations that are responsible for centronuclear myopathy in humans deregulate YAP/TAZ signaling both in vitro and in vivo. Thus, clathrin plaques and associated dynamin 2 act as sensors conveying mechanical cues and integrate cell signaling with cytoskeletal regulation.

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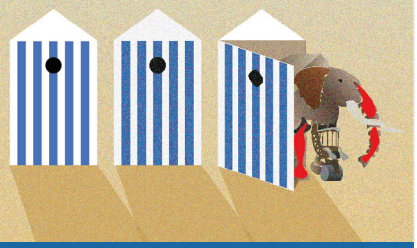


POSTER - P62 - GROUPE 4
Pathologie du nerf et motoneurone

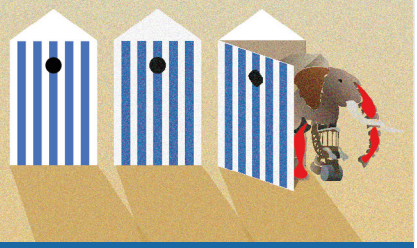
Elise DELAUNAY
Charlotte Lilien2, Jacqueline Montes3, Tina Duong4, Leslie Nelson5, Mercedes Martinez Moreno6, Heidi Rochau-Trumpp7, Enrica Rolle8, Romain Thomas9 , Irene Kanter-Schlifke10, Ayaka Yanagisawa1, Zsuzsanna Varga1, Sarah Clark11, Yacine Hadjiat1

1. Biogen, Paris, France
2. University of Oxford Medical Sciences Division, Oxford, UK
3. Columbia University Irving Medical Center, New York, NY, USA
4. Stanford University School of Medicine, Stanford, CA, USA
5. University of Texas Southwestern, Dallas, USA
6. Hospital Universitario La Paz, Madrid, Spain
7. University Hospital, Heidelberg, Germany
8. Department of Neuroscience, University of Turin, Torino, Italy
9. University Hospital, Lille, France
10. Biogen, Amsterdam, North Holland, Netherlands
11. Biogen, Baar, Switzerland

Developing a digital physical exercise solution for people living with neuromuscular disease: results from a co-creation process

People living with neuromuscular diseases (pwNMD) need tailored support to stay physically active. We addressed this need through a digital solution development to enable pwNMD to complete customized physical exercise programs developed by their physical therapist (PT). Physio.me has a patient-friendly user interface, with a 125-video library of pwNMD (ambulatory and non-ambulatory) performing exercises.
Biogen developed Physio.me through a process of co-creation with neurologists, expert PTs, and pwNMD which included interviews and 1-week diary project with pwNMD; literature reviews; input from 2 NMD expert neurologists, 1 physical medicine and rehabilitation specialist, and 7 PTs. NMD expert PTs and pwNMD collaborated to develop adapted exercise videos and a testing phase with 20 pwNMD and 3 healthcare professionals. The interviews, diary project, and literature reviews informed a robust assessment of the current state of physical exercise for pwNMD. Expert PTs described NMD clinical care pathways in different countries to ensure digital solution incorporation. Neurologists and PTs advised on medical roles associated with safety and exercise program development at their centers. Two groups will use Physio.me: PTs who create personalized exercise programs; pwNMD who view exercise videos for their individualized programs. A 6-week test at a French NMD center with 20 patients resulted in 5 key findings and >30 recommendations to improve Physio.me: pwNMD completed 79% of sessions, had an 80% retention and gave Physio.me an 'excellent' score for "easy to understand"; exercise videos featuring pwNMD were seen favorably; level of PT support impacted the experience of pwNMD with Physio.me; pwNMD feel more empowered when Physio.me allows individualization and further strengthens their connectivity with PTs; pwNMD wish to track progress towards personal goals and have more varied, evolving programs.
User-centered design is a powerful approach to ensure 2 key drivers of success for a digital solution: addressing true unmet needs and being easy to use with clear value for users. To gain the most insight on attitudes and shifts in behavior to physical activity, multiple quantitative and qualitative methodologies should be implemented to draw highly confident conclusions. Biogen, expert PTs, and pwNMD collaboration will ensure that Physio.me continues to evolve as an effective digital solution to improve access to individualized exercise programs.

20ÈME ÉDITION
JOURNÉES DE LA SOCIÉTÉ FRANÇAISE DE MYOLOGIE
15 - 17 Novembre 2023 • Palais des Congrès - Atlantia



POSTER - P63 - GROUPE 3
Physiologie / Fonction musculaire / Biomécanique / Métabolisme

Olivier BIONDI[1]
*S. Destinval[1], M. Kammoun[1], R. Saidi1, M. Erblang[1], Y.S. Gallot1, A. Malgoyre[1,2], C. Thomas-Junius[1],Tiphaine Mignot**

1. Laboratoire de Biologie de l'Exercice pour la Performance et la Santé (LBEPS), UMR, Université d'Evry, IRBA, Université de Paris Saclay, 91025 Evry-Courcouronnes, France
2. REF-Aero Department, French Armed Forces Biomedical Research Institute-IRBA, Brétigny-sur-Orge, France.
** Auteur Principal*

Exercise-specific effects on the motor performance, glycaemia regulation and muscle phenotype of a mouse model of Limb-Girdle Muscular Dystrophy R1 (Calpainopathy)

Calpainopathy is a common form of limb-girdle muscular dystrophy (LGMD R1) which arises from the homozygous deletion of the Calpain-3 gene, resulting in a progressive and symmetrical weakness of proximal muscles1. The CAPN3 mutation favors muscle sensitivity to exercise-induced damage and precludes proper adaptation to aerobic training2. Therefore, we investigated whether high-intensity non-damaging exercise could alleviate the disease progression in contrast to eccentric exercise in a mouse model of calpainopathy.

We observed a 13% decline in maximum aerobic performance in C3 mice compared to WT mice at each age examined. A 3-month swimming protocol, consisting of 30-min daily sessions between 2 and 5 months of age, improved their performance by 22% (from 3 months) and increased fatigue resistance by 54% (from 4 months), whereas a 3-month eccentric running protocol worsened both parameters by 22% (from 4 months) and 25% (from 3 months).

Additionally, we noted an 11% increase in the overall AUC on the glucose tolerance test in untrained C3 mice (at 4 months). The running protocol corrected this alteration while the swimming protocol did not. At 5 months of age, an 84% increase in regenerated myofibers was observed in the deltoid muscle of running trained C3 mice. In contrast, the swimming protocol had no significant impact on the dystrophic status of any of the muscles examined. Running and swimming resulted respectively in a 31% and 40% increase in type IIa myofibers in the deltoid muscle, and a 9% and 13% increase in type I myofibers in the soleus muscle, with no changes observed in the tibialis muscle. These adaptations remained below those observed in swimming-trained WT mice.

Our study demonstrates that high-intensity non-damaging exercise is well-tolerated in C3 mice. However, it failed to induce appropriate glucose and muscular adaptations under functional benefits, raising questions about the underlying mechanisms.

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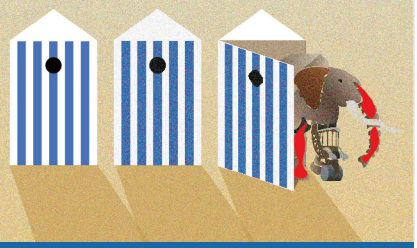

POSTER - P64 - GROUPE 4
Pathologie du nerf et motoneurone

Elise DELAUNAY[1]
Julie A. Parsons[3], *Nancy L. Kuntz*[4], *John F. Brandsema*[5], *Richard S. Finkel*[6], *Kathryn J. Swoboda*[7], *Riccardo Masson*[8], *Richard Foster*[10], *Yingying Liu*[9], *Corinne Makepeace*[10], *Samata Singhi*[9], *Angela Paradis*[9], *Zdenek Berger*[9], *Shweta Rane*[9], *Kathleen Somera-Molina*[9], *on behalf of the RESPOND Study Group, Crystal Proud*[1]*

1. Laboratoire BIOGEN
2. Children's Hospital of The King's Daughters, Norfolk, VA, USA
3. Children's Hospital Colorado, Aurora, CO, USA
4. Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
5. Children's Hospital of Philadelphia, Philadelphia, PA, USA
6. Center for Experimental Neurotherapeutics, St. Jude Children's Research Hospital, Memphis, TN, USA
7. Massachusetts General Hospital, Boston, MA, USA
8. Fondazione IRCCS Istituto Neurologico Carlo Besta Milan, Italy
9. Biogen, Cambridge, MA, USA
10. Biogen, Maidenhead, Berkshire, UK
* *Auteur Principal*

Interim results from the ongoing respond study evaluating nusinersen in children with spinal muscular atrophy previously treated with onasemnogene abeparvovec

Nusinersen has shown significant and clinically meaningful efficacy across a broad spectrum of SMA populations. Onasemnogene abeparvovec (OA) is an adeno-associated viral (AAV) vector gene replacement therapy. Animal models and limited human postmortem studies have demonstrated incomplete transduction of motor neurons by the AAV9 vector. Nusinersen has potential to increase SMN protein in untransduced motor neurons, which may provide additional clinical benefit to individuals with SMA. RESPOND (NCT04488133) is an open label, single-arm study evaluating nusinersen in children with SMA treated with OA >/=2 mo previously. We report interim results from the ongoing RESPOND study.

RESPOND participants have at least 1 SMN2 copy, are </=36 mo old, nusinersen-naive, and have investigator-determined suboptimal clinical status for at least 1 of these domains at baseline: motor function, respiratory support, swallowing/feeding ability, and other. Participants receive the approved 12-mg nusinersen regimen: 4 loading doses followed by maintenance doses every 4 mo. As of 15 November 2022, 38 children were enrolled and received nusinersen. Median (range) time from OA treatment to first nusinersen dose was 6.5 (3–31) mo. Median duration on nusinersen was 231 (range: 28–677) days. At baseline, 32/38 children demonstrated suboptimal clinical status in 2 or more domains after OA treatment; motor function (n=37) and respiratory function (n=25) were most common. Baseline mean (SD) HINE-2 total score was 6.1 (5.6) (n=37). Thirty-four of 38 participants had 2 SMN2 copies. AEs occurred in 31 (82%) participants. Thirteen [34%] participants had serious AEs; all considered unrelated to nusinersen. No events were considered related to the lumbar puncture procedure. No deaths were reported. Additional results including efficacy at Day 183 will be presented.

The majority of children enrolled in RESPOND to date showed suboptimal clinical status in multiple domains at baseline after previous treatment with OA. Preliminary safety data are consistent with nusinersen's safety profile, with no nusinersen-related serious AEs. Study recruitment is ongoing.

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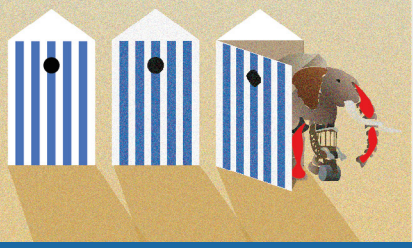


POSTER - P65* - GROUPE 3
Physiologie / Fonction musculaire / Biomécanique / Métabolisme

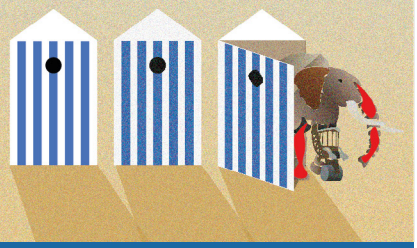
Maximilien BOWEN
Hourde Christophe , Durieux Anne-Cécile , Freyssenet Damien , Samozino Pierre , Morel Baptiste

Interuniversity laboratory in Biology of Movement, Savoie-Mont Banc University, Chambery, France
Interuniversity laboratory in Biology of Movement, Jean Monnet University, Saint-Etienne, France

Application of a force-velocity-endurance model to in situ muscle evaluation in mouse model

Introduction. The muscular contractile capacity is essential for human and animal movement and loco motion. Owing to their molecular structure, striated skeletal muscle cells produce a force that is a function of their rate of shortening. When the force production capacity of the neuromuscular system on an isolated muscle is explored, this relationship can be formulated mathematically by a rational function F(V) [1]. Moreover, the intensity of this force decreases as a function of the duration F(t), and converges towards a characteristic crit ical intensity [2]. The interaction between these two fundamental relationships has been studied only through independent comparisons. Considering them as two projections of a single force-velocity-time relationship [3] would make it possible to describe the force production capacities and their interactions in their entirety. The aim of this conceptual framework is to use an integrative model to unify a new Force-Velocity-Endurance (FVE) relationship that can define muscle properties and fatigability. Methods. This new theoretical framework proposes a model that is a function of two variables (time t and velocity V), and seven major parameters to describe muscle properties: initial fatigue-free capacities (initial force (F0i), initial velocity (V0i), initial curvature (Ci) coefficients), critical capacities (F0c ,V0c , Cc) and a characteristic time τ corresponding to the rate of capacity decline. To measure these parameters, a new 3 min all-out test with velocity variation was developed on an isokinetic ergometer (Aurora Scientific 300C) to scan the maximum capacities of the FVE surface, on both the velocity and time dimensions. The model was tested on 12 wild-type mice (six males and sixfemales) for the tibialis anterior (TA) and gastrocnemius (GA) muscles. Results and discussion. The goodness of fit of the model from the experimental data was excellent for all muscles ($r^2 > 0.97$). The proposed model revealed significant differences between the TA and GA muscle groups. For males, F0i , F0c and αwere higher for GA compared to TA. Considering females, F0i was significantly higher for GA but relative F0c was higher for TA. This new model also revealed differences in the muscle capacity as a function of sexual dimorphism. For instance, F0i was sgnificanlty higher for males compared to female only for TA but not GA muscles. Conclusions and perspectives. These results demonstrate that it is possible to determine the individual parameters of the proposed model (F0i, V0i, Ci, F0c, V0c, Cc and τ) from the experimental data obtained from the proposed all-out test. Validating the existence of a universal FVE relationship and its theoretical foundations would open a new conceptual framework for improving our understanding of muscle function. Although this project is fundamental, the practical applications resulting from this new framework could be numerous, such as functional analysis of gene therapy in myology or the impairment of neuromuscular function in patients.

**Éligible pour le prix du meilleur Poster*



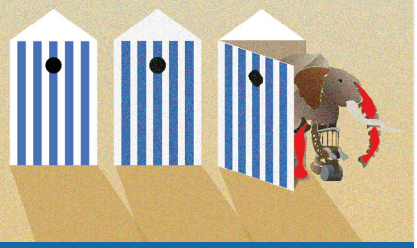
POSTER - P66 - GROUPE 4
Pathologie du nerf et motoneurone

Jean-Yves HOGREL
Joackim Audren, Audrey El Kaim, Valérie Decostre, Oriana Tarabay, Anthony Béhin, Marion Masingue, Guillaume Bassez, Tanya Stojkovic

Institut de Myologie

Test-retest reliability and associations of some functional tests for the follow-up of patients with SMA

The advent of therapies for the treatment of spinal muscular atrophy (SMA) has required the implementation of a consistent patient follow-up to identify the benefits of these therapies in the adult population. The neuromuscular disease reference centre at the Institute of Myology (University Hospital Pitié-Salpêtrière, Paris) has drawn up a roadmap in line with the Filnemus initiative. These assessments were initially synchronized with nusinersen injections, hence the same evaluations were done twice within a two-week intervals (D0 and D14). Assessments were then extended to all treated patients with the same modalities, providing an opportunity to explore the test-retest reliability of the selected assessments. The assessments were as follows: Vignos and Brooke scores, grip and pinch strength, MoviPlate test, nine-hole peg test (9HPT), Motor Function Measurement (MFM) scale, plus, for ambulant patients, a 6-minute walk test (6MWT) and a 30-s sit-to-stand test (30sSTS). Respiratory assessments (FVC, MIP and MEP) were also available as optional. The Revised Upper Limb Module (RULM) was also introduced more recently on a systematic basis. The aim of this study was to explore the test-retest reliability of the selected assessments, as well as the correlations between them.
Thirty-two patients with SMA type 1, 2 or 3 (n=1, 6 and 25, respectively) were included in the analysis, 22 started nusinersen and 10 initiated risdiplam treatment at D0. The results showed the absence of a learning or treatment effect between the D0 and D14 visits. They underlined the excellent reproducibility of the tests, with intra-class correlation coefficients all above 0.95. The standard error of measurement was below 12% for all tests except the 9HPT. The vast majority of the tests was also well correlated ($P<0.001$).
The tests classically used to assess treatment efficacy are generally reliable. Analysis of their variability can help in recommending the use of the most appropriate outcome measures to assess treatment. In addition, the correlations between the results of the various functional tests should make it possible to reduce the number of tests to be carried out. Based on the best reliability, lowest variability and correlations with other tests, our results suggest that grip strength, MFM, RULM, FVC and 6MWT are optimal outcome measures.



POSTER - P67 - GROUPE 3
Physiologie / Fonction musculaire / Biomécanique / Métabolisme

Caroline CIENIEWSKI-BERNARD[1]
Charlotte Claeyssen[1], *Onnik Agbulut*[3], *Nathan Bulangalire*[1,2]*

1. Univ. Lille, Univ. Artois, Univ. Littoral Côte d'Opale, ULR 7369 - URePSSS - Unité de Recherche Pluridisciplinaire Sport Santé Société, F-59000 Lille, France
2. Université de Lille, CHU Lille, F-59000 Lille, France
3. Sorbonne Université, Institut de Biologie Paris-Seine (IBPS), CNRS UMR 8256, Inserm ERL U1164, Biological Adaptation and Ageing, 75005, Paris, France
**Auteur Principal*

Impact of proteotoxic stress on αB-crystallin partition, post-translational modifications, and interaction with desmin intermediate filaments protein

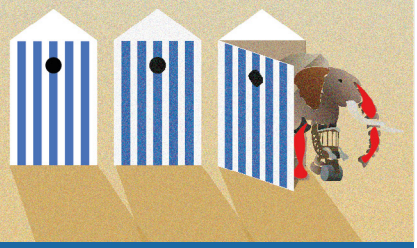
Myofibrillar myopathies are characterised by abnormal accumulation of misfolded myofibrillar proteins. In the case of desminopathies, desmin intermediate filaments aggregate taking away their partners, leading to a dramatic myofibrils disorganization and a loss of muscular function.

The alphaB-crystallin (HSPB5), a small heat shock protein (sHSP), is a sensor for assembly of desmin intermediate filaments and a major chaperone in striated muscle cells. Over its chaperone activity, alphaB-crystallin is involved in several cellular functions such as cell integrity, cytoskeleton stabilization, or aggresome formation.

The functions of alphaB-crystallin are modulated through post-translational modifications. Thus, alphaB-crystallin is known to be phosphorylated, phosphorylation interfering with its oligomerization and partition. Moreover, alphaB-crystallin is also modified by O-GlcNAcylation, an atypical glycosylation presenting a highly dynamic interplay with phosphorylation.

Although little is known about alphaB-crystallin O-GlcNAcylation in muscle cells, recent reports demonstrated that O-GlcNAcylation could be involved in the modulation of its interaction with protein partners and in stress-induced translocation of alphaB-crystallin.

Here we investigated in a cellular model of C2C12 myotubes how proteotoxic stress (i.e. proteasome inhibition) modifies the chaperone's expression, its sub-cellular localization, and its interaction with desmin. We connected these results to the O-GlcNAcylation and the phosphorylation status of the sHSP. We expect to identify a post-translational modifications pattern on alphaB-crystallin that would maximize the chaperone benefits towards desmin aggregation.



POSTER - P68 - GROUPE 4
Pathologie du nerf et motoneurone

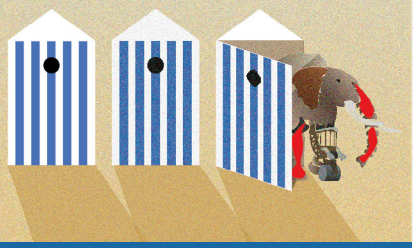
Nicolas JAN-LAFAGE[7]

Claudia A Chiriboga[3], Laurent Servais[4,6], Nicolas Jan-Lafage[7], Basil T Darras[8], John W Day[9], Nicolas Deconinck[10,11], Michelle A Farrar[12], Richard S Finkel[13], Enrico Bertini[14], Janbernd Kirschner[15], Riccardo Masson[2], Maria Mazurkiewicz-Bełdzińska[16], Dmitry Vlodavets[17], Silvia Bader-Weder[18], Ksenija Gorni[19], Birgit Jaber[18], Wai Yin Yeung[20], Gergely Papp[18], Renata S Scalco[21], Eugenio Mercuri[22] au nom des groupes d'étude FIREFISH, SUNFISH, JEWELFISH et RAINBOWFISH, Giovanni Baranello[1]*

1. The Dubowitz Neuromuscular Centre, NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Institute of Child Health University College London, & Great Ormond Street Hospital Trust, Londres, Royaume-Uni.
2. Developmental Neurology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italie.
3. Department of Neurology, Columbia University Irving Medical Center, New York, NY, États-Unis
4. MDUK Oxford Neuromuscular Centre, Department of Paediatrics, University of Oxford, Oxford, Royaume-Uni
5. Division of Child Neurology, Centre de Références des Maladies Neuromusculaires, Department of Pediatrics, University Hospital Liège & University of Liège, Liège, Belgique
6. I-Motion, Institut de Myologie AP-HP, Hôpital Armand Trousseau, Paris, France
7. Roche SAS, 92 100 Boulogne-Billancourt, France
8. Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, États-Unis
9. Department of Neurology, Stanford University, Palo Alto, CA, États-Unis
10. Centre de Référence des Maladies Neuromusculaires, Queen Fabiola Children's University Hospital, Université Libre de Bruxelles, Bruxelles, Belgique
11. Neuromuscular Reference Center, UZ Gent, Ghent, Belgique
12. Sydney Children's Hospital Network and UNSW Medicine, UNSW Sydney, Sydney, Australie
13. Center for Experimental Neurotherapeutics, St Jude Children's Research Hospital, Memphis, TN, États-Unis
14. Research Unit of Neuromuscular and Neurodegenerative Disorders, Bambino Gesù Children's Research Hospital IRCCS, Rome, Italie
15. Department of Neuropediatrics and Muscle Disorders, Faculty of Medicine, Medical Center-University of Freiburg, Freiburg, Allemagne
16. Department of Developmental Neurology, Medical University of Gdańsk, Gdańsk, Pologne
17. Russian Children Neuromuscular Center, Veltischev Clinical Pediatric Research Institute of Pirogov Russian National Research Medical University, Moscou, Russie
18. Pharma Development, Safety, F. Hoffmann-La Roche Ltd, Bâle, Suisse
19. PDMA Neuroscience and Rare Disease, F. Hoffmann-La Roche Ltd, Bâle, Suisse
20. Roche Products Ltd, Welwyn Garden City, Royaume-Uni
21. Pharma Development Neurology, F. Hoffmann-La Roche Ltd, Bâle, Suisse
22. Pediatric Neurology Institute, Catholic University and Nemo Pediatrico, Fondazione Policlinico Gemelli IRCCS, Rome, Italie
**Auteur Principal*

Actualisation des données groupées de tolérance issues du programme de développement clinique de risdiplam dans l'amyotrophie spinale (SMA)

Risdiplam (EVRYSDI®) est un modificateur d'épissage du pré-ARNm du gène SMN2, à distribution centrale et périphérique, administré per os, autorisé dans plus de 90 pays.
Le programme de développement clinique de risdiplam comprend 4 études :
• FIREFISH (NCT02913482) dans la SMA de type 1 ; critère d'inclusion (CI): âge 1-7 mois à l'inclusion;
• SUNFISH (NCT02908685) dans la SMA de type 2/3 ; CI : 2-25 ans à l'inclusion;
• JEWELFISH (NCT03032172) chez des patients prétraités (RG7800 (RO6885247), nusinersen, olesoxime ou onasemnogene abeparvovec, CI : 6 mois-60 ans à l'inclusion;
• RAINBOWFISH (NCT03779334) dans la SMA présymptomatique, CI : 0-6 semaines à la 1ère dose.
Les analyses précédentes sur 465 patients symptomatiques des études FIREFISH, SUNFISH et JEWELFISH (cut-off 23/11/2021, 06/09/2021 et 31/01/2022, respectivement) et 18 patients présymptomatiques de l'étude RAINBOWFISH (cut-off 01/07/2021) ont montré que risdiplam avait un profil de tolérance favorable, aucun événement indésirable (EI) lié à risdiplam n'ayant conduit à un arrêt du traitement. Aucun EI grave n'a été rapporté dans RAINBOWFISH et le profil de tolérance semble refléter l'âge du patient. Chez les patients symptomatiques, le taux global d'EI a diminué avec la poursuite du traitement. Les EI les plus fréquents selon la classification MedDRA étaient les infections et les EI gastro-intestinaux. Une baisse rapide du taux d'EI gastro-intestinaux a été observée au cours des 4 premières semaines de traitement. Aucune tendance n'est observée sur le taux d'EI infectieux au cours des 6 premiers mois. Les EI graves ont diminué dans la SMA de type 1 mais sont restés stables dans les SMA de type 2/3.
Les analyses de tolérance actualisées des études évaluant risdiplam seront présentées. Des données de tolérance actualisées seront publiées chaque année jusqu'à ce que les patients aient atteint 5 ans de traitement.



POSTER - P69 - GROUPE 3
Physiologie / Fonction musculaire / Biomécanique / Métabolisme

Catherine COIRAULT[2]
Emeline Cherchame[2], *Saline Jabre*[1*]

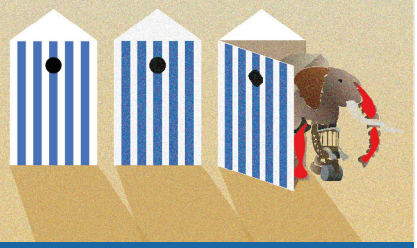
1. Sorbonne Universite; Inserm; Université Saint Esprit Kaslik
2. Sorbonne Université; Inserm; Paris Brain Institute, Data Analysis Core platform
** Auteur Principal*

A-type lamins are crucial to preserve chromatin states during mechanical loading in skeletal muscle

Background. Skeletal muscles are submitted to large loads and deformations that are transmitted to their myonuclei, regulating crucial roles in the maintenance and plasticity of these tissues.

Aims. Our general aim was to gain insights into the effects of acute mechanical stretch on chromatin modifications and their functional consequences in skeletal muscle. We tested whether acute mechanical loading could alter chromatin organization in human myotubes and analyzed the role of A-type lamins, encoded by the LMNA gene, to prevent such potential modifications.

Results. By studying human myotubes submitted to 10% cyclic mechanical stretch for 4hs, i.e., a mechanical loading that mimic acute muscle exercise, we found that mechanical loading in control myotubes did not increase condensed and transcriptionally inactive heterochromatin levels when compared to static controls, as attested by the no significant changes in H3K9me3 and H3K27me3 histone marks. H3K4me3 histone mark, which is associated with the transcriptionally active euchromatin did not change as well in control myotubes after stretch. Compared with static control, A-type lamin deficiency, done using the siRNA technique, reduced H3K27me3 and increase H3K9me3 histone marks. Mechanical loading was associated with significantly increased in H3K4me3 euchromatin marks and reduction in H3K27me3 in A-type lamin deficient myotubes. To confirm potential changes in chromatin states, we performed ATAC-seq analysis. Differential accessibility regions (DARs) analysis of static vs loaded control myotubes revealed only 29 upregulated peaks and 13 downregulated peaks in control after mechanical loading. Lamin deficiency was associated with a global increase in chromatin accessibility with 364 peaks up, and 177 peak down in static LMNA deficient myotubes compared to controls. Importantly, chromatin accessibility largely differed between stretched controls and stretched LMNA deficient myotubes, with 1739 upregulated and 1092 downregulated DA peaks.
Together, our findings indicate that A-type lamins are crucial to preserve chromatin states during acute mechanical load in human myotubes.



POSTER - P70* - GROUPE 4
Pathologie du nerf et motoneurone

Véronique MANEL[3]

John W Day[2], *Nicolas Deconinck*[4,5], *Elena S Mazzone*[6], *Andres Nascimento*[7], *Kayoko Saito*[8], *Carole Vuillerot*[9,10], *Giovanni Baranello*[11,12], *Odile Boespflug-Tanguy*[13,14], *Nathalie Goemans*[15], *Janbernd Kirschner*[16], *Anna Kostera-Pruszczyk*[17], *Laurent Servais*[13,18,19], *Jessica Braid*[20], *Marianne Gerber*[21], *Ksenija Gorni*[22], *Carmen Martin*[20], *Wai Yin Yeung*[20], *Renata S Scalco*[22], *Eugenio Mercuri*[6], *au nom du groupe d'étude SUNFISH, Maryam Oskoui*[1*]

1. Departments of Pediatrics and Neurology Neurosurgery, McGill University, Montréal, Canada
2- Department of Neurology, Stanford University, Palo Alto, CA, États-Unis
3- Service de Médecine physique et réadaptation pédiatrique, Hôpital Mère Enfant, CHU Lyon, Lyon, France
4- Neuromuscular Reference Center and Paediatric Neurology Department, Queen Fabiola Children's University Hospital, Université Libre de Bruxelles, Bruxelles, Belgique
5- Neuromuscular Reference Center, UZ Gent, Ghent, Belgique
6- Pediatric Neurology Institute, Catholic University and Nemo Pediatrico, Fondazione Policlinico Gemelli IRCCS, Rome, Italie
7- Neuromuscular Unit, Neuropaediatrics Department, Hospital Sant Joan de Déu, Fundacion Sant Joan de Déu, CIBERER - ISC III, Barcelone, Espagne
8- Medical Genetics Institute, Tokyo Women's Medical University, Tokyo, Japon
9- Department of Pediatric Physical Medicine and Rehabilitation, Hôpital Mère Enfant, CHU-Lyon, Lyon, France
10- Neuromyogen Institute, CNRS UMR 5310 - INSERM U1217, Université de Lyon, Lyon, France
11- The Dubowitz Neuromuscular Centre, NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Institute of Child Health University College London, & Great Ormond Street Hospital Trust, Londres, Royaume-Uni
12- Developmental Neurology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italie
13- IMotion Institut de Myologie AP-HP, Hôpital Armand Trousseau, Paris, France
14- Université Paris Cité, UMR 1141, NeuroDiderot, Paris, France
15- Neuromuscular Reference Centre, Department of Paediatrics and Child Neurology, University Hospitals Leuven, Louvain, Belgique
16- Department of Neuropediatrics and Muscle Disorders, Faculty of Medicine, Medical Center-University of Freiburg, Freiburg, Allemagne
17- Department of Neurology, Medical University of Warsaw, Varsovie, Pologe
18- MDUK Oxford Neuromuscular Centre, Department of Paediatrics, University of Oxford, Oxford, Royaume-Uni
19- Division of Child Neurology, Centre de Références des Maladies Neuromusculaires, Department of Pediatrics, University Hospital Liège & University of Liège, Liège, Belgique
20- Roche Products Ltd, Welwyn Garden City, Royaume-Uni
21- Pharma Development, Safety, F. Hoffmann-La Roche Ltd, Bâle, Suisse
22- PDMA Neuroscience and Rare Disease, F. Hoffmann-La Roche Ltd, Bâle, Suisse
23- Pharma Development Neurology, F. Hoffmann-La Roche Ltd, Bâle, Suisse.
** Auteur Principal*

SUNFISH Parties 1 et 2 :
Efficacité et tolérance à 4 ans de risdiplam dans l'amyotrophie spinale (SMA) de types 2 et 3

L'amyotrophie spinale (SMA) touche des individus avec un large spectre d'âge et de gravité. Risdiplam (EVRYSDI®) est un modificateur d'épissage du pré-ARNm du gène SMN2, à distribution centrale et périphérique, administré per os, autorisé dans plus de 90 pays.
SUNFISH (NCT02908685) est une étude multicentrique en double aveugle, randomisée, chez des patients atteints de SMA de type 2/3 (critère d'inclusion : âge 2-25 ans à l'inclusion). SUNFISH partie 1 (N=51) a évalué la tolérance et la pharmacocinétique / pharmacodynamie de différentes doses de risdiplam chez des patients atteints de SMA de type 2/3 (ambulants et non-ambulants). La partie 2 (N=180) a évalué l'efficacité et la tolérance, versus placebo, de la dose de risdiplam sélectionnée en partie 1 dans la SMA de type 2 ou de type 3 non-ambulants. Dans la partie 2, les patients ont reçu risdiplam ou placebo pendant 12 moins ; puis risdiplam en aveugle jusqu'au Mois 24. Au Mois 24 l'entrée dans l'étude d'extension en ouvert était proposée aux patients.
Le critère principal de la partie 2, portant sur l'évolution du score MFM-32 (32-item Motor Function Measure) depuis l'inclusion, chez les patients sous risdiplam (N=120) versus placebo (N=60) a été atteint au Mois 12. Ces améliorations des fonctions motrices ont été maintenues pendant les 2e et 3e années après le traitement avec risdiplam selon les évaluations des échelles MFM32, HFMSE et RULM. Au Mois 36 (cut-off 06/09/2021) aucun effet indésirable lié au traitement n'a conduit un patient à quitter l'étude, que ce soit la partie 1 ou la partie 2. Nous présentons ici les résultats d'efficacité et de tolérance de risdiplam à 4 ans (48 mois) de traitement.
SUNFISH est en cours et apportera des données supplémentaires d'efficacité et de tolérance à long terme dans une population d'enfants, adolescents et adultes atteints de SMA.

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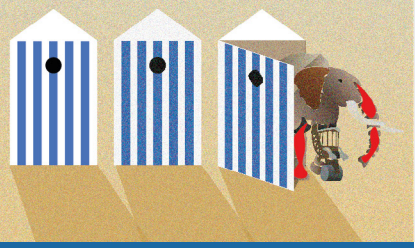

POSTER - P71* - GROUPE 3
Physiologie / Fonction musculaire / Biomécanique / Métabolisme

Carole DABADIE[1]
Anita Kneppers[1], *Elise Belaïdi*[2], *Rémi Mounier*[1]

1. Institut Neuromyogène - Laboratoire Physiopathologie et Génétique du Neurone et du Muscle - Université Claude Bernard Lyon 1 CNRS UMR 5261 - Inserm U1315 - Lyon, France
2. Laboratoire de Biologie Tissulaire et Ingénierie thérapeutique - Université Claude Bernard Lyon 1 - CNRS UMR 5305 - Lyon, France

Striated skeletal muscle resistance to metastasis: Understanding the molecular and cellular mechanisms

Cancer is a leading cause of mortality worldwide, which is mainly due to the development of secondary tumors at distant sites, called metastases. Metastasis formation relies on complex interactions between disseminated tumor cells and their environment. Interestingly, cancer rarely metastasizes to skeletal muscle. The muscle has the unique ability to contract, which influences its local metabolic environment. We therefore hypothesize that contraction-induced oxygen availability and metabolic changes, including metabolite release or depletion, in the muscle microenvironment, have anti-metastatic effects. The purpose is to comprehend the mechanisms conferring skeletal muscle resistance to metastasis.

Using a custom-made ex vivo muscle contraction setup, we first assessed the "physiological exercise-like response" of soleus (SOL) and extensor digitorum longus (EDL) to a 1-hour protocol of electrical pulse stimulation (EPS). EPS decreased maximal force by 95% and 97% for SOL and EDL respectively. Muscle glycogen was reduced by 58% and 29%. Lactate release was increased in the conditioned medium (CM) by 28% and 22%. Lactate dehydrogenase levels remained undetectable, suggesting no muscle damage. To evaluate the potential impact of muscle contraction on metastatic formation, we assessed the effect of CM collected after EPS on migration and proliferation of lung cancer cells (A549). Preliminary results suggest anti-metastatic effects of SOL contraction, as migration and proliferation tented to decrease in cells treated with CM after EPS compared to no-EPS controls. Importantly, we observed an effect of electrical current per se, potentially masking muscle contraction effects. Therefore, we developed a setup to induce muscle contraction by direct nerve stimulation, which will be used to validate the "physiological response" induced by field stimulation of EDL/SOL and to assess the effect of CM on metastatic properties. Moreover, to study metabolic alterations and oxygen availability interactions in the muscle microenvironment, we will perform the same experiments at physiological low O2 partial pressure.

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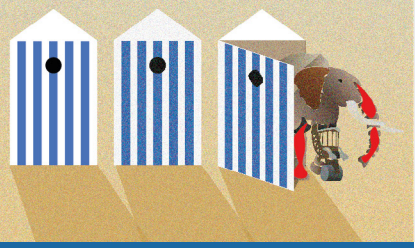

POSTER - P72 - GROUPE 4
Pathologie du nerf et motoneurone

Brice MARCHADIER[6]

Richard S Finkel[1], Michelle A Farrar[2], Laurent Servais[3,5], Brice Marchadier[6], Dmitry Vlodavets[7], Edmar Zanoteli[8], Mohammad Al-Muhaizea[9], Alexandra Prufer[10], Leslie Nelson[11], Carolyn Fischer[12], Marianne Gerber[13], Ksenija Gorni[14], Heidemarie Kletzl[15], Laura Palfreeman[12], Eleni Gaki[12], Paulo Fontoura[14], Enrico Bertini[17], au nom du groupe d'étude RAINBOWFISH,*

1. Center for Experimental Neurotherapeutics, St Jude Children's Research Hospital, Memphis, TN, États-Unis
2. Sydney Children's Hospital Network and UNSW Medicine, UNSW Sydney, Sydney, Australie
3. MDUK Oxford Neuromuscular Centre, Department of Paediatrics, University of Oxford, Oxford, Royaume-Uni
4. Division of Child Neurology, Centre de Références des Maladies Neuromusculaires, Department of Pediatrics, University Hospital Liège & University of Liège, Liège, Belgique
5. I-Motion Institut de Myologie AP-HP, Hôpital Armand Trousseau, Paris, France
6. Roche SAS, Boulogne-Billancourt, France
7. Russian Children Neuromuscular Center, Veltischev Clinical Pediatric Research Institute of Pirogov Russian National Research Medical University, Moscou, Russie
8. Department of Neurology, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brésil
9. Department of Neurosciences, King Faisal Specialist Hospital & Research Center-Riyadh, Riyadh, Arabie Saoudite
10. Federal Uni Rio de Janeiro, Rio de Janeiro, Brésil
11. UT Southwestern Medical Center, Dallas, TX, États-Unis
12. Roche Products Ltd, Welwyn Garden City, Royaume-Uni
13. Pharma Development, Safety, F. Hoffmann-La Roche Ltd, Bâle, Suisse
14. PDMA Neuroscience and Rare Disease, F. Hoffmann-La Roche Ltd, Bâle, Suisse
15. Roche Pharmaceutical Research and Early Development, Roche Innovation Center Basel, Bâle, Suisse
16. Pharma Development Neurology, F. Hoffmann-La Roche Ltd, Bâle, Suisse
17. Research Unit of Neuromuscular and Neurodegenerative Disorders, Bambino Gesù Children's Research Hospital IRCCS, Rome, Italie
** Auteur Principal*

RAINBOWFISH (NCT03779334) résultats préliminaires d'efficacité et tolérance du risdiplam dans une population pré-symptomatique de nouveaux nés atteints d'amyotrophie spinale (SMA)

Risdiplam (EVRYSDI®) est un modificateur d'épissage du pré-ARNm du gène SMN2, à distribution centrale et périphérique, administré per os, autorisé dans plus de 90 pays.
RAINBOWFISH, étude ouverte, simple bras, multicentrique, évalue l'efficacité, la tolérance et le profil PK/PD (pharmacocinétique/pharmacodynamique) de risdiplam. Les nourrissons inclus (0-6 semaines à la 1ère dose) ont un diagnostic génétique de SMA, sans critère sur le nombre de copies de SMN2 et sont pré-symptomatiques.
Le critère principal est la proportion de nourrissons – avec 2 copies SMN2 et une amplitude des potentiels d'action musculaires (CMPA) ⩾1,5 mV à l'inclusion – tenant assis sans soutien pendant ⩾5 secondes (selon item 22, BSID-III-ST [Gross Motor Scale of the Bayley Scales of Infant and Toddler Development, 3e édition]). Les critères secondaires comprennent : le développement des signes cliniques de SMA, la survie et ventilation permanente ; l'acquisition des étapes motrices, la fonction motrice, les mesures de croissance, l'état nutritionnel, la CMAP, PK/PD et la tolérance.
L'âge médian à la première dose était de 26,5 jours (min-max : 16-40 jours) pour les 18 premiers nourrissons inclus (cut-off : 01/07/2021). Aucun événement indésirable grave lié au traitement n'a été rapporté chez les nourrissons traités pendant ⩽22,8 mois. Une analyse préliminaire de sept nourrissons traités pendant ⩾12 mois a montré que la plupart avaient atteint des scores proches du maximum sur l'échelle CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) à l'âge de 4-5 mois et avaient les capacités motrices conformes aux critères de l'Organisation mondiale de la santé pour les enfants en bonne santé. Les sept nourrissons traités pendant ⩾12 mois étaient en vie sans ventilation permanente, conservaient leurs capacités de déglutition et d'alimentation, sans besoin d'hospitalisation.
Nous rapportons ici les résultats de l'analyse intermédiaire de RAINBOWFISH au Mois 12.

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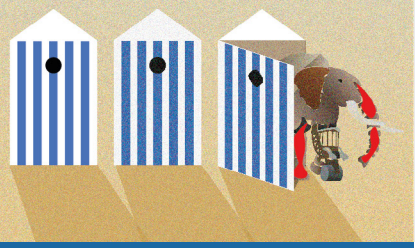

POSTER - P73* - GROUPE 3
Physiologie / Fonction musculaire / Biomécanique / Métabolisme

Tanushri DARGAR[1]
Estèle Lafont[1], *Alexandre Janin*[1], *Valérie Risson*[1], *Philippe Chevalier*[1], *Marie Abitbol*[1,2], *Vincent Gache**[1]

1. Institut NeuroMyoGène, CNRS UMR 5261 -INSERM U1315, University of Lyon - University Claude Bernard Lyon 1, France
2. VetAgro Sup, Marcy-l'Etoile, France
** Corresponding author*

Decoding the contribution of microtubule network organization in cardiac muscle cell functioning

Cells are continuously exposed to external physical forces which are converted into biochemical signals to induce adaptive response. This process, known as mechanotransduction, links the cell surface to DNA transcriptional activity through the network of cytoskeletal and nuclear envelope proteins. Consequently, mechanotransduction emerges as a key player in regulating numerous cellular processes and signaling pathways.

In a mechanically dynamic organ like the heart, cardiac cells are constantly under the influence of mechanical force emanating from themselves and the neighboring cells as they continuously undergo repeated contraction and relaxation cycles. Cardiac cells, due to the presence of contractile structures, have to adapt their mechanotransduction to these conditions to keep the behavior of cardiomyocytes. Mechanical stresses lead to pathological remodeling of cardiomyocytes which includes alteration of contractility, force generation, sarcomere length, intracellular signaling pathways and intercellular communication. Recently, cytoskeletal components, especially the microtubule (MT) network, have been implicated in the cardiac cell's functionality. Therefore, it is crucial to understand the role of the MT network in sustaining cardiac contraction and its mechanotransduction adaptation. Our project aims to decipher the contribution of two regulators of the MTs network: one directly involved in the control of MT polymerization (ALMS1), and the other one, as a modulator of the MT organization in muscle cells (LMNA).

We identified a feline missense mutation in the ALMS1 gene, suspected to cause hypertrophic cardiomyopathy in cats. ALMS1 is a centrosome associated protein, involved in microtubule polymerization, dynamics and architecture. We used CRISPR-Cas9 gene editing to introduce the mutation of interest in human iPS cells. In parallel, we identified a missense mutation in the LMNA gene in a patient suffering from dilated cardiomyopathy and developed patient-derived iPS cells.

We used iPSCs-derived cardiomyocyte protocols to study the effect of respective mutation on the behavior of myonuclei and cytoskeleton architecture, with a special interest in the MT network by performing molecular analysis using immunofluorescence imaging and gene expression profiles. We also assessed the contractile properties of cardiomyocytes.

We aim to gain insights into the pathophysiology associated with cardiac diseases with a precise interest in the MT network

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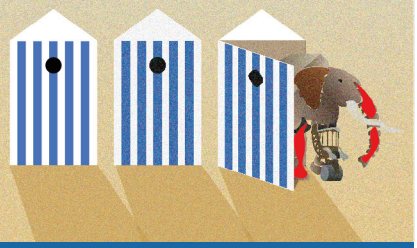


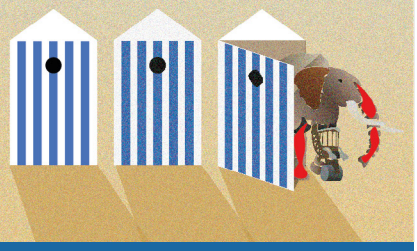
POSTER - P74 - GROUPE 4
Pathologie du nerf et motoneurone

Catherine SARRET
Céline Fabry, Bénédicte Pontier, Nelly Dubois, Yves Bourdeau, Christophe Prudhomme, Fanny Laffargue, Marie De Antonio

CHU Clermont-Ferrand

Evaluation longitudinale des maladies neuromusculaires pédiatriques par les MyoTools en pratique courante sur un centre de référence neuromusculaire

Les pathologies neuromusculaires entrainent une atteinte de la fonction motrice qui peut affecter les membres supérieurs et impacter les activités quotidiennes. Les MyoTools (MyoPinch, MyoGrip) sont des dynamomètres de haute précision validés dans les pathologies neuromusculaires qui mesurent de manière sensible, fiable, et reproductible la force musculaire du membre supérieur.
Notre étude rétrospective décrit l'évolution de la motricité du membre supérieur par les MyoTools dans différentes pathologies neuromusculaires chez les patients de 0 à 20 ans suivis dans le centre neuromusculaire pédiatrique de Clermont-Ferrand.
Les données étaient recueillies entre 2018 et 2023 comprenant les mesures des Myotools, le diagnostic neuromusculaire, l'âge, les mensurations, la latéralité, la MFM32, le 6MWT et le statut de marche. Le critère de jugement principal était l'évolution des mesures des Myotools. Les critères de jugement secondaires étaient la corrélation entre MyoTools, MFM32, statut de marche et 6MWT.
Les résultats obtenus sont superposables aux tendances déjà décrites dans l'amyotrophie spinale et les dystrophinopathies. Ils donnent une idée préliminaire du profil évolutif des patients dans d'autres pathologies neuromusculaires. Bien que la force musculaire rapportée à la valeur théorique pour l'âge évolue défavorablement dans certaines pathologies traitées, l'analyse évolutive des données brutes montre une relative stabilisation ou amélioration dans un contexte de thérapie innovante.
Cette étude confirme l'intérêt du suivi objectif longitudinal de la force des membres supérieurs chez les patients neuromusculaires et du développement de normes pour les différentes pathologies neuromusculaires pédiatriques.



POSTER - P75 - GROUPE 3
Physiologie / Fonction musculaire / Biomécanique / Métabolisme

Olivier DUPONT
Stéphane König,Maud Frieden

Département de Physiologie et Métabolisme, Université de Genève

Roles of the two STIM2 isoforms in human myotube formation and function

Store-operated Ca2+-entry (SOCE) is fundamental during myogenesis and involves the plasma membrane Ca2+ channel Orai and the sarcoplasmic reticulum (SR) resident Ca2+ sensor STIM. Ca2+ store depletion activates SOCE, and cytosolic Ca2+ is eventually pumped back into the SR by the SERCA pumps. Skeletal muscles express STIM1 and STIM2, both having as well splicing isoforms. Thus, STIM2.1 was shown to act as a negative regulator of SOCE, while STIM2.2 acts classically as an activator. We confirmed by qPCR the presence of both STIM2 isoforms, with STIM2.1 being more expressed in myotubes. Our study aims to understand the implication of STIM2.1 and STIM2.2 on human myogenesis, cell proliferation, differentiation, and function of human myotubes.
Myoblast proliferation was decreased upon STIM2.1 but not STIM2.2 downregulation. While STIM2.2 downregulation led to the formation of larger myotubes, no significant changes were observed in the siSTIM2.1 condition. However, upon STIM2.1 knockdown only, we noticed an increased basal Ca2+ level in myotubes associated with nuclear localization of NFATc1 at rest. This result confirms the negative role of STIM2.1 on SOCE while suggesting that NFATc1 activation by SOCE is not necessary for myotube fusion.
To mimic excitation-contraction (EC) coupling, we stimulated the cells with high K+. The cytosolic Ca2+ peak level was reduced when STIM2.1 or STIM2.2 were downregulated. In line, STIM2.1 and STIM2.2 downregulation decreased Ca2+ levels within the SR. Moreover, the three main players in EC coupling, DHPR, RyR1, and STAC3, were decreased (mRNA level) in the STIM2.1 downregulation condition only.
In conclusion, although STIM2.1 and STIM2.2 are involved in SR filling, they play very different roles during myotube differentiation: a role in EC coupling protein expression for STIM2.1 and in the control of myotube formation for STIM2.2. These results show that STIM2.1 and STIM2.2 involve mechanisms other than SR filling.

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JOURNÉES DE LA SOCIÉTÉ FRANÇAISE DE MYOLOGIE
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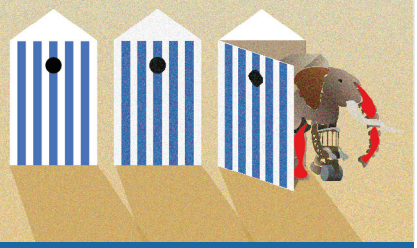


POSTER - P76 - GROUPE 4
Pathologie du nerf et motoneurone

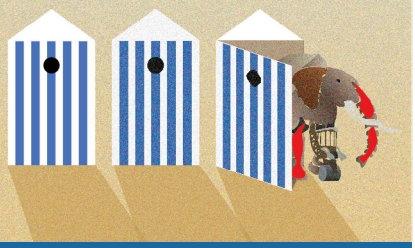
Audrey TRANCHAND[5]

Giovanni Baranello[1*], *Odile Boespflug-Tanguy*[3,4], *John W Day*[6], *Nicolas Deconinck*[7,8], *Andrea Klein*[9,10], *Riccardo Masson*, *Maria Mazurkiewicz-Be≈Çdzińska*[11], *Eugenio Mercuri*[12], *Kristy Rose*[13], *Laurent Servais*[3,14,15], *Dmitry Vlodavets*[16], *Hui Xiong*[17], *Edmar Zanoteli*[18], *Muna El-Khairi*[19], *Eleni Gaki*[19], *Marianne Gerber*[20], *Ksenija Gorni*[21], *Heidemarie Kletzl*[22], *Laura Palfreeman*[19], *Basil T Darras*[23] *au nom du groupe d'étude FIREFISH*

1. The Dubowitz Neuromuscular Centre, NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Institute of Child Health University College London, & Great Ormond Street Hospital Trust, Londres, Royaume-Uni
2. Developmental Neurology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italie
3. I-Motion Institut de Myologie AP-HP, Hôpital Armand Trousseau, Paris, France
4. Université de Paris, UMR 1141, NeuroDiderot, Paris, France
5. Roche SAS, 92 100 Boulogne-Billancourt, France
6. Department of Neurology, Stanford University, Palo Alto, CA, États-Unis.
7. Neuromuscular Reference Center, UZ Gent, Ghent, Belgique
8. Centre de Référence des Maladies Neuromusculaires, Queen Fabiola Children's University Hospital, Université Libre de Bruxelles, Bruxlles, Belgique
9. Paediatric Neurology, University Children's Hospital Basel, Bâle, Suisse
10. Division of Neuropaediatrics, Department of Paediatrics, Inselspital, Bern University Hospital, University of Bern, Berne, Suisse
11. Department of Developmental Neurology, Medical University of Gdańsk, Gdańsk, Pologne
12. Pediatric Neurology Institute, Catholic University and Nemo Pediatrico, Fondazione Policlinico Gemelli IRCCS, Rome, Italie
13. Discipline of Physiotherapy, Faculty of Medicine and Health, University of Sydney and Sydney Children's Hospital Network, Sydney, Australie
14. MDUK Oxford Neuromuscular Centre, Department of Paediatrics, University of Oxford, Oxford, Royaume-Uni
15. Division of Child Neurology, Centre de Références des Maladies Neuromusculaires, Department of Pediatrics, University of Liège, Liège, Belgique
16. Russian Children Neuromuscular Center, Veltischev Clinical Pediatric Research Institute of Pirogov Russian National Research Medical University, Moscou, Russie
17. Department of Pediatrics, Peking University First Hospital, Pekin, Chine
18. Department of Neurology, Faculdade de Medicina, Universidade de São Paulo (FMUSP), São Paulo, Brésil
19- Roche Products Ltd, Welwyn Garden City, Royaume-Uni
20- Pharma Development, Safety, F. Hoffmann-La Roche Ltd, Bâle, Suisse
21- PDMA Neuroscience and Rare Disease, F. Hoffmann-La Roche Ltd, Bâle, Suisse.
22- Roche Pharmaceutical Research and Early Development, Roche Innovation Center Basel, Bâle, Suisse
23- Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, États-Unis
** Auteur Principal*

FIREFISH Parties 1 et 2 :
Efficacité et tolérance à 4 ans de risdiplam dans l'amyotrophie spinale (SMA) de type 1

Risdiplam (EVRYSDI®), traitement oral, est un modificateur d'épissage du pré-ARNm de SMN2, à distribution centrale et périphérique, autorisé dans plus de 90 pays à travers le monde.
FIREFISH (NCT02913482) est une étude ouverte multicentrique en deux parties, évaluant risdiplam chez des nourrissons avec SMA de type 1 et 2 copies de SMN2 (âge 1-7 mois à l'inclusion). La partie 1 a évalué la tolérance, la pharmacocinétique/pharmacodynamie de risdiplam à différentes doses. La partie 2, pivotale, a évalué la tolérance et l'efficacité de risdiplam sur une période de 24 mois à la dose sélectionnée dans la partie 1. Par la suite, les nourrissons sont entrés dans une phase d'extension en ouvert de 3 ans et continuent de recevoir risdiplam à la dose pivot.
Des données regroupées de tolérance/efficacité étaient disponibles pour 58 nourrissons ayant reçu risdiplam (Partie 1 cohorte dose élevée, n=17 ; et Partie 2, N=41). Au cut-off (12/11/2020), aucun événement indésirable lié au traitement n'a conduit à un retrait de l'étude, il n'y a pas eu de décès supplémentaire et aucun nouveau nourrisson n'a eu besoin de ventilation permanente depuis le Mois 24. Au Mois 36, 84 % des nourrissons étaient en vie sans besoin de ventilation permanente. Les nourrissons ont maintenu ou amélioré leurs capacités motrices en termes d'étapes de développement et de fonction motrice entre les Mois 24 et 36, ce qui n'est pas observé dans l'histoire naturelle de la maladie.
Nous présentons ici des données de tolérance et d'efficacité regroupées à plus long terme chez des nourrissons ayant reçu risdiplam à la dose pivot pendant au moins 48 mois.
Les parties 1 et 2 de FIREFISH sont toujours en cours à travers le monde et apporteront des données supplémentaires sur la tolérance et l'efficacité de risdiplam dans le traitement de la SMA de type 1.



POSTER - P77 - GROUPE 3
Physiologie / Fonction musculaire / Biomécanique / Métabolisme

Sestina FALCONE
Amélie Vergnol, Alain Sureau, Massiré Traoré, Xavière Lornage, Geneviève Gourdon, Denis Furling, France Piétri-Rouxel,

Sorbonne Université, Inserm, Institut De Myologie, Centre De Recherche En Myologie F-75013 - Paris, France

CaVβ1A and CaVβ1E embryonic isoforms in adult skeletal muscle: a Mbnl1 related-expression

CaVβ1, encoded by Cacnb1 gene, exists as several transcript variants in skeletal muscle. Our recent work demonstrates CaVβ1D as the constitutive adult isoform, localized with CaVα1 at the triad. On the other hand, our previous and present works show that CaVβ1E and CaVβ1A are expressed at late embryogenesis and peri-natal stages and that these embryonic isoforms are re-expressed after sciatic nerve resection in adult skeletal muscle, both at mRNA and protein level.

We identified MuscleBlind-Like 1 (Mbnl1) as a potential factor modulating Cacnb1 expression. Accordingly, its expression decreases after denervation. Interestingly, literature describes a mis-splicing of CACNB1 in Myotonic Dystrophy (DM) human muscle cells, in which Mbnl1 is sequestrated in nuclear aggregates. Consistently, we showed an increased expression of CaVβ1A and CaVβ1E isoforms in HSA mouse model of DM1, raising the question of the implication of Mbnl1 in Cacnb1 isoform expressions. We found that in a shMbnl1 mouse model, CaVβ1A and CaVβ1E mRNA and protein levels were increased and that this model displayed myotonia, consistently with previous observations.

The team earlier demonstrated that when electrical activity is impaired in adult muscle, the re-expression of CaVβ1E isoform plays a crucial role in muscle mass homeostasis by enabling the activation of the compensatory response limiting muscle mass loss. Therefore, the second part of this study aims to decipher the function of these isoforms in DM1 pathophysiology.
We implemented a mouse model shMbnl1 + shCaVbeta1A/E and demonstrated that the myotonic profile is worsened in the absence of these embryonic isoforms.
These results bring new insights in the regulation of expression of CaVβ1 isoforms in adult skeletal muscle after impairment of electrical activity and suggest a role of CaVβ1A and/or CaVβ1E in DM1 pathophysiology.

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JOURNÉES DE LA SOCIÉTÉ FRANÇAISE DE MYOLOGIE
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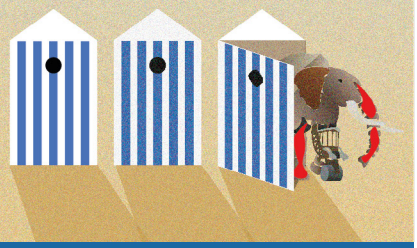

POSTER - P78* - GROUPE 4
Pathologie de la jonction neuromusculaire

Edouard BERLING[1]
Pascal Laforêt[1], *Guillaume Nicolas*[1], *Hélène Prigent*[1], *Ghislain N'Dah-Sekou*[1], *Angéline Plaud*[2], *Dellini Ravindra*[2], *Margaux Pendelio*[2], *Juliette Narcy*[2], *Emma Touré Cuq*[2], *Alizé Vives*[2], *Clarissa Gorin*[2], *David Orlikowski*[3]

1. *Centre de référence neuromusculaire Nord-Est/Ile-de-France, UMR 1179, Service de Neurologie, Hôpital Raymond-Poincaré, Garches, et FHU PHENIX, France*
2. *Ad Scientiam, 75013 Paris, France*
3. *Centre de référence des maladies neuromusculaires Nord-Est/Ile-de-France, UMR 1179, CIC 1429, Service de Neurologie, Hôpital Raymond-Poincaré, Garches, et FHU PHENIX, UVSQ Université Paris-Saclay, France*

Développement de biomarqueurs digitaux permettant l'auto-évaluation à distance des patients atteints de myasthénie généralisée : Preuve de concept

La myasthénie auto-immune généralisée (MAIg) est caractérisée par une fluctuation de symptômes et une faiblesse musculaire variable. La littérature relate un manque d'outils de mesure objectifs pour l'auto-évaluation des symptômes de la MAIg, résultant d'une perception différente de l'impact de la maladie entre médecins et patients.
L'objectif était d'identifier des nouveaux biomarqueurs digitaux (dBMKs) cliniquement significatifs destinés à suivre les symptômes de la MAIg et de préparer le développement de ME&MG®, un dispositif médical logiciel pour l'auto-évaluation non supervisée des patients.
Nous avons utilisé la méthode du double diamant pour identifier les dBMKs d'intérêt pour les patients et évaluer leur pertinence clinique auprès de cliniciens. Les dBMKs ont été priorisés lors d'une étude de preuve de concept (PoC). L'acceptabilité, l'utilisabilité et la sécurité du dispositif ont été étudiées par des méthodes d'ingénierie de l'aptitude à l'utilisation, au travers d'entretiens utilisateurs (France, USA). Les concepts de santé et leurs dBMKs associés ont été identifiés grâce à une revue de la littérature ainsi qu'à l'expertise de 9 experts médicaux. 22 patients MAIg ont confirmé la faisabilité des dBMKs pour auto-évaluer leurs symptômes neurologiques. Une étude PoC sur sujets sains a démontré la faisabilité de l'analyse des données brutes collectées par les capteurs du smartphone. Cinq mesures digitales inspirées des normes cliniques ont été sélectionnées avec leurs dBMKs associés (ptosis, fonction respiratoire, dysarthrie, fatigabilité musculaire du membre supérieur et inférieur). Des questionnaires électroniques de données rapportées par les patients seront également intégrés.
Les tests utilisateurs ont démontré la facilité d'utilisation de ME&MG® (facilité d'utilisation perçue de 9/10), avec un taux de réussite >90 %.
Après avoir confirmé sa faisabilité, ME&MG® a été développé afin d'améliorer la communication patients-médecins. Prochainement, une étude multicentrique en France et aux Etats-Unis sera menée pour valider ME&MG®, comparé aux standards de référence dont le score QMG.

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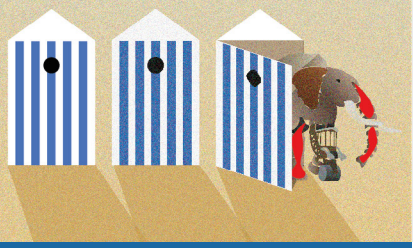

POSTER - P79 - GROUPE 3
Physiologie / Fonction musculaire / Biomécanique / Métabolisme

Melinda GYENGE[1]
Abdessamad Kachal[1*], *Melinda Gyenge*[1], *Dalil Hamroun*[2], *Filnemus Myotonic Dystrophy Study Group*, *Guillaume Bassez*[1]

1- Neuromuscular Reference Center, Institute of Myology, 75013 Paris, France
2- CHU de Montpellier, 34090 Montpellier, France
** Auteur Principal*

Development of prediction model to identify DM1 individuals at higher risk of requiring non-invasive ventilation

Myotonic dystrophy type 1 (DM1) is an autosomal-dominant inherited disorder with multiple organ complications, and progressively worsening symptoms, in which the impairments of respiratory systems represent one of the main causes of death. Non-invasive ventilation (NIV) is commonly used for treating respiratory failure in DM1 as it can improve the symptoms of chronic respiratory failure and normalize blood gas levels. Starting NIV is thus an important step in the respiratory care of DM1 patients.

The aim of our study was to develop a prediction model to identify associate factors that could predict the requirement of non-invasive ventilation in DM1, using the French DM-Scope registry data.

461 genetically confirmed DM1 adult patients (median age: 39.33 years [18.00–72.00], male/female ratio: 0.80 (205/256) without NIV at baseline, with minimum two consultations between the period of January 2012 and December 2022 were analyzed to build a prediction model, using Lasso regression method and cross-validation technique. At the last consultation, out of 461 patients, 121 patients (26%) required NIV initiation.

We identified obesity, gender and patient age as associated factors of respiratory dysfunction. Our results showed that increasing age, male gender and obesity were associated with a higher probability of NIV initiation.

This prediction model may help practitioners to identify DM1 adult patients who are at higher risk of developing respiratory failure and therefore help in defining specific interventions early in the disease course to prevent respiratory complications.

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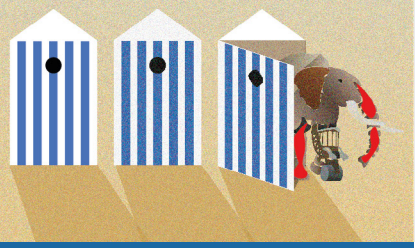


POSTER - P80 - GROUPE 4
Pathologie de la jonction neuromusculaire

Grégory CHOLLET

Angela Genge[1], Yessar Hussain[2], Henry J. Kaminski[3], M. Isabel Leite[4], Renato Mantegazza[5], Kimiaki Utsugisawa[6], Tuan Vu[7], Céline Tard[8], Sophie Demeret[9], Melissa Brock[10], Babak Boroojerdi[11], Mark Vanderkelen[12], Guillemette de la Borderie[13], Petra W. Duda[14], James F. Howard Jr.[15] and the RAISE study group*

1. Clinical Research Unit, The Montreal Neurological Institute, Montreal, QC, Canada
2. Department of Neurology, Dell Medical School, The University of Texas at Austin, Austin, TX, USA
3. Department of Neurology & Rehabilitation Medicine, George Washington University, Washington DC, USA
4. Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
5. Neuroimmunology and Neuromuscular Diseases Department, Fondazione Istituto Neurologico, PV, Italy
6. Department of Neurology, Hanamaki General Hospital, Hanamaki, Japan
7. Department of Neurology, University of South Florida Morsani College of Medicine, Tampa, FL, USA
8. CHU Lille, Lille France
9. Hôpitaux Universitaires Pitié Salpêtrière, AP-HP, Paris, France
10. UCB Pharma, Raleigh, NC, USA
11. UCB Pharma, Monheim, Germany
12. UCB Pharma, Braine-l'Alleud, Belgium
13. UCB Pharma, Brussels, Belgium
14. UCB Pharma, Cambridge, MA, USA
15. The University of North Carolina at Chapel Hill, Department of Neurology, Chapel Hill, NC, USA
** Auteur Principal*

Safety and tolerability of zilucoplan in RAISE-XT: A multicenter, open-label extension study in patients with myasthenia gravis

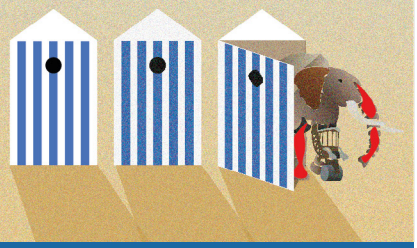
Introduction: Generalized myasthenia gravis (gMG) is a rare, chronic, autoimmune disease. Collating long-term clinical data will contribute to an increased understanding of the safety profile of zilucoplan in gMG.

Objective: To evaluate the safety and efficacy of zilucoplan in an interim analysis of RAISE-XT (NCT04225871).

Methods: RAISE-XT, a Phase 3, multicenter, open-label extension study, recruited patients with gMG who participated in randomized Phase 2 (NCT03315130) and Phase 3 (NCT04115293) zilucoplan studies. All patients self-administered daily SC injections of 0.3 mg/kg zilucoplan. Primary outcome was incidence of treatment-emergent adverse events (TEAEs). Key secondary outcomes included Myasthenia Gravis-Activities of Daily Living (MG-ADL) score.

Results: 199 patients enrolled in RAISE-XT; 104 continued zilucoplan from their qualifying study (zilucoplan group), 95 switched to zilucoplan from placebo (placebo-switch group). Median exposure at data cut-off was 253.0 days (range 29–765). 169 (84.9%) patients experienced a TEAE; 46 (23.1%) patients experienced a serious TEAE. Most common TEAEs were headache and worsening of MG, both in 33 (16.6%) patients. At extension study Week 12, after 24 weeks of zilucoplan, the zilucoplan group achieved a least square mean change in MG-ADL score from double-blind study baseline of −6.30 (95% CI: −7.44, −5.15). MG-ADL reduction from baseline for the placebo-switch group, after 12 weeks of zilucoplan, was −6.32 (95% CI: −8.00, −4.65).

Conclusion: In this interim analysis of RAISE-XT, zilucoplan demonstrated a favorable long-term safety profile. Efficacy in patients who had previously received zilucoplan continued to improve and was demonstrated for those who switched from placebo. The study is ongoing.
Funded by UCB Pharma.



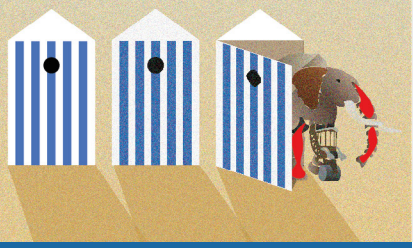
POSTER - P81 - GROUPE 3
Physiologie / Fonction musculaire / Biomécanique / Métabolisme

Stéphane KOENIG
Olivier Dupont, Loann Laubry, Axel Tollance and Maud Frieden

Département de Physiologie Cellulaire et Métabolisme. Université de Genève

Characterization of skeletal muscles from STIM1L KO mice

The Store Operated Calcium Entry (SOCE) mechanism is a ubiquitous process in cellular physiology responsible for replenishing calcium within the endoplasmic/sarcoplasmic reticulum (ER/SR). SOCE activation hinges upon the concerted actions of calcium-sensing proteins from the STIM family (STIM1, 2) and the plasma membrane calcium channels belonging to the Orai family (Orai1, 2, 3). Our research unveiled a unique alternative splicing variant of STIM1, termed STIM1L, that exhibits robust expression in skeletal muscles. This STIM1L isoform accelerates the activation of SOCE, facilitating a response within seconds, as opposed to the minutes typically observed in other cell types.
To investigate the functional consequences of STIM1L deficiency, we developed genetically modified mice with constitutive knockout of STIM1L while preserving the expression of the ubiquitous STIM1 isoform. These STIM1L knockout (KO) mice displayed normal development and lacked overt disabling phenotypes. However, an assessment of spontaneous physical activity through running wheel experiments in 18-week-old male and female STIM1L KO mice revealed reduced running capacity compared to control mice, potentially indicative of muscle fatigue. Notably, this phenotype was absent in younger mice. To comprehensively assess muscle function, we conducted experiments on isolated muscles, specifically the extensor digitorum longus (EDL) and soleus muscles, revealing no significant differences between wild-type (WT) and KO mice. Immunofluorescence analysis of isolated muscle fibers displayed a correct pattern of alpha-actinin expression. Intriguingly, Western blot analysis revealed an upregulation of STIM1 in the muscles of KO mice, concomitant with the absence of STIM1L, which might explain the subtle muscle phenotype observed.
Our findings collectively suggest that STIM1L KO mice exhibit a mild phenotype. We postulate that STIM1L could play a pivotal role in specific aging-related conditions, which is, however, partially obscured by the compensatory overexpression of STIM1.



POSTER - P82 - GROUPE 4
Pathologie de la jonction neuromusculaire

Mariana CIUMAS[6]
James F. Howard, Jr[1]*, George Li*[2]*, Tuan Vu*[3]*, Vera Bril*[4]*, Sophie Steeland*[5]*, Benjamin Van Hoorick*[5]*, Jana Podhorna*[5]*, Heinz Wiendl*[7]*, Jan De Bleecker*[8]*, Renato Mantegazza*[9]*, au nom d'ADAPTsc study group*

1.Département de neurologie, Université de Caroline du Nord, Chapel Hill, Caroline du Nord, États-Unis
2. Centre de Recherche Clinique Medsol Inc., Port Charlotte, Floride, États-Unis
3.Service de Neurologie, Université de Floride du Sud, Collège de Medicine Morsani, Tampa, Floride, États-Unis
4.Centre de neurosciences Krembil, Réseau universitaire de santé, Toronto, ON, Canada
5. Argenx, Ghent, Belgique
6. Argenx France, Issy les Moulineaux, France
7. Service de Neurologie, Université de Münster, Münster, Allemagne
8. Ghent University Hospital, Ghent, Belgique
9. Département de neuroimmunologie et maladies neuromusculaires, Fondazione Istituto Neurologico Carlo Besta, Milan, Italie

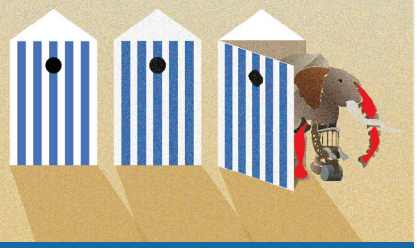
Étude pharmacodynamique de non-infériorité comparant les injections sous-cutanées d'efgartigimod PH20 avec les perfusions intraveineuses d'efgartigimod : résultats de l'étude de phase 3 adaptsc

L'efgartigimod, fragment Fc d'anticorps IgG1 humain, bloque le récepteur Fc néonatal, diminuant le recyclage des IgG et réduisant ainsi leur taux. L'efgartigimod a été bien toléré et efficace lorsqu'il a été administré en IV dans l'étude de phase 3 ADAPT chez des patients atteints de myasthénie auto-immune. ADAPTsc est une étude de non-infériorité pharmacodynamique (PD) de phase 3 comparant un cycle d'injections sous-cutanées (SC) d'efgartigimod PH20 avec un cycle de perfusions d'efgartigimod IV chez des patients atteints de myasthénie auto-immune.

110 patients adultes atteints de myasthénie ont été randomisés 1:1 pour recevoir 4 injections hebdomadaires d'efgartigimod PH20 SC 1000 mg ou 4 perfusions hebdomadaires d'efgartigimod IV 10 mg/kg. Le critère d'évaluation principal était le pourcentage de réduction par rapport à la valeur initiale des taux d'IgG totales à la semaine 4.

L'efgartigimod PH20 SC a démontré une non-infériorité de la PD par rapport à l'efgartigimod IV, avec des réductions observées des taux d'IgG totales par rapport à la valeur initiale au jour 29 de 64,7 % (IC: 1,95 %) contre 62,3 % (IC : 1,24 %), respectivement. Des résultats d'efficacité clinique similaires ont été observés entre les groupes. Les deux formulations ont été bien tolérées, conformément aux études IV précédentes. Les céphalées sont survenues de manière comparable dans les deux bras de traitement. Les autres EI fréquents dans le bras de traitement SC étaient les réactions locales au site d'injection et l'aggravation de la myasthénie. Les EI étaient principalement légers à modérés et n'ont pas entraîné l'arrêt du traitement.

La réduction des taux d'IgG totales répondait aux critères de non-infériorité prédéfinis après l'administration SC d'efgartigimod par rapport à la formulation IV, avec des profils d'innocuité et d'efficacité similaires. La formulation SC de l'efgartigimod offre une option de traitement supplémentaires pour les patients atteints de myasthénie auto-immune.



POSTER - P83* - GROUPE 3
Physiologie / Fonction musculaire / Biomécanique / Métabolisme

Benjamin LAIR
Marlène Lac[1], Lucas Frassin[1], Manon Brunet[2], Marie Buléon[2], Guylène Feuillet[2], Claire Maslo[1], Marie Marquès[1], Laurent Monbrun[1], Geneviève Tavernier[1], Emilie Montastier[1], Nathalie Viguerie[1], Virginie Bourlier[1], Claire Laurens[1], and Cedric Moro[1]

1. Institut des Maladies Métaboliques et Cardiovasculaires, INSERM, Université Toulouse 3, UMR1297

Common mouse models of chronic kidney disease are not associated with cachexia

Cachexia is a typical feature of Chronic Kidney Disease (CKD) and the resulting muscle wasting strongly associates with mortality in humans.

The 5/6 nephrectomy and adenine-induced nephropathy mouse models have been extensively used to study the pathophysiology of CKD-related cachexia. One common caveat of these CKD models is the cross-sectional nature of comparisons made versus controls. We here performed a comprehensive longitudinal assessment of body composition and energy metabolism in both models.

The most striking finding is that weight loss is largely driven by reduced food intake which promotes rapid loss of lean and fat mass. However, in both models, mice catch up weight and lean mass a few days after the surgery or when they are switched back to standard chow diet. Muscle force and mass are fully recovered and no sign of cachexia is observed. Our data demonstrate that the time-course of kidney failure and weight loss are unrelated in these common CKD models. Although they may be suitable models to induce CKD in mice, they do not faithfully recapitulate the pathophysiology of CKD-related cachexia.

These data highlight the need to reconsider the relative contribution of direct and indirect mechanisms to muscle wasting observed in CKD.

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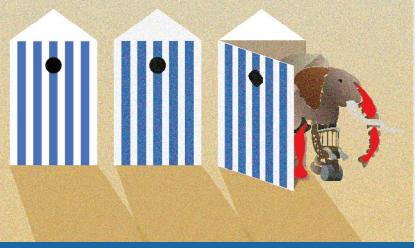


POSTER - P84 - GROUPE 4
Pathologie de la jonction neuromusculaire

Sabrina SACCONI[1]
John Vissing[2], *Artur Drużdż*[3], *Julian Grosskreutz*[4], *Ali A Habib*[5], *Renato Mantegazza*[6], *Kimiaki Utsugisawa*[7], *Tuan Vu*[8], *Marion Boehnlein*[9], *Bernhard Greve*[9], *Franz Woltering*[9], *Maryam Gayfieva*[10], *Vera Bril*[11]

1. Université Côte d'Azur, Peripheral Nervous System & Muscle Department, Pasteur 2 Hospital, Centre Hospitalier Universitaire de Nice, Nice, France
2. Department of Neurology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
3. Department of Neurology, Municipal Hospital Poznań, Poznań, Poland
4. Precision Neurology, Department of Neurology, University of Lübeck, Lübeck, Germany
5. MDA ALS and Neuromuscular Center, University of California, Irvine, Orange, CA, USA
6. Fondazione IRCCS, Istituto Nazionale Neurologico Carlo Besta, Milan, Italy
7. Department of Neurology, Hanamaki General Hospital, Hanamaki, Japan
8. Department of Neurology, University of South Florida Morsani College of Medicine, Tampa, FL, USA
9. UCB Pharma, Monheim, Germany
10. UCB Pharma, Slough, UK
11. University Health Network, Toronto, Canada.

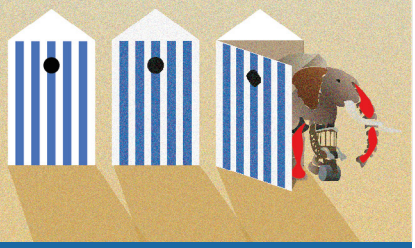
Rozanolixizumab responder and minimal symptom expression rates in generalised MG: Pooled Phase 3 and extension studies

Introduction: The Phase 3 MycarinG (MG0003/NCT03971422) trial demonstrated efficacy of one 6-week cycle of rozanolixizumab in generalised myasthenia gravis (gMG). We assessed consistency of cyclical rozanolixizumab efficacy and safety over time.

Methods: After 6 weeks of weekly rozanolixizumab/placebo in MycarinG, patients entered MG0004 (NCT04124965: ⩽52 weeks of weekly rozanolixizumab) or MG0007 (NCT04650854: initial 6-week cycle; subsequent cycles administered on symptom worsening as determined by investigator's discretion, e.g. Myasthenia Gravis Activities of Daily Living [MG-ADL] increase ⩾2/Quantitative Myasthenia Gravis [QMG] increase ⩾3; "symptom-driven cycles") (Figure 1). Efficacy pool: data for patients with ⩾2 symptom-driven cycles pooled across MycarinG, MG0004 (first 6 weeks) and MG0007 (interim analysis); safety pool: data for patients with ⩾1 cycle across MycarinG (symptom-driven) and MG0007 (fixed/symptom-driven).

Results: 127 patients received ⩾2 symptom-driven cycles of rozanolixizumab 7mg/kg (initial dose, n=69) or 10mg/kg (initial dose, n=58). MG-ADL change from baseline to Day 43, responder rates at Day 43 for MG-ADL, Myasthenia Gravis Composite and QMG and minimal symptom expression at any visit were consistent across cycles (Figure 2, Table). Treatment-free intervals (time from previous dose to first dose in symptom-driven cycle 1) were <4 weeks for 9.0%, 4–13 weeks for 59.3%, 13–26 weeks for 13.8% and ⩾26 weeks for 4.2% of patients, with similar proportions at the next cycle. Treatment-emergent adverse events (most mild to moderate) occurred in 77.4% and 91.6% of patients receiving ⩾1 cycle of rozanolixizumab 7mg/kg and 10mg/kg.

Conclusions: Rozanolixizumab efficacy was maintained over symptom-driven cyclical treatment and multiple endpoints.
Funding: UCB Pharma.



POSTER - P85* - GROUPE 3
Physiologie / Fonction musculaire / Biomécanique / Métabolisme

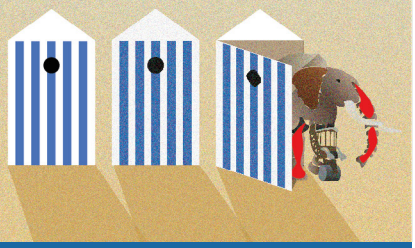
Loann LAUBRY
Jessica Brunetti, Stéphane König, Maud Frieden

Department of Cell Physiology and Metabolism, University of Geneva, Medical Center.

STIM1 and STIM1L in skeletal muscle: Central regulators of calcium circuitry

In most cell types, the depletion of the endoplasmic reticulum (ER) Ca2+ stores leads to a mechanism called the Store Operated Ca2+ Entry (SOCE). The main players of this mechanism are STIM1, a Ca2+ sensor of the ER, and Orai1, a plasma membrane Ca2+ channel. Our group previously reported that two isoforms of STIM1 are highly expressed in skeletal muscle: STIM1 and a longer splice variant, STIM1L. Since Ca2+ signals are essential for proper muscle differentiation, especially at an early stage of development, our aim was to determine the specific functions of STIM1 and STIM1L during myogenesis. To do so, we infected human primary myoblasts with a lentivirus encoding a doxycycline-inducible shRNA-mir expression to downregulate both STIM1/1L isoforms or only STIM1L. The knock-down was triggered simultaneously with the differentiation of the myoblasts or after 4 days of differentiation, during the maturation process. Electrical stimulations-induced Ca2+ transients revealed that STIM1/1L and STIM1L down-regulation impacts the amplitude of Ca2+ transients only at an early stage of myogenesis, while the cytosolic Ca2+ clearance was slowdown upon both down-regulations and at both early and late stages of differentiation. To investigate this defect, we divided the Ca2+ clearance into 2 different mechanisms: Ca2+ extrusion and Ca2+ repumping within the stores. First, we observed that STIM1 but not STIM1L affected the Ca2+ extrusion, and using siRNA against the different extrusion systems (PMCA1/4 and NCX3), we showed that only PMCA1 is of importance in myotubes. Preliminary results of co-IP experiments showed indeed an interaction between STIM1 and PMCA1 in myotubes, that could explain the modulation of PMCA1 activity by STIM1. Then, surprisingly, only STIM1L downregulation increased the SR Ca2+ content and accelerated the rate of SR Ca2+ repumping, pointing to a negative effect of STIM1L on SERCA activity. This remains however to be confirmed.
Overall, our data reveal an alteration of the Ca2+ circuitry upon down-regulation of STIM1 and STIM1L. The Ca2+ clearance is impaired during early and late stages of myogenesis with evidence that STIM1 and STIM1L are modulators of Ca2+ extrusion and Ca2+ repumping, respectively.

*Éligible pour le prix du meilleur Poster



POSTER - P86 - GROUPE 4
Pathologie de la jonction neuromusculaire

Guilhem SOLÉ[1]
Jean-Philippe Camdessanché2, Annie Archer[3]*, Pierre Boulanger*[4]*, Anne Crochard*[5]*, Jean-Philippe Bertocchio*[6]*, Pierre-Edouard Villy*[5]*, Aliénor Richard*[5]*, Sabrina Sacconi*[7]

1. Service de Neurologie et Maladies Neuromusculaires, CHU de Bordeaux, Centre de Référence des Maladies Neuromusculaires AOC, Hôpital Pellegrin, Bordeaux, France
2. Service de Neurologie, Centre de Référence des Maladies Neuromusculaires PACA-Réunion-Rhône Alpes, CHU de Saint-Étienne, Hôpital Nord, Saint-Etienne, France
3. AFM TELETHON Groupe d'intérêt Myasthénies, Evry, France
4. AMIS, La Chapelle en Serval, France
5. UCB Pharma, Colombes, France
6. SKEZI, Annecy, France
7. Système nerveux périphérique et muscle, CHU de Nice, Université Côte d'Azur, Nice, France

Perceptions and expectations of patients with myasthenia gravis in France: The SPOON Study

Myasthenia gravis (MG) carries a high burden in terms of impaired quality of life (QOL) and psychological distress. Little information is available concerning patient's direct experience of the disease. We performed a qualitative survey of expectations of MG patients to address these gaps in knowledge. The objective of this cross-sectional study was to identify patients' aspirations in terms of disease control and treatment needs. Adult patients with MG were recruited through mailing from patient associations, social media, and advertisements in reference centres. Participants completed an online MG expert-built questionnaire in French, including several validated patient-reported outcome measures, and two open-ended questions on disease and treatment expectations. Themes from replies to these two questions were analysed using grounded theory and cluster analysis. 246 patients completed the questionnaire (187 women and 59 men aged 41 to 67 years). In reply to the question 'What would you like to do in your life with illness that you currently find difficult or impossible to do?', an average of 2.3 dimensions (themes) were identified by patients in six domains (physical activity/leisure, activities of daily living, psychological burden, social activities, work/school, other). The most frequently cited dimensions were sport (82 citations), mobility (56 citations) and endurance (37 citations). Younger age, female gender, recent diagnosis, poorer QOL and low treatment satisfaction were associated with citing more themes. In reply to the question 'What improvements do you think could be made to treatments for myasthenia?', an average of 1.4 dimensions were cited in three domains (medication characteristics [eg effectiveness, dosing], safety and care paradigm). The most cited treatment-related dimensions were limiting side-effects (40 citations), fewer daily medication intakes (21 citations) and less digestive side-effects (20 citations). The information collected here could help healthcare professionals to better understand and address patients' needs and to stimulate the development of more acceptable treatments.

20ÈME ÉDITION
JOURNÉES DE LA SOCIÉTÉ FRANÇAISE DE MYOLOGIE
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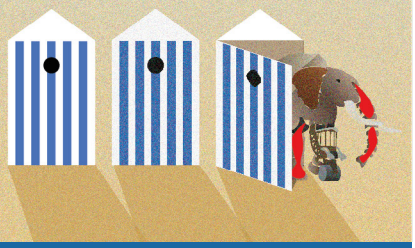


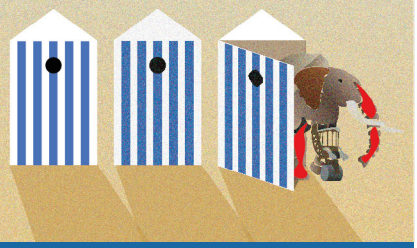
POSTER - P88 - GROUPE 4
Dystrophie musculaire

Mireille COSSEE[1,4]
Marion Larrieux[1#]*, Corinne Thèze1*[*]*, Quentin Sabbagh2*[*]*, Marie-Claire Vincent1-4, Vincent Gatinois2-3, Christine Coubes3, Jacques Puechberty2-3, Franck Pellestor2-3, Michel Koenig1-4, Sylvie Tuffery-Giraud4, Anouck Schneider2-3*

1. Laboratoire de Génétique Moléculaire, CHU de Montpellier, France
2. Unité de Génétique Chromosomique, CHU de Montpellier, France
3. Département de Génétique Médicale, CHU de Montpellier, France
4. PhyMedExp, Université de Montpellier, Inserm U1046, France
[#] Auteur Principal

Le mosaïcisme confiné au placenta, un piège dans le diagnostic prénatal des dystrophinopathies : À propos d'un cas

Dans un contexte de diagnostic prénatal réalisé pour une hyperclarté nucale, nous rapportons un cas de mosaïcisme confiné au placenta, évènement mutationnel rapporté dans les aneuploïdies mais rarement dans les maladies monogéniques.
Après réception d'un prélèvement de villosités choriales au laboratoire de cytogénétique, pour hyperclarté nucale pouvant être associée à un risque accru d'aneuploïdie, une Analyse Chromosomique sur Puces à ADN (ACPA) a révélé une délétion d'environ 47kb emportant les exons 56 à 57 du gène DMD en mosaïque, évaluée à environ 23%, sans lien avec le phénotype fœtal. Aucune contamination maternelle n'a été détectée. Cette délétion a été confirmée au laboratoire de génétique moléculaire par Multiplex Ligation-dependent Probe Amplification (MLPA), avec un taux de cellules porteuses de la délétion estimé à 30%. Le gène DMD, porté par le chromosome X et codant pour la dystrophine, est impliqué dans les dystrophies musculaires de Duchenne et Becker. L'ADN maternel ne portant pas la délétion, nous avons conclu à un événement sporadique chez le fœtus. Afin de tester l'hypothèse d'une délétion du gène DMD en mosaïque confinée au placenta, comme décrite par Winerdal et al., 2020, la délétion a été recherchée ultérieurement sur les cellules d'un prélèvement de liquide amniotique (LA). Les nouvelles analyses par MLPA-DMD et ACPA n'ont pas retrouvé la délétion des exons 56 à 57 du gène DMD sur le LA.
Ce résultat en faveur de l'hypothèse d'une délétion en mosaïque confinée au placenta, nous a ainsi permis d'être rassurant quant au risque de dystrophinopathie chez le fœtus.



POSTER - P89* - GROUPE 3
Thérapie

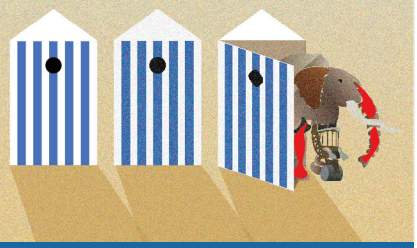
Aly BOURGUIBA
Sestina Falcone, Sonia Pezet, Massiré Traoré, Thibaut Marais, Christel Gentil, Julien Mésseant, Steve Cottin, Bruno Cadot, Laure Strochlic, Maria-Grazia Biferi, Piera Smeriglio, France Piétri-Rouxel

Sorbonne Université, Inserm, Institut De Myologie, Centre De Recherche En Myologie - Paris, France

Unraveling the role of GDF5 therapeutic potential in Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal progressive motor neuron disease characterized by motor neuron degeneration and pyramidal neuron damage at the motor cortex. This degeneration induces neuromuscular connectivity defects and skeletal muscle decline leading to paralysis and death of patients.
Two disease forms have been described: sporadic (sALS), 90-95% of the cases, with different etiologies, or familial (fALS), less frequent (10-15% of the cases) with genetic origin. Few drugs are available, though showing limited efficacy, and gene therapy approaches hold promise to treat some fALS types, like the one associated to mutation in superoxide dismutase1 (SOD1) gene. Thus, novel therapeutic strategies are strongly needed at this time, for ALS, aimed at decreasing motor neuron death and protecting skeletal muscle mass and function.
In this context, Growth Differentiation Factor 5 (GDF5) appears to be an interesting candidate for the treatment of ALS. Indeed, GDF5 has been described to support neurite growth in vitro and its signaling pathway has been shown to decrease neuronal excitotoxicity. In addition, GDF5 has been demonstrated as required in promoting skeletal muscle re-innervation after nerve crush and limiting denervation-related atrophy. Notably, we described that its overexpression is important to limit age-related muscle mass loss and force decline.
We hypothesized that GDF5-based treatments could preserve innervation, muscle mass and function in ALS, have a beneficial impact on the disease progression. Thus, using SOD1G93A mice, one the best characterized ALS mouse model, we overexpressed GDF5 by systemic adeno-associated virus (AAV) injection and showed a therapeutic benefit of this treatment on the maintenance of skeletal muscle mass, reinnervation markers and neuromuscular junction integrity.
These study will generate important insights on the beneficial effects of GDF5 on neuromuscular system and shed light on the potential of a therapy based on this factor applicable to ALS and potentially other neuromuscular diseases.

*Éligible pour le prix du meilleur Poster



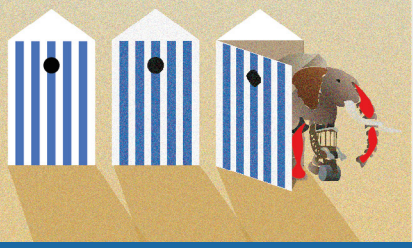
POSTER - P90 - GROUPE 4
Dystrophie musculaire

Erwan DELAGE
Ester Cotali, Maria L. Naylor, Cody A. Desjardins, Reshmii Venkatesan, John Hall, Ryan Russo, Kim Tang, John W. Davis II, Timothy Weeden, Stefano Zanotti, Chris Mix, Baoguang Han, Oxana Beskrovnaya, Ashish Dugar

Dyne Therapeutics

Robust preclinical data support development of DYNE-251 as a potential treatment for individuals with DMD mutations amenable to exon 51 skipping

Duchenne muscular dystrophy (DMD) is characterized by progressive loss of muscle function leading to premature death. Current therapeutic approaches use exon skipping phosphorodiamidate morpholino oligomers (PMOs) that enable the translation of a shortened, functional dystrophin protein, but their success has been hampered by poor muscle delivery. We developed the FORCETM platform, which harnesses the natural expression of transferrin receptor (TfR)1 on muscle cells for targeted delivery of oligonucleotides. DYNE-251, an investigational therapeutic for the treatment of DMD, consists of an exon 51 skipping PMO conjugated to an antigen-binding fragment (Fab) targeting TfR1. In non-human primates, DYNE-251 led to pronounced exon skipping in cardiac and skeletal muscle and demonstrated a favorable safety profile. We also demonstrated that a single dose of FORCE-M23D, a mouse-specific Fab-PMO conjugate designed to skip exon 23 of the murine Dmd pre-mRNA, led to robust and durable exon skipping and dystrophin restoration, and improved functional outcomes in mdx mice, compared to unconjugated PMO. These preclinical data supported the initiation of DELIVER, a randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) study of DYNE-251 administered intravenously to ~46 ambulant and non-ambulant males (4-16 years) with exon 51 skip-amenable mutations (NCT05524883). The purpose of the study is to evaluate the safety, tolerability, and dystrophin levels in muscle following multiple doses of DYNE-251. Primary outcomes are the number of participants with treatment-emergent adverse events and the change from baseline in dystrophin levels in muscle at Week 25. The DELIVER study will inform the potential of DYNE-251 as a treatment for DMD.



POSTER - P91* - GROUPE 3
Thérapie

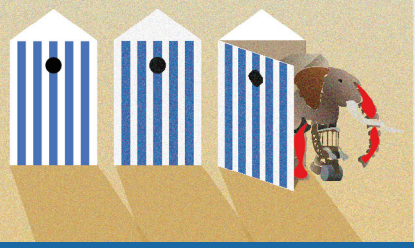
Céline BRUGE
Nathalie Bourg, Emilie Pellier, Johana Tournois, Jerome Polentes, Manon Benabides, Noella Grossi, Anthony Brureau, Anne Bigot, Lucile Hoch, Isabelle Richard and Xavier Nissan

INSERM, U951, INTEGRARE research Unit / Center for Research in Myology, Sorbonne Universities, UPMC University, INSERM UMRS974

Identification of bazedoxifene for the treatment of LGMD R2 by high throughput screening

Limb-girdle muscular dystrophies (LGMD) refer to a group of rare genetic disorders characterized by progressive proximal muscle weakness and wasting. Among LGMD, LGMD R2 is caused by a recessive loss of dysferlin function, a transmembrane protein that plays a key role in plasma membrane repair in skeletal muscles. Over the years, more than a thousand mutations in the DYSF gene have been described in patients with LGMD R2. At least a third are missense mutations, leading for some to dysferlin misfolding, aggregation within the endoplasmic reticulum (ER) and subsequent degradation by the endoplasmic reticulum-associated protein degradation machinery (ERAD I) or the alternative autophagy/lysosome degradation system (ERAD II). Although no treatment is currently available for LGMD R2, research directed towards missense protein refolding, or targeting cellular quality control to inhibit premature degradation of proteins in the ER with small molecules, opens up a therapeutic avenue for LGMD R2. Thus, recent in vitro findings suggest that several missense-mutated dysferlin might be functional if relocated to the sarcolemma of muscle fibers.
We report here the development of an in vitro high-throughput assay using immortalized myoblasts that allows monitoring of the expression and reallocation of an aggregated mutant form of dysferlin (DYSFL1341P). Using this assay, we screened a library of 2239 clinically approved drugs and bioactive compounds, and identified two autophagy inducers, saracatinib and bazedoxifene, as potential drugs to repurpose for LGMD R2 patients carrying the DYSFL1341P mutation. Functional characterization of these drugs revealed that saracatinib and bazedoxifene had a protective effect on the plasma membrane in osmotic shock assay. While saracatinib restores functionality in membrane resealing through a specific rescue of L1341P dysferlin from degradation, bazedoxifene's in vitro effect is not related to the genotype and demonstrates an additional protective effect on Bla/J mice muscle fibers. Beyond the identification of a new therapeutic option for LGMD R2 patients, our results shed light on a reusable procedure to evaluate the effect of thousands of repurposable drugs on similar muscular disorders caused by missense mutations that are degraded by ERAD system.

*Éligible pour le prix du meilleur Poster



POSTER - P92 - GROUPE 4
Dystrophie musculaire

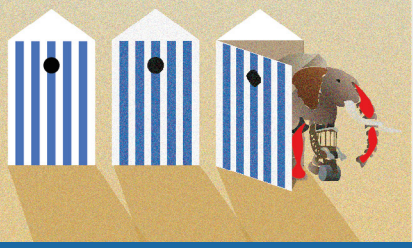
Maitea GURIDI[7]

Crystal M. Proud[1#], C.M. Zaidman[2], P.B. Shieh[3], C.M. McDonald[4], J.W. Day[5], S. Mason6, M. Guridi[7], L. Yu[6], C. Reid[8], E. Darton[6], C. Wandel[7], J. Richardson[6], T. Singh[6], L.R. Rodino-Klapac[6], J.R. Mendell[9,10]*

1. Children's Hospital of the King's Daughters, Norfolk, VA, USA
2. Department of Neurology, WUSTL, Washington, MO, USA
3. UCLA Medical Center, Los Angeles, CA, USA
4. UC Davis Health, Sacramento, CA, USA
5. Department of Neurology, Stanford University, Palo Alto, CA, USA
6. Sarepta Therapeutics, Inc., Cambridge, MA, USA
7. F. Hoffmann-La Roche Ltd, Basel, Switzerland
8. Roche Products Ltd, Welwyn Garden City, UK
9. Center for Gene Therapy, Nationwide Children's Hospital, Columbus, OH, USA
10. The Ohio State University, Columbus, OH, USA
 # Auteur Principal

Integrated analyses of data from clinical trials of delandistrogene moxeparvovec in Duchenne muscular dystrophy

Delandistrogene moxeparvovec is an rAAV vector-based gene therapy, designed to compensate for the absence of functional dystrophin in DMD by delivering a transgene encoding delandistrogene moxeparvovec micro-dystrophin, an engineered dystrophin protein that retains key functional domains of the wild-type protein. As of August 2023, it is approved in the USA and UAE for treating ambulatory paediatric patients aged 4 through 5 years with DMD with a confirmed mutation in the DMD gene.
The objective of this study was to evaluate 1-year functional data in patients following a single IV infusion of delandistrogene moxeparvovec versus a propensity score-weighted external control (EC) cohort.
Ambulatory patients with DMD (≥4 to ≤8 years) received a single dose of delandistrogene moxeparvovec (1.33x1014 vg/kg). The dataset included patients treated with delandistrogene moxeparvovec from three studies: Study 101 (SRP-9001-101; NCT03375164), Study 102 (SRP-9001-102; NCT03769116), and ENDEAVOR (Study 103; SRP-9001-103; NCT04626674). The EC cohort (N=131), comprising natural history and external clinical trial data from three studies, was used for comparison. The primary endpoint was 1-year change from baseline in North Star Ambulatory Assessment (NSAA) total score. Exploratory endpoints included 1-year change from baseline in timed function tests. Collective safety data are also presented.
The integrated functional analyses evaluated data from Study 101 (n=4), Study 102 (n=28), and Cohort 1 of ENDEAVOR (n=20). A statistically significant difference of 2.4 points (P<0.0001) was observed in NSAA change from baseline to Year 1 in treated patients versus the EC cohort (n=105). No adverse events led to study discontinuation and there were no deaths.
Delandistrogene moxeparvovec resulted in statistically significant and clinically meaningful differences in functional outcomes at 1 year versus a propensity score-weighted EC cohort, suggesting a beneficial modification of the DMD disease trajectory. Collective safety data were consistent and manageable across studies.



POSTER - P93* - GROUPE 3
Développement / Cellules souches / Régénération musculaire

Andréa CARLIER
Inès Barthélémy, Nicolas Blanchard-Gutton, Frédéric Relaix, Laurent Tiret, Stéphane Blot, Isabel Punzón

U955-IMRB, INSERM, Université Paris-Est Créteil, École nationale vétérinaire d'Alfort, EFS, «Biology of the neuromuscular system» Team, F-94700 Maisons-Alfort, France - Paris, France

Pan-therapy, CRISPR/Cas13-mediated, for Centronuclear myopathies by targeting DYNAMIN 2

Centronuclear myopathies (CNM) are congenital myopathies characterized by hypotrophy and muscle weakness. They are mainly linked to mutations in the MTM1, BIN1 and DNM2 genes. These proteins interact in the muscle as a network, and are involved in the stability and trafficking of muscle fiber membranes. There is currently no treatment for CNMs.
Our group has contributed to the characterization of a unique spontaneous DNM2R465W/+ dog model carrying the R465W mutation, the most common in DNM2 patients. This mutation confers a gain-of-function to the DNM2 protein. It has been demonstrated in mice that reduction of DNM2 protein by specific knockdown of DNM2 transcripts resolves the phenotype of CNMs linked to BIN1, MTM1 and DNM2. This observation opens the door to a pan-therapy targeting multiple CNMs by regulating the expression of a single protein, DNM2. The recently discovered CRISPR/Cas13 system has the capacity, via the Cas13 protein, to degrade the target RNA in a highly specific way. We propose to use this system to reduce DNM2 transcript levels in our canine model as a pan-therapy for CNMs.
From canine muscle biopsies, we obtained cultures of healthy and DNM2R465W/+ myoblasts. A characterization of these myoblasts allowed us to identify quantifiable elements to measure phenotypic improvement after treatment. Transient cell transfections of the CRISPR/Cas13 system showed a significant reduction in DNM2 mRNA transcript with a reduction in the GTPase activity of DNM2R465W/+ cells. In vivo proof-of-principle of this strategy recently began with intramuscular injections of our CRISPR/Cas13 system via AAV in DNM2R465W/+ dogs. Muscle samples will be taken at one month and two months post-injection.
To assess the impact of the DNM2R465W/+ mutation on muscle stem cells, these were quantified over time. In the cranial tibial muscle, a reduction in their number was identified from 4 months onwards compared with healthy dogs. These quantifications are currently being carried out in other muscles differently affected by the disease, and an in vivo regeneration test is envisaged.

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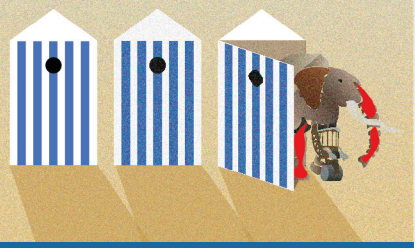

POSTER - P94 - GROUPE 4
Dystrophie musculaire

Maitea GURIDI[6✿]

Francesco Muntoni[1#], *E. Mercuri*[2], *U. Schara-Schmidt*[3], *H. Komaki*[4], *J. Richardson*[5], *T. Singh*[5], *S. Mason*[5], *A.P. Murphy*[7], *L. Yu5*, *C. Reid*[7], *E. Darton*[5],*C. Wandel*[6], *J.R. Mendell*[8,9]

1. The Dubowitz Neuromuscular Centre, NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Institute of Child Health University College London, & Great Ormond Street Hospital Trust, London, UK
2. Pediatric Neurology Institute, Catholic University and Nemo Pediatrico, Fondazione Policlinico Gemelli IRCCS, Rome, Italy
3. Department of Pediatric Neurology, Center for Neuromuscular Disorders in Children and Adolescents, University Clinic Essen, University of Duisburg-Essen, Essen, Germany
4. Translational Medical Center, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan
5. Sarepta Therapeutics, Inc., Cambridge, MA, USA
6. F. Hoffmann-La Roche Ltd, Basel, Switzerland
7. Roche Products Ltd, Welwyn Garden City, UK
8. Center for Gene Therapy, Nationwide Children's Hospital, Columbus, OH, USA
9. The Ohio State University, Columbus, OH, USA
 # Auteur Principal

EMBARK, a Phase 3 trial evaluating safety and efficacy of delandistrogene moxeparvovec in DMD: Study design and baseline characteristics

Delandistrogene moxeparvovec is an rAAV vector-based gene therapy, designed to compensate for the absence of functional dystrophin in DMD by delivering a transgene encoding delandistrogene moxeparvovec micro-dystrophin, an engineered dystrophin protein that retains key functional domains of the wild-type protein. As of August 2023, it is approved in the USA and UAE for treating ambulatory paediatric patients aged 4 through 5 years with DMD with a confirmed mutation in the DMD gene.

We report the design and participant baseline characteristics of EMBARK (Study 301; NCT05096221), a Phase 3, global, randomized, double-blind, two-part, placebo-controlled study assessing safety and efficacy of commercial process delandistrogene moxeparvovec material in ambulatory individuals with a confirmed DMD mutation within exons 18ơ79 (excluding those with a mutation fully contained within exon 45), aged ⩾4 to <8 years (N=125).

In Part 1 (52-week follow-up period), participants are stratified by age (⩾4 to <6 years or ⩾6 to <8 years) and North Star Ambulatory Assessment (NSAA) total score (⩽22 points or >22 points) at screening and randomized 1:1 to receive a single IV dose of delandistrogene moxeparvovec (1.33x1014 vg/kg by linear standard qPCR) or placebo. In Part 2 (52-week follow-up period), participants randomized to placebo in Part 1 will receive delandistrogene moxeparvovec, and participants randomized to delandistrogene moxeparvovec in Part 1 will receive placebo.

Primary endpoint is change from baseline (CFBL) to Week 52 in NSAA total score (Part 1). Secondary endpoints include safety; delandistrogene moxeparvovec micro-dystrophin expression at Week 12 by Western blot (Part 1); and CFBL to Week 52 (Part 1) in: key timed function tests, stride velocity 95th centile measured by a wearable device, and Patient-Reported Outcomes Measurement Information System® (mobility and upper extremity function).

EMBARK will provide placebo-controlled information on efficacy and safety of delandistrogene moxeparvovec in a large population of ambulatory patients with DMD.

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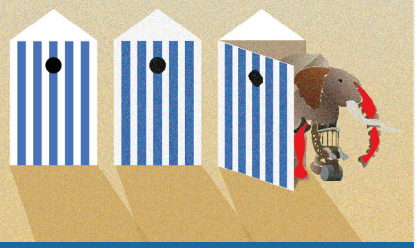


POSTER - P95 - GROUPE 3
Thérapie

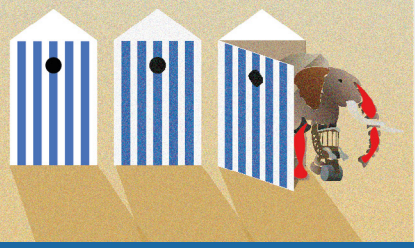
Anne FORAND[1]

Moog Sophie[1], *Mougenot Nathalie*[2], *Lemaitre Mégane*[2], *Sevoz-Couche Caroline*[3], *Guesmia Zoheir*[4], *Virtanen Laura*[4], *Giordani Lorenzo*[4], *Muchir Antoine*[4#] *and Pietri-Rouxel France*[4*,#]

1. *Inovarion, 251 rue St Jacques 75005 Paris*
2. *Sorbonne Université-UPMC Paris 06-INSERM UMS28-Phénotypage du petit animal-Faculté de Médecine Pierre et Marie Curie, 91 boulevard de l'Hôpital 75013 Paris*
3. *Sorbonne Université-UPMC Univ Paris 06-INSERM UMRS1158-Neurophysiologie Respiratoire Expérimentale et Clinique-Faculté de Médecine Pierre et Marie Curie, 91 boulevard de l'Hôpital 75013 Paris*
4. *Centre de Recherche en Myologie-Sorbonne Université-UMRS974-Inserm-Institut de Myologie-Faculté de Médecine de la Pitié Salpêtrière, 105 boulevard de l'Hôpital 75013 Paris.*

Assessment of cardiac structure and function in a Dys-/-;Utr-/- mouse model of DMD treated with long term dystrophin replacement therapies

Duchenne muscular dystrophy (DMD) is a severe and progressive inherited muscular dystrophy, affecting children with an incidence of 1:3,500 - 1:5,000 live male births. It is one of the most severe pediatric degenerative myopathies. DMD is caused by X-linked mutations in the DMD gene leading to the loss of dystrophin, a structural protein located at the sarcolemma. Patients display progressive muscle weakness starting at a young age, lose ambulation around the age of 10–12 years old, and die from cardiorespiratory failure during the second or third decade of life. With improved disease management, cardiomyopathy has emerged as a leading cause of death in patients. Extensive research over the last three decades has shown promising results, notably the capacity of micro-dystrophin, expressed using AAV-based gene therapy, to rescue heart function. We here studied the long-term effect of dystrophin replacement strategies to assess the structural and functional benefits of replacement therapy as well as cardiac consequences in a severe model of DMD, the dKO (Dys-/-;Utr-/-) mice. The AAV-micro-dystrophin treatment restored normal weight gain and remarkably improved survival of DMD mice. We next assessed cardiac structure and function. While the treatment led to a significant improvement in cardiac function after 1 year post treatment, we were able to reveal an increased septum thickness, which could be the result of tissue remodeling. We further asked what cellular population could participate in this cardiac remodeling and identified the presence of leukocytes in AAV-micro-dystrophin treated dKO animals. Our data warrant consideration that micro-dystrophin replacement therapy in the dKO mouse model may be associated with cardiac muscle inflammation despite improved cardiac function and survival.



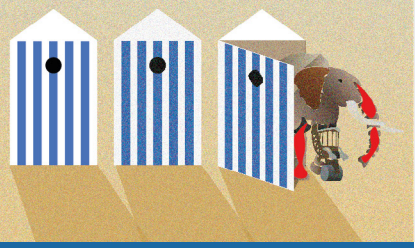
POSTER - P96 - GROUPE 4
Dystrophie musculaire

Catherine KERTING[1]
F Muntoni[2], *E. Mercuri*[3], *C. McDonald*[4], *I. Desguerre*[5], *M. Tulinius*[6], *C. Proud*[7], *M. Furgerson*[8], *A.P. Murphy*[9], *C. De Ford*[10], *T. Feng*[8], *C. Reid*[9], *C. Wandel*[10], *N. Shelton*[8]

1. Roche SAS Direction Science, Paris, France
2. The Dubowitz Neuromuscular Centre, NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Institute of Child Health University College London, & Great Ormond Street Hospital Trust, London, UK
3. Pediatric Neurology Institute, Catholic University and Nemo Pediatrico, Fondazione Policlinico Gemelli IRCCS, Rome, Italy
4. UC Davis Health, Sacramento, CA, USA
5. Departments of Pediatric Neurology and Medical Genetics, Hospital Necker Enfants Malades, Université Paris Cité, Paris, France
6. Department of Pediatrics Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
7. Children's Hospital of the King's Daughters, Norfolk, VA, USA
8. Sarepta Therapeutics, Inc., Cambridge, MA, USA
9. Roche Products Ltd, Welwyn Garden City, UK 10 - F. Hoffmann-La Roche Ltd, Basel, Switzerland

ENVISION, a Phase 3, randomized trial evaluating the safety and efficacy of delandistrogene moxeparvovec in Duchenne muscular dystrophy: Study design

Delandistrogene moxeparvovec is an rAAV vector-based gene therapy, designed to compensate for the absence of functional dystrophin in DMD by delivering a transgene encoding delandistrogene moxeparvovec micro-dystrophin, an engineered dystrophin protein that retains key functional domains of the wild-type protein. As of August 2023, it is approved in the USA and UAE for treating ambulatory paediatric patients aged 4 through 5 years with a confirmed mutation in the DMD gene.
ENVISION (Study 303; NCT05881408) is a Phase 3, multinational, randomized, double-blind, placebo-controlled, 2-part study to assess safety and efficacy of commercial process delandistrogene moxeparvovec material.
The study includes 2 cohorts of male patients with a DMD mutation within exons 18ơ79. Cohort 1 (n=~120): non-ambulatory patients (all ages) with a Performance Upper Limb (PUL) entry-item score ⩾3 and a total PUL score ⩾20 and ⩽40 at screening. Cohort 2 (n=~28): ambulatory patients, aged ⩾8 to <18 years, with a PUL entry item score >3 and <6, total PUL score ⩾20 and ⩽40, and North Star Ambulatory Assessment (NSAA) score ⩾12 and ⩽26 at screening.
In Part 1 (72-week follow-up), patients will be randomized 1:1 to delandistrogene moxeparvovec (single IV 1.33x1014 vg/kg) or placebo. In Part 2 (52-week follow-up), patients randomized to placebo in Part 1 will receive delandistrogene moxeparvovec, and patients randomized to delandistrogene moxeparvovec in Part 1 will receive placebo. The primary endpoint is change from baseline (CFBL) to Week 72 in PUL total score. Secondary endpoints are CFBL to Week 72 in predicted forced vital capacity, peak expiratory flow, global circumferential cardiac strain, Patient-Reported Outcomes Measurement Information System Upper Extremity Function, and NSAA score (Cohort 2); delandistrogene moxeparvovec micro-dystrophin expression at Week 12; and safety.
ENVISION will allow for evaluation of safety and efficacy of delandistrogene moxeparvovec in a large population of late-ambulatory and non-ambulatory patients with DMD.



POSTER - P97* - GROUPE 3
Thérapie

Charlotte GINESTE
D. Reiss, J. Laporte

IGBMC, CNRS UMR 7104 - Inserm U 1258, Dépt Médecine translationnelle et neurogénétiques, Equipe Physiopathologie des maladies neuromusculaires, 67404 Illkirch, France

Testing tamoxifen as a potential therapeutic approach for recessive RYR1-related myopathy

Centronuclear myopathies (CNM) are congenital disorders characterized by muscle weakness and abnormal centralization of nuclei within muscle fibers. The main genes associated with CNM are MTM1, DNM2, BIN1, RYR1 and SPEG. To date, no effective treatment is available. However, we previously reported an improvement in muscle function in three mice models for mild and severe MTM1-, DNM2- and BIN1-related CNM, suggesting that tamoxifen may serve as a common therapeutic strategy for all CNM forms. Therefore, we investigated the effects of tamoxifen-enriched diet (65 mg/kg of food) over a 5-week period starting at 3 weeks of age on Ryr1TM/Indel mice modeling the severe form of RYR1-related CNM.

In vivo and in vitro phenotyping were assessed and thereafter compared with untreated (i.e. regular diet) Ryr1TM/Indel mice, and treated and untreated wild-type (WT) littermates. Body weight and in vivo whole-body hanging performances were measured weekly over the 5-weeks of tamoxifen exposure. At the end of the treatment period, force of the tibialis anterior muscle (TA) was measured at incremental frequencies (1 to 150 Hz) and during fatiguing exercise (40 Hz, 1 sec on, 3 sec off). At the cellular level, fiber size of the TA was measured from the whole section.

Untreated Ryr1TM/Indel mice display lower body weight, muscle weakness in vivo and in situ and reduced muscle fiber size compared to untreated WT mice. Neither body weight nor hanging performance were ameliorated in Ryr1TM/Indel mice upon tamoxifen exposure. In situ muscle force was not improved in tamoxifen-treated Ryr1TM/Indel mice in comparison with untreated Ryr1TM/Indel mice regardless of the stimulation frequency and neither during fatiguing exercise. Finally, fiber size was not enhanced in tamoxifen-treated Ryr1TM/Indel mice compared to untreated Ryr1TM/Indel.

Overall, our results indicate that this dose of tamoxifen (15 mg/kg of mouse/d) did not antagonize muscle weakness or muscle atrophy. Thus, tamoxifen may not serve as a therapeutic approach for RYR1-related myopathy. Further investigations will be performed in order to confirm or disconfirm these preliminary data and to assess molecular markers predicting responsive versus non-responsive myopathies.

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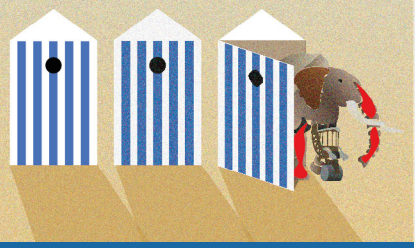


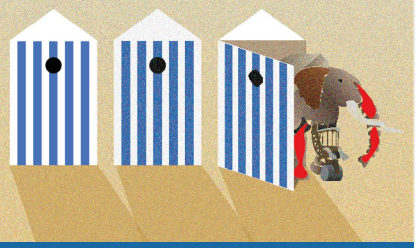
POSTER - P98 - GROUPE 4
Dystrophie musculaire

Catherine KERTING[1]
E. Mercuri[2], I. Desguerre[3], A. Gangfuss[4], L. Servais[5,6], A. Nascimento[7], B.B. Zhang[8], A.P. Murphy[10], C. Reid[10], C. Wandel[9], T.Singh[11], M. Guridi[9], F. Muntoni[12]

1. Roche SAS Direction Science, Paris, France
2. Pediatric Neurology Institute, Catholic University and Nemo Pediatrico, Fondazione Policlinico Gemelli IRCCS, Rome, Italy
3. Departments of Pediatric Neurology and Medical Genetics, Hospital Necker-Enfants Malades, Université Paris Cité, Paris, France
4. Department of Paediatric Neurology, Center for Neuromuscular Disorders in Children and Adolescents, Center for Translational Neuro- and Behavioral Sciences, University Clinic Essen, University of Duisburg-Essen, Essen, Germany
5. MDUK Oxford Neuromuscular Centre, Department of Paediatrics, University of Oxford, Oxford, UK
6. Division of Child Neurology, Centre de Références des Maladies Neuromusculaires, Department of Pediatrics, University Hospital Liège & University of Liège, Liège, Belgium
7. Neuromuscular Unit, Neuropaediatrics Department, Hospital Sant Joan de Déu, Fundacion Sant Joan de Déu, CIBERER - ISC III, Barcelona, Spain
8. F. Hoffmann-La Roche Ltd, Mississauga, Canada
9. F. Hoffmann-La Roche Ltd, Basel, Switzerland
10. Roche Products Ltd, Welwyn Garden City, UK
11. Sarepta Therapeutics, Inc., Cambridge, MA, USA
12. The Dubowitz Neuromuscular Centre, NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Institute of Child Health University College London, & Great Ormond Street Hospital Trust, London, UK

ENVOL, a Phase 2, open-label trial evaluating the safety and expression of delandistrogene moxeparvovec in Duchenne muscular dystrophy: Study design

Delandistrogene moxeparvovec is an rAAV vector-based gene therapy, designed to compensate for the absence of functional dystrophin in DMD by delivering a transgene encoding delandistrogene moxeparvovec micro-dystrophin, an engineered dystrophin protein that retains key functional domains of the wild-type protein. As of August 2023, it is approved in the USA and UAE for treating ambulatory paediatric patients aged 4 through 5 years with DMD with a confirmed mutation in the DMD gene.
We describe the study design of ENVOL, a Phase 2, open-label, two-part study assessing safety and expression of commercial process delandistrogene moxeparvovec material in patients (aged <4 years) with a confirmed DMD mutation within exons 18–79.
In Part 1 (52-week follow-up), four cohorts (target enrollment ~21 patients) will receive a single intravenous 1.33x1014 vg/kg dose of delandistrogene moxeparvovec: Cohort A (aged ≥3 to <4 years); Cohort B (aged ≥2 to <3 years); Cohort C (aged >6 months to <2 years); Cohort D (aged ≤6 months).
In Part 2 (208-week follow-up), patients will be monitored to evaluate safety and delandistrogene moxeparvovec micro-dystrophin expression. The primary endpoint is safety, measured by the incidence of treatment-emergent adverse events, serious adverse events, and other relevant assessments including electrocardiogram and echocardiogram. The secondary endpoint is change from baseline to Week 12 in delandistrogene moxeparvovec micro-dystrophin expression measured by western blot. Key exploratory endpoints include change from baseline to Week 12 in delandistrogene moxeparvovec micro-dystrophin expression as measured by immunofluorescence (IF) fiber intensity and IF percent dystrophin-positive fibers; vector genome copies; and change from baseline in functional (North Star Ambulatory Assessment, 10-meter Walk/Run, Time to Rise, 4-stair Climb, and 100-meter Walk/Run) and ambulation assessments including stride velocity 95th percentile measured by a wearable device (functional assessments will be age dependent).
These findings will be used to evaluate delandistrogene moxeparvovec in younger patients with DMD.



POSTER - P99 - GROUPE 3
Thérapie

Lucile HOCH[1]
Lucille Rossiaud[1,2], *Pascal Fragner*[1], *Elena Barbon*[2], *Antoine Gardin*[2], *Manon Benabides*[1], *Emilie Pellier*[1], *Jérémie Cosette*[2], *Lina El Kassar*[1], *Karine Giraud-Triboult*[1], *Xavier Nissan*[1], *Giuseppe Ronzitti*[2]

1. I-STEM, Institute for Stem Cell Therapy and Exploration of Monogenic Diseases, Corbeil-Essonnes, France
2. INTEGRARE, Genethon, Inserm, Evry University, Paris-Saclay University, Evry, France.

Pathological modeling of Glycogen Storage Disease type III with CRISPR/Cas9 edited human pluripotent stem cells

Glycogen storage disease type III (GSDIII) is a rare genetic disease caused by mutations in the AGL gene encoding the glycogen debranching enzyme (GDE). The deficiency of this enzyme leads to pathological glycogen accumulation in liver, skeletal muscles and heart inducing severe liver impairments in children and progressive myopathy in adults. No curative treatment is currently available. Here, we combined the self-renewal and differentiation capabilities of human induced pluripotent stem cells (hiPSCs) with cutting edge CRISPR/Cas9 gene editing technology to establish a stable AGL knockout cell line and to explore glycogen metabolism in GSDIII. Following skeletal muscle cells differentiation of the edited and control hiPSC lines, our study reports that the insertion of a frameshift mutation in AGL gene results in the loss of GDE expression and persistent glycogen accumulation under glucose starvation conditions. Phenotypically, we demonstrated that the edited skeletal muscle cells faithfully recapitulate the phenotype of differentiated skeletal muscle cells of hiPSCs derived from a GSDIII patient. We also demonstrated that treatment with recombinant AAV vectors expressing the human GDE cleared the accumulated glycogen. These cellular models will be used as a platform to assess the therapeutical potential of pharmacological inducers of glycogen degradation.

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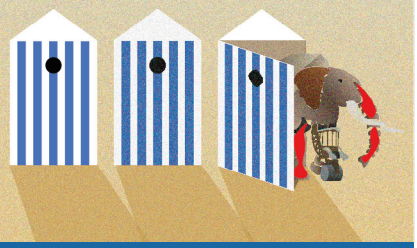

POSTER - P100* - GROUPE 4
Dystrophie musculaire

Camille VEREBI
Victor Gravrand, Thierry Bienvenu, France Leturcq, Juliette Nectoux

Fédération de Génétique et de Médecine Génomique, Service de Médecine Génomique des Maladies de Système et d'Organe, Université Paris Cité, Hôpital Cochin, 75014 Paris, France

Mosaïques germinales dans les Dystrophies Musculaires de Duchenne et Becker : Étude de cohorte, synthèse de la littérature et conseil génétique associé

Lorsqu'un variant causal du gène DMD n'est pas détecté dans leur sang, les mères de patients atteint de Dystrophie Musculaire de Duchenne (DMD) ou Dystrophie Musculaire de Becker (BMD) possèdent un statut de potentielles transmettrices, en raison du risque de mosaïque germinale. Un variant dit en mosaïque germinale, correspond à un variant génétique qui n'est pas retrouvé dans le sang mais confiné aux gonades et pouvant être transmis. Dans les dystrophinopathies, environ un tiers des cas surviennent suite à l'apparition de variants de novo. Compte tenu du risque important de mosaïque germinale, son intégration dans le conseil génétique est impérative.

Nous présentons les données de la plus large cohorte française de Diagnostics Prénataux (DPN) DMD en vue d'estimer le risque de mosaïque germinale dans les dystrophinopathies. Entre octobre 2006 et mai 2023, 499 DPN ont été analysés, représentant 332 familles. Un mosaïcisme germinal n'a été prouvé que dans 5 familles (8,1%). L'incidence globale du mosaïcisme germinal documenté dans la cohorte est donc de 1,5 %.

Une revue exhaustive de la littérature disponible concernant la mosaïque germinale dans les dystrophinopathies a été réalisée : Parmi les familles dans lesquelles un variant de novo avait été mis en évidence, 7,6% d'entre elles en moyenne présentaient une mosaïque germinale documentée. Pour les mères de patients porteurs d'un variant causal de novo confirmé, le risque de récurrence était de 5,8% en moyenne pour un fœtus masculin.

En fournissant l'étude des mosaïques germinales dans la plus large cohorte française de DPN DMD et le premier panorama exhaustif de la littérature sur le sujet, cette étude vise à faire progresser notre compréhension des évènements de mosaïque germinale dans les dystrophinopathies. Ceci permet un conseil génétique mieux documenté pour l'évaluation du risque de récurrence pour les familles touchées par des événements de novo du gène DMD.

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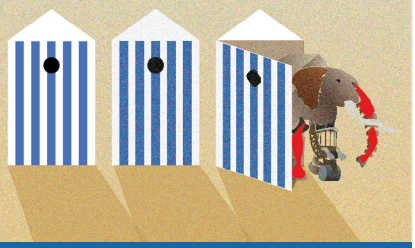

POSTER - P101* - GROUPE 3
Thérapie

Alexis OSSENI
Laurent Schaeffer

Pathophysiology and Genetics of Neuron and Muscle (INMG-PGNM), CNRS UMR 5261, INSERM U 1315, Université de Lyon, Lyon, France

Inhibition of HDAC6 improves muscle integrity in Duchenne Muscular Dystrophy mouse model

Duchenne muscular dystrophy (DMD) is the most common and fatal form of muscular dystrophy. The absence of dystrophin is associated with loss of the dystrophin-associated glycoprotein (DGC) complex, making muscle fibers more susceptible to contraction-induced membrane damage eventually leading to myofiber death. This pathologic process is accompanied by inflammation and fibrosis that contribute to fatal muscle wasting and loss of function in skeletal muscles and the heart, resulting in fiber fragility and atrophy, associated with disorganization of microtubules and of the neuromuscular junction. Even though, glucocorticoids still serve as the gold standard therapy, acting mostly as anti-inflammatory drugs, despite tremendous research efforts, no cure is available for DMD patients yet.

Conversely to other histone deacetylases (HDACs), HDAC6 is strictly cytoplasmic and does not deacetylate histones. Its substrates are cytoplasmic proteins such as α-tubulin or the chaperon HSP90. We have recently shown that HDAC6 inhibition represses TGF-β signaling via SMAD3 acetylation. In vivo, we have shown that HDAC6 pharmacological inhibition greatly improves the phenotype of the DMD mouse model (mdx) via the innovative combined action of TGF-β signaling inhibition and microtubules stabilization. Selective HDAC6 inhibitors (HDAC6i) thus provides additional benefit compared to pan-HDACi. A series of experiments were performed based on the therapeutic relevance of HDAC6 inhibitor (tubastatin A) in mdx mice.

Four weeks of tubastatin A treatment of mdx mice cause myofiber hypertrophy. Our results reveal that tubastatin A-treated mdx mice display a significant decrease in the percentage of central nucleation and an increase of quantification of SDH staining both in EDL and SOL muscles. An oxidative fiber-type switch observed in tubastatin A-treated mdx mice is also associated with significantly increased expression of proteins involved both in mitochondrial biogenesis pathway and OXPHOS proteins. These findings seem indicate that the beneficial effects of TubA treatment could be dependent of the activation of AMPK.

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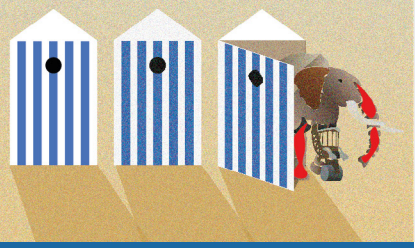

Erwan DELAGE
Ester Cotali, Daniel Wolf, Tyler Picariello, Lydia Schlaefke, Ryan Russo, Ann Chang, Scott Hildebrand, John Najim, Qifeng Qiu, Timothy Weeden, John W Davis II, Chris Mix, Baoguang Han, Stefano Zanotti, Oxana Beskrovnaya, Wildon Farwell

Dyne Therapeutics

Preclinical Data Support the Initiation of the ACHIEVE Trial of DYNE-101 in Individuals with Myotonic Dystrophy Type 1 (DM1)

Myotonic dystrophy type 1 (DM1) is caused by expansion of CUG repeats in the 3'-untranslated region of the dystrophia myotonica protein kinase (DMPK) RNA. The expanded CUG repeats form hairpin-loop structures that sequester splicing regulators into toxic nuclear foci, leading to a spliceopathy that drives DM1 clinical manifestations. No disease-modifying treatments are approved, limiting current treatment to symptom management. We developed the FORCETM platform, which harnesses the natural expression of transferrin receptor (TfR)1 on muscle cells for targeted delivery of oligonucleotides. DYNE-101 is a TfR1-targeting antigen-binding fragment conjugated to a gapmer antisense oligonucleotide that targets nuclear DMPK RNA. In hTfR1/DMSXL mice, a novel model of DM1, DYNE-101 led to reduction of toxic human DMPK RNA and a corresponding splicing correction in cardiac and skeletal muscle that were accompanied by reduction of DMPK nuclear foci in the heart. Additionally, DYNE-101 led to a substantial suppression of WT DMPK expression in cardiac, skeletal, and smooth muscle after repeat monthly dosing in non-human primates, and had a favorable safety profile. These data supported the initiation of the ACHIEVE trial, a randomized, double-blinded, placebo-controlled, multiple ascending dose (MAD) Phase 1/2 study assessing safety, tolerability, pharmacodynamics, and pharmacokinetics of DYNE-101 administered intravenously to ~64 adults with DM1 aged 18-49 years (NCT05481879). The primary outcome is the number of participants with treatment-emergent adverse events. Change from baseline in splicing index in skeletal muscle is a secondary outcome. The ACHIEVE study will inform the potential of DYNE-101 as a treatment for DM1.

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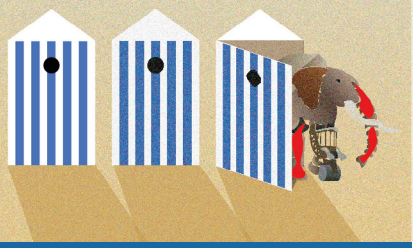

POSTER - P103* - GROUPE 3
Thérapie

Teoman OZTURK[1]
Julien Mignot[1], *Francesca Gattazzo*[1], *Béatrice Laurent*[1], *Frédéric Relaix*[1,2,3], *Hélène Rouard*[1,3], *Nathalie Didier*[1]

1. Univ Paris Est Créteil, INSERM, EFS, IMRB, F-94010 Créteil, France.
2. EnVA, IMRB, F-94700 Maisons-Alfort, France. 3 - AP-HP, Hôpital Mondor, Service d'histologie, F-94010 Créteil, France.

Restricting p38 MAPK activity in human MuSCs from their niche withdrawal to their ex vivo expansion is a key factor to preserve their therapeutic potential

Muscle stem cells possess a remarkable regenerative potential rendering them attractive for cell-based therapeutic strategies. However, their clinical use is hampered by their restrained number in adult muscle, the inability to efficiently amplify them in vitro while preserving their therapeutic potential and their purification process. Indeed, recent studies showed that massive activation of stress pathways, notably p38 MAPK and JNK, occurs during muscle enzymatic dissociation, leading to premature loss of quiescence. We investigated PAX7 protein dynamic during this process and demonstrated a bi-phasic reduction. An immediate and drastic decline independent of p38 and JNK activities, followed by a slower decrease that was counteracted by their inhibition. We showed that inhibiting these two pathways could prevent MuSC premature activation and stemness markers downregulation (i.e. Pax7, CalcR, Sprouty, Itga7) leading to higher amplification rate in vitro and increased engraftment potential in vivo. Interestingly, the combined inhibition of p38 and JNK during the whole isolation process of murine and human MuSC significantly increased their purification yield.
In addition, through multi-omics analyses, we identified a p38 MAPK/Thrombospondin-1 (THBS1)/CD47 axis that triggered a progressive decrease of hMuSC fusion capacity in vitro, and ultimately a loss of their myogenic identity. In agreement, exposure to a pharmacological inhibitor of p38 (SB) during the amplification phase, preserved hMuSC fusion capacity and the expression of myogenic factors, leading to enhanced engraftment potential in vivo.
Overall, our data demonstrate the importance of limiting stress signaling activation during MuSC isolation process and highlight p38 MAPK as a key target to preserve hMuSC therapeutic potential.

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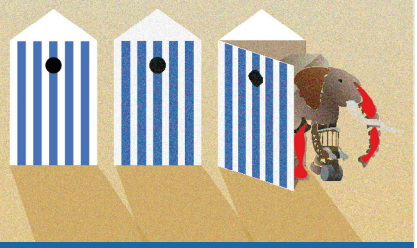

POSTER - P104 - GROUPE 4
Dystrophies myotoniques

Sabrina SACCONI[1]
B. Sanson[1*], *C. Guien*[2], *S. Rabarimeriarijaona*[3], *H. Delattre*[4], *R. Bernard*[3], *C. Béroud*[2]

1. Université Côte d'Azur, Service Système Nerveux Périphérique & Muscle, Centre Hospitalier Universitaire de Nice, Nice, France
2. Aix Marseille Univ, INSERM, MMG, Bioinformatics & Genetics, Marseille, France
3. APHM, Hôpital Timone Enfants, Laboratoire de Génétique Moléculaire, Marseille, France
4. Medical Affairs Department, AFM-Telethon, Evry, France
** Auteur Principal*

L'Observatoire national français de la DMFSH, un hub de projets collaboratifs

La dystrophie musculaire facioscapulohumérale (DMFSH) est l'une des myopathies les plus fréquentes. Aucun traitement n'existe, et le mécanisme physiopathologique n'est pas pleinement élucidé. Des registres nationaux ont été établis pour compléter les connaissances sur la pathologie et en améliorer la prise en charge. Avec ~1200 malades inclus et 39 sites participants, l'Observatoire français figure parmi les registres neuromusculaires les plus riches.

Notre registre est conçu pour faciliter et accélérer la mise en place de projets variés. Avec l'arrivée des essais thérapeutiques, c'est un outil de choix pour le développement et la validation de tests et indicateurs pertinents, affiner les protocoles et rassembler rapidement les cohortes adéquates.

Une palette de projets satellites y sont progressivement connectés sous forme d'un réseau en étoile (hub). L'essai Clinical Trial Readiness Network FSHD France (NCT04038138), visant à valider des indicateurs de mesure chez des patients FSH type 1 ambulatoires, a été conçu comme un premier module. Un essai spécifique a été mis en place pour les patients non-ambulatoires. De futurs essais cibleront les populations pédiatriques, et celles de type 2. Une étude ancillaire vise à valider de nouveaux biomarqueurs et à préparer la collecte de données de vie réelle.

La stratégie de collecte double, auprès des malades et des médecins, a été validée par une analyse statistique publiée. La qualité des données ainsi mise en évidence permet d'envisager l'utilisation d'algorithmes de machine learning, pour développer, notamment, des modèles prédictifs de l'évolution de la DMFSH.

Enfin, le développement d'une application mobile contribuera à stimuler la participation, mais aussi à rendre possible la collecte de données d'un nouveau type, augmentant les chances de succès de la mise en œuvre de l'IA sur nos données, et renforçant le rôle du registre comme lien éducatif entre les patients et les médecins.

Ce projet est financé par l'AFM-Téléthon.

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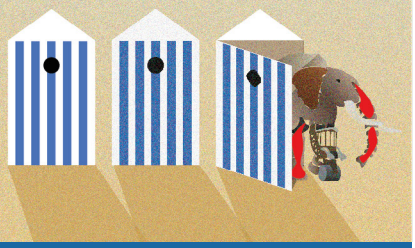
15 - 17 Novembre 2023 • Palais des Congrès - Atlantia



POSTER - P105* - GROUPE 3
Thérapie

Emmanuelle ROTA GRAZIOSI[1]
François Sabine[1,2], *Pateux Jérôme*[1], *Gauthier Michel*[1], *Drouet Michel*[1,2], *Riccobono Diane*[1,2], *Jullien Nicolas*[1]

1. French Armed Forces Biomedical Research Institute (IRBA), Brétigny-sur-Orge, France
2. INSERM Unit UMR1296 «Radiations: Defense, Health, Environment», Lyon and Brétigny-sur-Orge, France

High dose localized skeletal muscle irradiation: Hedgehog pathway as a new therapeutic target?

Acute localized irradiation accidents may evolve into a musculocutaneous radiation syndrome which leaves, in spite of a reference treatment, an important underlying muscle defect. Therefore, identification of new therapeutic targets to improve post-irradiation muscle regeneration is necessary.

The effect of the pro-myogenic Hedgehog signaling pathway modulation by recombinant Sonic Hedgehog (rShh; agonist) or cyclopamine (antagonist) was studied in vitro on irradiated pre-myoblasts C2C12 (5 Gy, X-Rays). Analysis of proliferation, survival and expression of myogenic markers confirmed the deleterious effect of irradiation and highlighted the favorable effect of the rShh stimulation on cell proliferation and survival, as well as the pro-differentiation effect of cyclopamine blockade. Comparative studies between cyclopamine and two other antagonists, sonidegib and vismodegib, suggested that sonidegib presented an effective alternative to cyclopamine for in vivo studies, with the added advantage of being FDA-approved.
Concurrently, to evaluate a potential therapeutic strategy in vivo, the validation of a model of radiation-induced muscle injury was initiated. The gastrocnemius/soleus muscles of C57Bl/6 mice were irradiated at different doses (50-80 Gy; X-Rays). Macroscopic, biochemical and histological analyses performed 90 days post-irradiation showed that the animals presented muscle atrophy and a variation of specific markers.

The results obtained in vitro suggest that a sequence of (1) activation of the Hedgehog pathway, allowing a pool of myogenic precursors to survive and proliferate, followed by (2) a blockade favoring the differentiation of progenitors and thus muscle regeneration, could constitute a potential treatment. The in vivo model developed by our team aims to describe the physiopathology of the radiation-induced muscular injury, identify new targets and test potential therapeutic strategies that have previously demonstrated efficacy in vitro.

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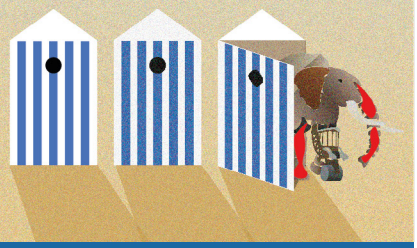

POSTER - P106 - GROUPE 4
Dystrophies myotoniques

Emmanuelle SALORT-CAMPANA[1]
K. Wahbi[2], *J. Duchateau*[3], *J.M. Sellal*[4], *J.C. Deharo*[5], *G. Bassez*[6], *F. Labombarda*[7], *S. Vicart*[8]

1. Centre de référence neuromusculaire coordonnateur PACA Réunion Rhône alpes, service du Pr Attarian, Hôpital de la Timone, CHU de Marseille, France1
2. Centre de référence constitutif des maladies neuromusculaires, département de cardiologie, Ap-Hp Cochin, Paris, France
3. Service de cardiologie, électrophysiologie et stimulation cardiaque, Hôpital Haut Lévèque, CHU de Bordeaux, France
4. Département de cardiologie, CHU de Nancy, France
5. Département de cardiologie, Hôpital de la Timone, CHU de Marseille, France
6. Centre de référence constitutif des maladies neuromusculaires, service de neuro-myologie, Ap-Hp Pitié-Salepêtrière - Paris, France
7. Département de cardiologie, CHU de Caen, France
8. Centre national de référence des canalopathies musculaires, Service de Neuro-Myologie, Assistance Publique-Hôpitaux de Paris, Hôpital universitaire de la Pitié-Salpêtrière, Sorbonne Université, INSERM UMR 974, Institut de Myologie Paris, France

Recommendations of an expert group for cardiac assessment of non-dystrophic myotonic adult patients treated with mexiletine

Mexiletine (NaMuscla™) is indicated for the symptomatic treatment of myotonia in adults with non-dystrophic myotonia (NDM). A cardiac assessment is required as mexiletine may have a pro-arrhythmic effect. Long-term safety data supporting use of mexiletine in patients with NDM combined with the extensive clinical experience of an expert group resulted in creation of an algorithm for cardiac monitoring of NDM patients treated with Mexiletine.
To define the treatment algorithm, several workshops with experts including 3 neurologists and 5 cardiologists from different French neuromuscular reference centres were set up. These workshops aimed to define the screening and surveillance tools required to avoid cardiac events in mexiletine-treated patients.
The recommendations are based on the summary of product characteristics (SmPC), a review of the literature on the safety of mexiletine-treated NDM patients and on the expertise of the authors.
The expert group concluded that the cardiac safety profile of mexiletine in NDM patients appears similar to that of the general population. Therefore, NDM patients treated with Mexiletine should be monitored as any patient treated with a class 1b anti-arrhythmic. Cardiac assessment should be performed before initiation of mexiletine and at least every 2 years under treatment.
In summary, an algorithm for cardiac safety monitoring in patients with NDM treated with mexiletine has been developed to assist the neurologists and cardiologists managing these patients.

Data were first presented at the 9th Congress of the European Academy of Neurology, Budapest, July 1–4, 2023. Poster # A-23-06846/EPO-411. They are presented also at the 28th annual congress of the World Muscle Society, Charleston, USA, 3rd-7th October 2023. Poster # P395.

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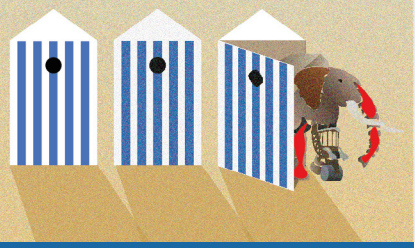
15 - 17 Novembre 2023 • Palais des Congrès - Atlantia



POSTER - P107* - GROUPE 3
Ingénierie / Biomatériel / Organoïde

Marion BOUVET[2]
Louise Griveau[1,2*], *Cloé Paret*[1,2], *Émilie Christin*[2], *Jérôme Sohier*[1], *Vincent Gache*[2]

1. LBTI CNRS UMR5305, Lyon, France
2. INMG CNRS UMRS5310, INSERMU1217, Lyon, France
** Auteur Principal*

Innovative injectable and porous hydrogel as support for striated skeletal muscle tissue engineering.

Background: Volumetric muscle loss (VML) resulting from traumatic incidents drastically decreases muscle regeneration capacity and lacks treatments. Hydrogels are promising materials for the repair of damaged tissues, providing a hydrated and versatile support for cells. We hypothesized that an injectable biomaterial that perfectly conforms to the muscle defect shape would enhance muscle repair. To achieve this, we developed an effervescent porous hydrogel (EPH) made from biocompatible and biodegradable materials, specifically poly-lysine dendrimers, and polyethylene glycol. These hydrogels offer customizable mechanical properties and facilitate natural cell interactions.

Objectives: Our goal is to demonstrate the potential of our porous injectable hydrogels in promoting muscle fiber recovery within rat VML models of various sizes.
Methods: After creation of VML defect in rat's tibialis anterior, the porous hydrogel was injected and harvested after 7 to 21 days. Masson's Trichrome allowed to evaluate inflammation, vascularization, hydrogel degradation over time and to quantify cellularization and inflammatory tissue. Emb-MyHC, MyHC and MyoD immunofluorescence staining's were used to characterize muscle cell types and their behavior in the hydrogel.

Results: Hydrogel injection into the VML effectively resulted in porous matrices that perfectly filled the defect. The rats could walk and showed no signs of distress or pain over implantation times. After 7 days, empty VML were filled by granular tissue whereas important cellularization was observed in the porous structures with inflammatory cells and collagen deposition. By the 21st day, granular tissue was reduced both in empty defects and around the hydrogel while cellularization further increased. The hydrogel size was reduced, possibly due to degradation by macrophages. Blood vessels were observed within the pores and muscle fibers were in close contact to the hydrogel margins, comforting its suitability to chaperone muscle regeneration. Indeed, MyoD+ cells and myotubes (MyHC+) were observed in pores at days 7 with also neo-formed fibers (emb-MyHC+) through the hydrogel pores, both at 7 and 21 days.

Conclusion: To conclude, the injectable porous hydrogels can readily be injected into VML of various sizes. Their bio-integration underlines their promising role in guiding the muscle repair process. Ongoing research into cell behavior within the hydrogel will further confirm their potential.

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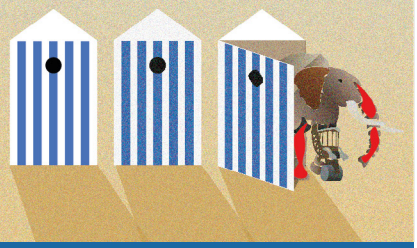

POSTER - P108 - GROUPE 4
Dystrophies myotoniques

Céline TARD[1]
V. Sansone[2], *E.J. Ashley*[3], *F. Montagnese*[4], *C. Gagnon*[5], *U. Nowak*[6], *U. Dang*[7], *C. Turner*[8], *N. Nikolenko*[9], *R. Dufresne*[10], *A. Zozulya-Weidenfeller*[11]

1. Centre Hospitalier Régional Universitaire de Lille, France
2. The NeMO Clinical Centre, Neurorehabilitation Unit, University of Milan, Italy
3. Cure Myotonic Dystrophy UK Charity, UK
4. Friedrich-Baur Institut, University Clinic Munich, Germany
5. Sherbrooke University Faculty of Medicine and Health Sciences, Canada
6. admedicum, Cologne, Germany
7. Carleton University, Canada
8. University College London Hospitals NHS Foundation Trust, UK
9. University College London Hospitals NHS Foundation Trust, UK
10. Lupin France, Paris, France
11. Lupin EMEA, Zug, Switzerland

RevEal the burdeN on daily life for myotonic dyStrophy patients due to myotoniA: The ENSA survey

Introduction: Myotonia is a symptom of myotonic dystrophy (DM) type 1 and 2. This can be debilitating and affects patients' everyday living, with a significant burden on Quality of Life (QoL) (1). Impact of DM on QoL has been evaluated (2,3), however, the specific contribution of myotonia remains unclear. The ENSA survey will assess the impact of myotonia on DM patients' daily lives.

Methods: Patients living in Europe, UK and North America, aged ⩾18 years with a confirmed diagnosis of DM1/DM2, (or caregivers) will be invited to complete an anonymised online survey. Questions will explore the patient's description of DM symptom onset, time to medical consultation, the nature, frequency and location of myotonia, muscle weakness, fatigue, daytime sleepiness, gastrointestinal, and cardiorespiratory symptoms, along with disease management, treatment history and impact on daily life.

Results: Findings will aim to provide insight into the burden of myotonia on the daily life for DM patients, as well as increasing understanding of symptoms to support future clinical-trial outcome measures.

Conclusions: The ENSA survey will quantify the impact of myotonia on DM1 and DM2 patients' daily life and raise awareness of the need for appropriate management.

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1. Diaz-Manera J, et al. EMJ 2021;6[2]:37-46.
2. Rakocevic Stojanovic, S et al; J. Neurological Sciences, 2016;365, 158-161.
3. Landfeldt, E et al; Patient, 2019; 12(4): 365–373.

Data were first presented at the 9th Congress of the European Academy of Neurology, Budapest, July 1–4, 2023. Poster # A-23-06846/EPO-411.

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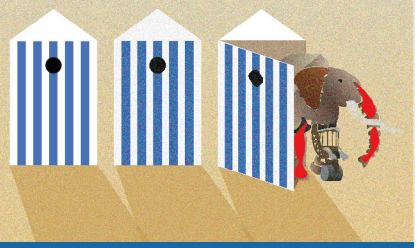

POSTER - P109 - GROUPE 3
Ingénierie / Biomatériel / Organoïde

Mélanie MARQUIS
A. Zykwinska[2], B. Novales[3], S. Cuenot[4], K. Rouger[1]

1. Oniris, INRAE, UMR PAnTher, 44307 Nantes, France
2. IFREMER, Laboratoire EM3B, 44311 Nantes, France
3. INRAE, BIA, 44316 Nantes, France
4. Institut des Matériaux Jean Rouxel (IMN), Université de Nantes-CNRS, 44322 Nantes, France

Impact de l'environnement matriciel 3D sur la biologie des cellules souches adultes humaines MuStem

L'identification de cellules souches adultes (CSA) et la démonstration de leur potentiel myogénique ont conduit à de nouvelles propositions thérapeutiques pour les myopathies. Les données précliniques acquises sur un type de CSA (appelé cellule MuStem) que nous avons caractérisé in vitro et in vivo1,2 positionnent cet agent comme un potentiel candidat pour la thérapie cellulaire des myopathies. Cependant, sa capacité de survie et d'intégration dans le tissu hôte, bien que supérieure à celle décrite pour les autres candidats, limite son impact thérapeutique global. L'essor des approches de biomimétisme tissulaire, basées sur l'encapsulation cellulaire dans des biomatériaux performants, biocompatibles et biodégradables, offre de nouvelles opportunités pour surmonter les limites de la thérapie cellulaire en termes de viabilité et potentialisation des effets. C'est ainsi que l'environnement matriciel utilisé in vitro a été présenté comme ayant un impact majeur sur les caractéristiques myogéniques in vitro mais aussi sur les propriétés comportementales in vivo3.
Dans ce contexte, nous avons (1) élaboré un type de matrice 3D correspondant à des hydrogels d'alginate de calcium, (2) définis leurs propriétés physicochimiques, mécaniques et de diffusion puis (3) étudié leur impact sur les cellules hMuStem. Nous avons obtenu des hydrogels présentant des modules élastiques compris entre 1 et 25 kPa selon le mode de gélification (externe vs interne) et les concentrations en alginate et calcium. Nous avons montré l'impact du mode de gélification sur la structure et les propriétés de diffusion des hydrogels. Nous avons établi que le procédé d'encapsulation n'altère pas la viabilité des cellules hMuStem et préserve leur morphologie et capacité de différenciation myogénique une fois libérées. Par cette démarche, nous avons défini une modalité d'encapsulation des cellules hMuStem tout en conservant leurs fonctionnalités, offrant de nouvelles opportunités pour développer des protocoles originaux en médecine régénérative musculaire.

[1] Rouger et al., American Journal of Pathology. 179, 5; 2501-2518, 2011
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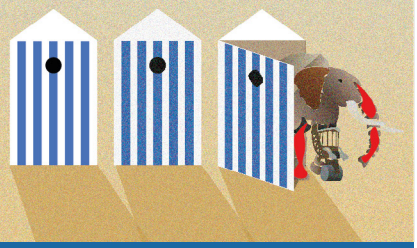
[3] Raab et al., Stem Cell Research and Therapy. 1, 38, 2010



POSTER - P110 - GROUPE 4
Dystrophies myotoniques

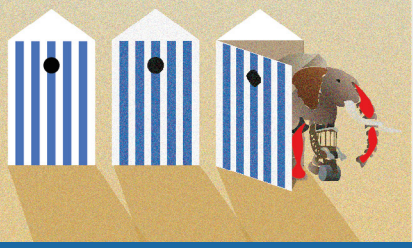
Karim WAHBI[1]
B. Bassez[2], *J. Duchateau*[3], *E. Salort-Campana*[4], *S. Vicart*[5], *F. Labombarda*[6], *J.M. Sellal*[7], *J.C. Deharo*[8]

1.Centre de référence constitutif des maladies neuromusculaires, département de cardiologie, Ap-Hp Cochin
2. Centre de référence constitutif des maladies neuromusculaires, service de neuro-myologie, Ap-Hp Pitié-Salepêtrière - Paris, France
3. Service de cardiologie, électrophysiologie et stimulation cardiaque, Hôpital cardiologique du Haut l'Evêque, CHU de Bordeaux, France
4. Centre de référence neuromusculaire coordonnateur PACA Réunion Rhône alpes, service du Pr Attarian, Hôpital de la Timone, CHU de Marseille, France
5. Centre national de référence des canalopathies musculaires, Service de Neuro-Myologie, Assistance Publique-Hôpitaux de Paris, Hôpital universitaire de la Pitié-Salpêtrière, Sorbonne Université, INSERM UMR 974, Institut de Myologie Paris, France
6. Département de cardiologie, CHU de Caen, France
7. Département de cardiologie, CHU de Nancy, France
8. Département de cardiologie, Hôpital de la Timone, CHU de Marseille, France

Initiation and follow-up of mexiletine treatment in adult myotonic dystrophy patients: An expert opinion

Mexiletine is an effective symptomatic treatment for myotonia and is approved as NaMuscla in the European Union and United Kingdom for treating myotonia in adults with non-dystrophic myotonia (NDM). Mexiletine has historically been used to treat myotonia in patients with myotonic dystrophy (DM), and in France can be prescribed for people with DM under a compassionate-use program. Cardiac assessments before mexiletine initiation, which are repeated periodically throughout treatment, are required because of mexiletine's potential pro-arrhythmic effects. The presence of progressive cardiac impairment in DM mandates by itself repeated cardiac evaluations in this patient population and becomes key when patients receive mexiletine.
An expert group of 5 cardiologists and 3 neurologists from French neuromuscular reference centers conducted a series of meetings to define and ratify the surveillance tools required to avoid cardiac events in mexiletine-treated adults with DM. Ultimately the expert group created an algorithm for cardiac monitoring in these patients. Recommendations within the algorithm are based on the compassionate-use protocol, a review of literature on the safety of mexiletine-treated DM patients, and on authors' collective experiences.
The expert group concluded that although safety data in mexiletine-treated DM patients are reassuring, a thorough cardiac assessment should be reinforced in DM patients in comparison to NDM patients. In particular, cardiac monitoring of DM patients before treatment initiation should entail systematic cardiac evaluations including electrocardiogram (ECG), echocardiography and Holter ECG.
This expert opinion for thorough cardiac assessments prior to mexiletine treatment initiation and throughout the treatment course should contribute to enhancing the clinical management of this patient group, and improving the dialogue between specialists involved in DM patient care.

Data are presented at the 28th annual congress of the World Muscle Society, Charleston, USA, 3rd-7th October 2023. Poster # P387.



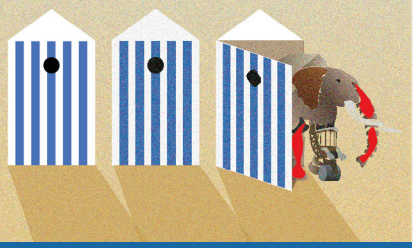
Alicia MAYEUF-LOUCHART[4]

Anne Danckaert[1], Aurélie Trignol[2], Guillaume Le Loher[1,3], Sébastien Loubens[4,5], Bart Staels[4], Hélène Duez[4], Spencer L. Shorte[1]*

1. Institut Pasteur, Université Paris Cité, UTechS Photonic BioImaging/C2RT, F-75015 Paris, France
2. French Armed Forces Biomedical Research Institute (IRBA), France; Université Paris Cité, VIFASOM (UPR 7330 Vigilance Fatigue, Sommeil et Santé Publique), France
3. Present Address: École Centrale d'Electronique (ECE), Paris, France
4. Univ. Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011- EGID, F-59000 Lille, France
5. CHU Lille, Service Neuropédiatrie, 59000 Lille, France

MuscleJ2: a rebuilding of MuscleJ with new features for high-content analysis of skeletal muscle immunofluorescence slides

Histological analysis of skeletal muscle is of major interest to understand its behavior in different pathophysiological conditions, such as its response to different environments or myopathies. In this context, many softwares have been developed to perform high content analysis in an automated way. Among them, we have created MuscleJ, a macro running on ImageJ/Fiji on batches of images. MuscleJ is a multi-analysis tool that initially allows the analysis of muscle fibers, capillaries and satellite cells. Since its creation, it has been used in many studies and we have further developed the software and added new features, which are presented in this article. We have converted the macro into a Java-language plugin with an improved user interface. MuscleJ2 provides quantitative analysis of fibrosis, vascularization and cell phenotype in whole muscle sections. It also performs analysis of the peri-myonuclei, the individual capillaries and any staining in the muscle fibers, providing accurate quantification in regional sub-localizations of the fiber. A multi-cartography option allows users the ability to visualize multiple results simultaneously. The plugin is freely available to the muscle science community.



Lise MORIZUR
Céline Leteur, Jérôme Polentes, Claire Boissart, Cécile Martinat

I-STEM, CECS / Inserm UMR861 / UEVE - Corbeil-Essonnes, France

3D skeletal muscle constructs from human pluripotent stem cells for complex muscle disease modeling

Rational: For over a decade human pluripotent stem cells (hPSCs) have offered new perspectives for modeling muscle pathologies. Nevertheless, the majority of these modeling approaches have predominantly relied on creating two-dimensional (2D) culture models, which lack the ability to replicate the complex organization and functionality found in native muscle tissue. The generation of miniaturized, functional biomimetic skeletal muscle tissues from hPSCs is thus instrumental for complex disease modeling and drug screening.

Results: We implemented a transgene-free protocol to differentiate three distinct hPSC lines into a highly homogeneous and expandable population of myogenic progenitor cells. Myotubes derived from these myogenic progenitor cells in 2D culture exhibited a high fusion index, well-organized sarcomeric structures and spontaneous contractions. Notably, a small fraction of cells expressed Pax7 adjacent to muscle fibers. A cardiotoxin (CTX) injury assay further revealed these satellite-like cells were capable of muscle regeneration characterized by progressive regrowth, differentiation and sarcomerogenesis. We next formed functional skeletal muscle constructs by embedding myogenic progenitors within 3D hydrogel scaffolds using culturing platforms with anchoring pillars. Myobundles engineered from three hPSC lines reproducibly exhibited the formation of cross-striated myotubes capable of generating active twitch in response to acetylcholine or electrical stimulation in as early as 7 days of differentiation. Myobundle contractions correlated with strong calcium transients immediately after exposure to acetylcholine.

Conclusion: Our objective is now to apply this 3D skeletal muscle platform to hPSCs derived from patients affected by Myotonic Dystrophy type 1 (DM1) in order to gain deeper insights into the underlying pathophysiological mechanisms and test novel therapeutics.

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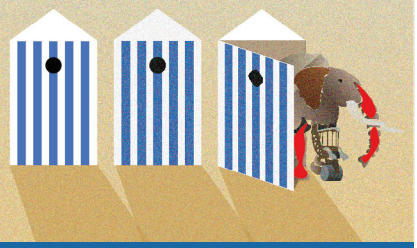

POSTER - P113* - GROUPE 3
Ingénierie / Biomatériel / Organoïde

Laura PALMIERI[1,2]
Melissa Moula[1,2], *Abbass Jaber*[1,2], *Ai Vu Hong*[1,2], *Riyad El-Khoury*[1,2,3], *Guy Brochiet*[3,4], *Anne Bigot*[5], *David Israeli*[1,2], *IsabelleRichard*[1,2], *Sonia Albini*[1,2]*

1 Genethon, 91100 Evry, France
2. Université Paris-Saclay, Univ Evry, Inserm, Généthon, Integrare research unit UMR_S951, 91000, Evry, France
3. Institut de Myologie, Neuromuscular Morphology Unit, Groupe Hospitalier Pitié-Salpêtrière, Paris, France
4. AP-HP, Centre de Référence de Pathologie Neuromusculaire Nord/Est/Ile de France, Groupe Hospitalier Pitié-Salpêtrière, Paris, France
5. Sorbonne Université, Inserm, Institut de Myologie, Centre de Recherche en Myologie, F-75013 Paris, France

Generation of pro-fibrotic human engineered contractile MYOtissues suitable for muscle function analysis and gene therapy screening in Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a lethal muscle wasting disease caused by absence of dystrophin, a protein essential to preserve muscle integrity continuously challenged by contractions. Gene therapy utilizing adeno-associated virus (AAV) to deliver truncated forms of dystrophin (µDys) is currently the most promising therapeutic approach. However, the therapeutic outcome in treated patients has not been as successful as anticipated by animal studies, underscoring the need of improved and high-throughput models for accurate and fast prediction of human response. Here, we describe the generation of MYOtissues, an in vitro 3D muscle platform based on direct myogenic conversion of human induced pluripotent stem cells (iPSC), whose structural and functional maturation is enhanced by fibroblasts incorporation. MYOtissues derived from DMD-iPSC including DMD fibroblasts, show exacerbated pathogenic hallmarks such as fibrosis and muscle force loss, allowing their use as reliable therapeutic readouts. As a proof of concept, we showed that AAV-mediated µDys gene transfer in DMD-MYOtissues improved muscle resistance and partially recovered membrane stability with consequent reduction of the inflammatory environment. This study highlights the suitability of our human in vitro system for gene therapy screening with the potential to expand its applications for personalized medicine.

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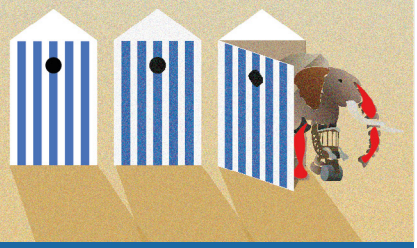

POSTER - P114 - GROUPE 4
Pathologie du nerf et motoneurone

Susana QUIJANO ROY[1]
Marta Gomez Garcia De La Banda[1], *Batoul Samarji*[2], *Emmanuelle Lagrue*[3], *Nadia Blu Genestine*[4], *Laetitia Ouillade*[5]

1. APHP, University Hospital Raymond-Poincaré, Paris, France
2. CHU Nantes, Nantes, France
3. iMotion, Groupe Hospitalier Trousseau La Roche-Guyon, Paris, France
4. Association ECLAS, Ensemble Contre L'Amyotrophie Spinale de type 1, France
5. AFM Téléthon, Evry, France

Évaluation gastro-intestinale dans l'amyotrophie spinale (SMA) : l'expérience des professionnels de santé en France

L'avènement de thérapies ciblées a modifié l'histoire naturelle de la SMA. Cependant, malgré l'émergence de nouveaux phénotypes, les symptômes gastro-intestinaux (sGI) restent fréquents chez les patients atteints de SMA. L'objectif de ce travail était d'évaluer l'approche médicale actuelle des manifestations gastrointestinales de la SMA et les besoins non satisfaits en France.
Dans cette étude observationnelle, un questionnaire a été transmis via la filière Filnemus auprès de médecins spécialisés dans la SMA. Ce questionnaire portait sur les troubles digestifs, les complications nutritionnelles et métaboliques, les examens auxiliaires et la prise en charge globale. Notamment, le questionnaire a évalué si le symptôme était systématiquement recherché par le médecin, ou s'il était pris en charge uniquement lorsque les patients ou leurs aidants en faisaient mention.
Les 32 médecins participants exerçaient dans des centres du réseau FILNEMUS (59% des centres pédiatriques neuromusculaires français).
Les troubles digestifs les plus fréquemment rapportés étaient la constipation et les difficultés de mastication. Les médecins ont déclaré rechercher systématiquement pendant l'examen clinique les troubles de la déglutition (97%) et de la mastication (87%) et les complications gastriques (67%) ou abdominales (63%). Des symptômes fréquents comme les rots excessifs, les nausées, les diarrhées et les régurgitations étaient plutôt considérés après mention de la famille. Le suivi des sGI n'était pas systématique, en particulier pour la limitation de l'ouverture de la bouche (risque d'intubation difficile), les ballonnements abdominaux et/ou l'incontinence fécale.
Ces résultats confirment la nécessité d'un consensus sur les soins et la surveillance gastro-intestinale systématique des patients atteints de SMA. L'évaluation et le traitement des sGI pourraient en effet améliorer la qualité de vie des patients et réduire le fardeau des soignants. Pour améliorer la prise en charge clinique de la SMA, notre groupe d'étude souhaite maintenant créer un questionnaire court, facile à administrer lors d'un suivi multidisciplinaire.

CONTINUONS D'AGIR

Pour que leur quotidien reste à leur portée

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Evrysdi® risdiplam

Evrysdi® est indiqué dans le traitement de l'amyotrophie spinale (SMA) 5q chez les patients avec un diagnostic clinique de SMA de Type 1, Type 2 ou Type 3 ou avec une à quatre copies du gène SMN2.[1]

Place dans la stratégie thérapeutique[2] :
Evrysdi® (risdiplam) est un traitement de 1ère intention, à utiliser :
- chez les patients symptomatiques atteints de SMA de type 1, au même titre que Spinraza® (nusinersen) et Zolgensma® (onasemnogene abeparvovec),
- chez les patients atteints de SMA de type 2 et 3, au même titre que Spinraza® (nusinersen).

Actuellement, il n'existe pas de recommandation relative à la place dans la stratégie thérapeutique d'Evrysdi® chez les patients pré-symptomatiques et/ou < à 2 mois atteints de SMA 5q avec jusqu'à 4 copies du gène SMN2.

En raison de la complexité de la prise en charge de cette maladie, la décision de traitement par Evrysdi® (risdiplam) devra être prise au cas par cas lors de réunions de concertation pluridisciplinaire au sein des centres de référence et de compétence des maladies neuromusculaires de la filière FILNEMUS. De plus, conformément au RCP, le traitement doit être instauré par un médecin expérimenté dans la prise en charge des patients atteints de SMA.

Conditions de prescription et de délivrance[1] :
Liste I.
Médicament soumis à prescription hospitalière.
Prescription réservée aux spécialistes en neurologie ou en neuropédiatrie.

Conditions de prise en charge :
AMM obtenue le 26/03/2021.
Médicament agréé aux collectivités, inscrit sur la liste en sus SSR et inscrit sur la liste des spécialités remboursables aux assurés sociaux avec un taux de remboursement à 65%, dans l'indication chez les patients âgés de 2 mois et plus avec un diagnostic clinique de SMA de type 1, type 2 et type 3.

Médicament non évalué par la Commission de la Transparence, non remboursable et non agréé aux collectivités, dans l'indication chez les patients pré-symptomatiques et/ou < à 2 mois atteints de SMA 5q avec jusqu'à 4 copies du gène SMN2.

Pour une information complète, consultez le Résumé des Caractéristiques du Produit disponible sur la base de données publique des médicaments https://base-donnees-publique.medicaments.gouv.fr/ ou en flashant ce code. Vous pouvez également retrouver ces informations sur evrysdi.roche.fr.

Références :
1. Résumé des Caractéristiques du Produit Evrysdi®.
2. HAS. Avis de la commission de la Transparence Evrysdi® du 8 septembre 2021.

▼ Ce médicament fait l'objet d'une surveillance supplémentaire qui permettra l'identification rapide de nouvelles informations relatives à la sécurité. En signalant les effets indésirables, vous contribuez à fournir davantage d'informations sur la sécurité du médicament. Déclarez immédiatement tout effet indésirable suspecté d'être dû à un médicament à votre Centre régional de pharmacovigilance (CRPV) ou sur https://signalement.social-sante.gouv.fr/

M-FR-00009256 -1.0 - 23/07/68009899/PM/004 - V0823 - Etabli en octobre 2023

Unis dans notre engagement à améliorer la vie des patients

Chez argenx, nous nous engageons à améliorer la vie des personnes souffrant de maladies auto-immunes graves.

En tant que partenaire, notre mission est de développer des innovations thérapeutiques qui permettent de mieux comprendre les maladies rares et d'en faire bénéficier les patients du monde entier.

Nous sommes à l'écoute des patients et de leurs représentants ; nous entendons leur vécu et partageons leur détermination.

Vous êtes notre moteur,
nous sommes là pour vous et avec vous.

Découvrons,
Ensemble

argenx

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