23ème Édition

Journées de la Société Française de Myologie

18 - 20 Novembre 2026

PARC DES EXPOSITIONS - ENTRÉE A MONTPELLIER

sfm
SOCIÉTÉ FRANÇAISE DE MYOLOGIE



LIVRET DES RÉSUMÉS

COMITÉ LOCAL

Mireille Cossée · Ulrike Walther-Louvier
Alain Lacampagne · Raul Juntas Morales
Pascal de Santa Barbara · Stéphan Matecki · Clément Hersent

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PARTENAIRES BRONZE

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PROGRAMME SCIENTIFIQUE

MERCREDI 18 NOVEMBRE

10h30 - 11h00 *Accueil des participants*

11h00 - 13h00 **Session d'enseignement mixte SFM/FILNEMUS** *- Salle Plénière*
Modération : Capucine Trollet, Paris & Pascal Cintas, Toulouse

11h00 - 12h00 A la frontière du muscle et du nerf : les chevauchements génétiques
Tanya Stojkovic, Paris

12h00 - 13h00 Epigenetic Regulation of Gene Expression: Effects and Consequences for Neuromuscular Health and Disease
Fiorella-Carla Grandi, Paris

13h00 - 14h00 *Déjeuner autour des partenaires*

14h00 - 15h00 **Conférence d'ouverture JSFM 2026** *- Salle Plénière*
Modération : Mireille Cossée, Montpellier & Bénédicte Chazaud, Lyon

Les outils de la danse pour l'accompagnement des patients
Léonardo Montecchia, Montpellier



MERCREDI 18 NOVEMBRE

15h00 - 16h00 **SESSIONS PARALLÈLES 1**

15h00 - 16h00 **Symposium UCB** - *Salle Clinique*

Diagnostic et prise en charge des maladies neuromusculaires mitochondriales

Modération : Mireille Cossée, Montpellier

· Évolution des registres dans les maladies mitochondriales
Pascal Laforêt, Garches

· Complications respiratoires dans les myopathies mitochondriales
Gorka Fernández-Eulate, Paris

· Expérience sur une myopathie mitochondriale ultra rare (TK2d)
Cristina Domínguez-González, Madrid - Espagne

· Discussion

OU

15h00 - 16h00 **Session fondamentale 1** - *Salle Plénière*

Modération : Joana Esteves de Lima, Paris & Capucine Trollet, Paris

15h00 - 15h15 Dystrophin controls clathrin-mediated endocytosis and endolysosomal homeostasis
Eline Lemerle, Paris

15h15 - 15h30 Role of epitranscriptomics in the regulation of gene expression during myogenic differentiation under normal condition and in patients with DMD
Tom Del Ben, Montpellier

15h30 - 15h45 Inducible CRISPR/Cas9-mediated gene targeting in vivo: a versatile model for screening of muscle stem cell regulators
Alireza Ghasemizadeh, Paris

15h45 - 16h00 Combined exercise and nutrition countermeasures against severe inactivity muscle loss
Julian Theuil, Montpellier

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

MERCREDI 18 NOVEMBRE

17h00 - 18h30 **SESSIONS PARALLÈLES 2**

17h00 - 18h30 **Session Clinique 1** - *Salle Clinique*
Modération : Jean-Baptiste Davion, Lille & Ulrike Walther-Louvier, Montpellier

17h00 - 17h12 Un an de dépistage néonatal de l'amyotrophie spinale en France
Christine Barnerias, Paris

17h12 - 17h24 Active NBS : Une étude à distance pour le suivi longitudinal de la fonction motrice chez les enfants atteints d'amyotrophie spinale (SMA) identifiés par dépistage néonatal : premiers résultats
Marie Machiels, Liège - Belgique

17h24 - 17h36 La métabolomique révèle de multiples altérations métaboliques et des biomarqueurs de la sévérité de la dystrophie facio-scapulo-humérale
Marco Spinazzi, Angers

17h36 - 17h48 COL6 : biopsie de muscle, fibroblastes, imagerie et génétique, qui dit vrai ?
Lola Lessard, Bron

17h48 - 18h00 Les anti-agrine dans la myasthénie auto-immune
Alexandre Jentzer, Montpellier

18h00 - 18h12 Caractérisation de l'atteinte musculaire en IRM dans les myopathies mitochondriales
Paula Panos Basterra, Paris

18h12 - 18h30 Discussion

OU

17h00 - 18h30 **Session fondamentale 2** - *Salle Plénière*
Modération : Alicia Mayeuf-Louchart, Lille & Anita Kneppers, Lyon

17h00 - 17h15 A novel human 3D muscle-FAPs organoid platform recapitulates OPMD-associated fibrosis and enables anti-fibrotic drug screening
Maria Bergas Buades, Paris

17h15 - 17h30 AMPK activation enhances Pax7 expression in human muscle reserve cells via fatty acid metabolism
Diego Michel, Genève - Suisse

17h30 - 17h45 Loss of SETDB1 in myofibers alters the extracellular matrix niche and the muscle stem cell dynamic during muscle regeneration
Sabrina Jagot, Lyon

17h45 - 18h00 Unravelling cellular and molecular defects in congenital myotonic dystrophy using human neuromuscular organoids
Caroline Hermitte, Corbeil-Essonnes

18h00 - 18h15 Activation of TGF-βR1/ALK5 Signaling in Adult Mouse Myofibers Rapidly Disrupts Proteostasis and Triggers Progressive Mitochondrial Metabolism Defects
Zélia Chauvaud, Lyon

18h15 - 18h30 The SAA1-TLR4 axis promotes skeletal muscle wasting in pancreatic cancer cachexia (SFM/IIM prize 2026)
Gabriele Guarnaccia, San Diego - USA

18h30 - 19h15 **Muscle quizz** - *Salle Plénière*

19h15 - 21h00 *Cocktail dînatoire & Session Posters 2 (19h30 - 20h30)*

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FR-DMD-25-00034 - Octobre 2025

JEUDI 19 NOVEMBRE

07h30 - 08h00 *Accueil des participants*

08h00 - 09h00 **SCHOLAR ROCK Morning Session with Breakfast** - *Salle Clinique*

Aller plus loin, du motoneurone au muscle : l'intérêt de cibler la myostatine dans l'amyotrophie spinale (SMA)

Modération : Jean-Baptiste Davion, Lille

· Myokines et myostatine dans les maladies neuromusculaires : De la biologie du muscle aux cibles thérapeutiques
Jean-Baptiste Davion, Lille

· Besoin non couverts et futures directions dans l'amyotrophie spinale et les maladies neuromusculaires
Ulrike Walther-Louvier, Montpellier

· Discussion générale sur la myostatine et ses inhibiteurs
Jean-Baptiste Davion, Lille & Ulrike Walther-Louvier, Montpellier

09h00 - 10h30 **SESSION PLÉNIÈRE 1** - *Salle Plénière*

DÉCONDITIONNEMENT MUSCULAIRE ET RÉHABILITATION

Modération : Marie-Christine Nouguès, Montpellier & Cyril Gitiaux, Paris

09h00 - 09h30 Déconditionnement musculaire en réanimation
Stephan Matecki, Montpellier

09h30 - 10h00 Nouveaux leviers nutritionnels dans le déconditionnement musculaire : focus sur les composés bioactifs
Christine Feillet-Coudray, Montpellier

10h00 - 10h30 Influence de la modulation par l'exercice de la typologie de fibre, du métabolisme énergétique dans le contrôle de la masse musculaire
Florian Britto, Paris

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

JEUDI 19 NOVEMBRE

11h00 - 12h00 **SESSIONS PARALLÈLES 3**

11h00 - 12h00 **Symposium LUPIN** - *Salle Clinique*

Les Patient-Reported Outcomes Measures (PROMs) dans les myotonies : enjeux et application pratique

Modération : Françoise Bouhour, Lyon

· Comprendre les PROMs : principes, intérêt et limites dans l'évaluation des maladies neuromusculaires
Sabrina Sacconi, Nice

· Application des PROMs aux myotonies : outils, paramètres évalués et intégration en pratique
Céline Tard, Lille

· Discussion

OU

11h00 - 12h00 **Session fondamentale 3** - *Salle Plénière*

Modération : Laure Strochlic, Paris & Bénédicte Chazaud, Lyon

11h00 - 11h15 Contribution of Skeletal Muscle Cell Subpopulations to the Pathophysiology of Facioscapulohumeral Muscular Dystrophy (FSHD)
Loeva Morin, Marseille

11h15 - 11h30 Role of microtubule glutamylation in skeletal muscle formation and function
Damien Caillol, Lyon

11h30 - 11h45 Role of FUBP1 in the transcriptome diversity of human skeletal muscle cells
Julie Miro, Montpellier

11h45 - 12h00 A Scalable hiPSC-Based Screening Framework for ACTN2-, PYROXD1-, and FHL1-Related Congenital Myopathies
Hugo Lenoir, Corbeil-Essonnes

12h00 - 12h30 **Assemblée Générale de la SFM**

12h30 - 13h30 *Déjeuner autour des partenaires*

13h30 - 14h00 *Café & Session Posters 4*

JEUDI 19 NOVEMBRE

14h00 - 16h00 **SESSION PLÉNIÈRE 2** - *Salle Plénière*
AVANCÉES TECHNOLOGIQUES EN GÉNÉTIQUE AU SERVICE DU DIAGNOSTIC ET DU PRONOSTIC DES MALADIES NEUROMUSCULAIRES
Modération : Caroline Espil-Taris, Bordeaux & Sylvie Tuffery-Giraud, Montpellier

14h00 - 14h30 Apport du génome dans le diagnostic des myopathies
Anthony Maino, Grenoble

14h30 - 15h00 Séquençage long reads pour caractérisation des répétitions dans la maladie de Steinert
Stéphanie Tomé, Paris

15h00 - 15h30 Diagnostic des maladies neuromusculaires par RNA-seq : de l'analyse ciblée aux signatures transcriptomiques
Svetlana Gorokhova, Marseille

15h30 - 16h00 Les analyses multiomiques et leur apport dans le diagnostic des titinopathies : de la clinique à la protéomique
Raul Juntas Morales, Montpellier & Mireille Cossée, Montpellier

16h00 - 16h45 **Présentation des prix SFM 2025** - *Salle Plénière*

· Prix master 2025 : ***Gaëtan Lopez, Genève***

· Prix master 2024 : ***Dimitrios Kourtzas, Paris***

· Prix impulsion 2025 : ***Pierre Klein, Paris***

· Prix coup de pouce 2025 : ***Shams Ribault, Lyon***

· Prix interne de médecine 2025 : ***Romain Labouyrie, Bordeaux***

16h45 - 17h45 *Pause et échanges autour des partenaires & Session Posters 5*

JEUDI 19 NOVEMBRE

17h45 - 19h15 **SESSION PLÉNIÈRE 3** - *Salle Plénière*
QUOI DE NEUF DANS LE MUSCLE ?
Modération : Coralie Sengenes, Toulouse & Florence Esselin, Montpellier

17h45 - 18h15 Obésité, sarcopenie et GLP1
Christelle Guillet, Clermont-Ferrand

18h15 - 18h45 Nucleic Acid-Based Approaches in Neuromuscular Disorders: Progress and Limitations
Virginia Arechavala Gomeza, Bilbao

18h45 - 19h15 Effets d'une supplémentation antioxydante personnalisée sur la force musculaire dans la FSHD1 : étude longitudinale en vie réelle
Sandrine Arbogast, Montpellier

SOIRÉE DU CONGRÈS
Inscription obligatoire

19h20 *Premier départ en bus*

19h50 *Dernier départ en bus*
Lieu de pick up : Parc des Expositions

20h00 *Dîner et Soirée du Congrès au Domaine des Grands Chais*

23h00 - 01h00 *Bus retour*
Lieu de dépose : 4 Bus - Centre Ville à proximité des hôtels
1 Bus - Parc des Expositions



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Le 1er et le seul traitement oral de la SMA[2,6#]

INDICATION[2] :
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.

PLACE DANS LA STRATÉGIE THÉRAPEUTIQUE[6-7] :
Evrysdi® (risdiplam) est un traitement de 1ère intention, à utiliser :

- Chez les patients pré-symptomatiques ayant une amyotrophie spinale génétiquement confirmée avec 1 à 4 copies du gène SMN2, au même titre que SPINRAZA (nusinersen) pour les patients ayant 2 ou 3 copies du gène SMN2 et que ZOLGENSMA (onasemnogene abeparvovec) pour les patients ayant jusqu'à 3 copies du gène SMN2. Evrysdi® est la seule possibilité thérapeutique pour les patients pré-symptomatiques avec 4 copies du gène SMN2.
- Chez les patients atteints d'amyotrophie spinale 5q de type 1, au même titre que SPINRAZA et ZOLGENSMA.
- Chez les patients atteints d'amyotrophie spinale 5q de type 2 et 3, au même titre que SPINRAZA. ZOLGENSMA est une option thérapeutique dans l'amyotrophie spinale 5q de type 2.

Evrysdi® n'a pas de place dans la stratégie thérapeutique des patients symptomatiques atteints d'amyotrophie spinale de type 4.

En raison de la complexité de la prise en charge de cette maladie rare, la Commission recommande que la décision de traitement soit 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 et que l'utilisation de ce médicament soit réservée aux médecins spécialistes de la SMA.

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CONDITIONS DE PRISE EN CHARGE :
Evrysdi® 0,75 mg/mL, poudre pour solution buvable :

- **Indication chez les patients symptomatiques âgés de 2 mois et plus avec un diagnostic de SMA de type 1, 2 et 3**
- **Indication chez les patients pré-symptomatiques avec 1 à 4 copies du gène SMN2 ou symptomatiques < à 2 mois atteints de SMA 5q :** AMM obtenue le 16/08/2023 -
  Agréé aux collectivités - Inscrit sur la liste des spécialités remboursables aux assurés sociaux avec un taux de remboursement à 100 % . Inscrit sur la liste en sus SMR.

Evrysdi® 5 mg, comprimés pelliculés : AMM obtenue le 02/06/2025.

- Agréé aux collectivités - Inscrit sur la liste des spécialités remboursables aux assurées sociaux avec un taux de remboursement à 100%. Inscrit sur la liste en sus SMR.

Pour une information complète, consultez les Résumés des Caractéristiques du Produit disponibles sur la base de données publique des médicaments https://base-donnees-publique.medicaments.gouv.fr/index.php?page=1&choixRecherche=medicament&txtCaracteres=EVRYSDI ou en flashant ce QR code.

Vous pouvez également retrouver ces informations sur evrysdi.roche.fr.

* Sur la base des patients traités post-commercialisation, des patients des accès précoces et des patients ayant participé aux essais cliniques, à Août 2025. # AMM d'Evrysdi® poudre pour solution buvable obtenue le 26/03/2021.

Références : 1. PBRER Août 2025. **2.** Résumé des Caractéristiques du Produit Evrysdi®. **3.** Masson R, *et al.* Lancet Neurol. 2022;21(12):1110-1119. **4.** Mercuri E, *et al.* Lancet. 2022;21(1):42-52. **5.** Oskoui M, *et al.* J Neurol. 2023;270(5):2531-46. **6.** HAS. Avis de la Commission de la Transparence Evrysdi® du 23/04/2025. **7.** HAS. Avis de la Commission de la Transparence Evrysdi du 18/02/2026.

En signalant les effets indésirables, vous contribuez à fournir davantage d'informations sur la sécurité du médicament.

M-FR-00016985 - 1.0 - 25/07/68009899/PM/003 - V0626-2 - Établi en juin 2026

VENDREDI 20 NOVEMBRE

08h30 - 09h00 *Accueil des participants*

09h00 - 10h30 **SESSION PLÉNIÈRE 4** - *Salle Plénière*
PATHOLOGIES ASSOCIÉES AUX DÉFAUTS DE RYR1
Modération : Clément Hersent, Montpellier & Stéphane Vassilopoulos, Paris

09h00 - 09h30 Actualités du PNDS
Klaus Dieterich, Grenoble

09h30 - 10h00 An example to resolve genetic dealocks: from RyR1 structural modeling to AI-based variant classification
John Rendu, Grenoble

10h00 - 10h30 Le récepteur de la ryanodine : une cible potentielle dans la prise en charge des patients avec myopathie de Duchenne
Alain Lacampagne, Montpellier

10h30 - 11h00 *Pause et échanges autour des partenaires & Session Posters 6*

11h00 - 12h00 **SESSIONS PARALLÈLES 4**

11h00 - 12h00 **Symposium ROCHE** - *Salle Clinique*
La SMA au fil des âges, nouvelles opportunités et défis
Modération : Ulrike Walther-Louvier, Montpellier

· Dernières données et enjeu thérapeutique chez les patients présymptomatiques, porteurs de 4 copies du gène SMN2
Caroline Espil, Bordeaux

· Évaluer objectivement la fatigabilité : outils actuels et perspectives dans la SMA
Guillaume Millet, Saint-Étienne

· Fatigue : comment aligner ressenti des patients et mesure avec les échelles
Louise Debergé, Bordeaux

· Discussion

OU

11h00 - 12h00 **Session fondamentale 4** - *Salle Plénière*
Modération : Thomas Laumonier, Genève & Alexis Boulinguiez, Paris

11h00 - 11h15 LAMA2-related Muscular Dystrophy: How Nonsense-Associated Alternative Splicing Offers Cellular Protection
Louise Benarroch, Paris

11h15 - 11h30 First multi-scale profiling of the musculoskeletal fascia in aging: from resident stromal cell signatures to in vivo ultrasound biomarkers
Corentin Pigeon, Toulouse

11h30 - 11h45 Neuromuscular electrical stimulation training minimizes sepsis-induced skeletal muscle dysfunctions
Eurydice Lamirault, Lyon

11h45 - 12h00 Unlocking Muscular Dystrophies Using Patients' Induced Pluripotent Stem Cells
Imane Ben Daoud, Marseille

VENDREDI 20 NOVEMBRE

12h00 - 13h00 **SESSIONS PARALLÈLES 5**

12h00 - 13h00 **Session Clinique 2** - *Salle Clinique*
Expression musculaire de Protéinopathies multisystémiques
Modération : John Rendu, Grenoble & Pascal Cintas, Toulouse

12h00 - 12h12 TUBA4A : présentation des phénotypes musculaires
Guilhem Solé, Bordeaux & Emmanuelle Salort-Campana, Marseille

12h12 - 12h24 ANXA11 : présentation des phénotypes musculaires
Raul Juntas Morales, Montpellier

12h24 - 12h36 Valeur prédictive de l'expression musculaire d'ISG15 (Interferon-Stimulated Gene 15) pour le diagnostic de la dermatomyosite
François-Jérôme Authier, Créteil

12h36 - 12h48 Caractérisation du spectre histopathologique des myosites associées aux inhibiteurs de checkpoint immunitaire : développement et validation d'un score diagnostique
Béatrice Labella, Paris

12h48 - 13h00 Une Myasthénie du sujet âgé
Marion Masingue, Paris

OU

12h00 - 13h00 **Session Fondamentale 5** - *Salle Plénière*
Modération : Julien Gondin, Lyon & Laure Weill, Paris

12h00 - 12h15 Gene therapy for dysferlinopathies: from minigene strategy using muscle specific viruses to naked DNA sonodelivery
Alizée Dangreaux, Marseille

12h15 - 12h30 DNA damage in LMNA-related congenital muscular dystrophy
Marine Leconte, Paris

12h30 - 12h45 Engineered human myobundles as a proof-of-concept preclinical platform for therapeutic testing in Myotonic Dystrophy Type 1
Khong Minh Ngoc, Corbeil Essonnes

12h45 - 13h00 Nucleus-mitochondria cross-talk in a mouse model of premature skeletal muscle aging
Liudmila Afanaseva, Lyon

13h00 - 14h00 *Déjeuner autour des partenaires*

VENDREDI 20 NOVEMBRE

14h00 - 15h30 **SESSION PLÉNIÈRE 5** - *Salle Plénière*
PHYSIOPATHOLOGIE DES AUTRES MUSCLES
Modération : Martial Mallaret & Vincent Gache, Lyon

14h00 - 14h30 Plasticité du muscle lisse digestif : de la physiologie aux myopathies viscérales
Pascal de Santa Barbara, Montpellier

14h30 - 15h00 Physiologie et physiopathologie du muscle lisse vasculaire (MLV)
Carmen Martinez, Montpellier

15h00 - 15h30 Healing Hearts: Regeneration Mechanisms in Zebrafish and Their Promise for Human Cardiac Repair
Chris Jopling, Montpellier

15h30 - 15h45 **Remise des prix SFM 2026** - *Salle Plénière*
& Clôture de la 23ème Éditions des JSFM



COMMUNICATIONS ORALES

SESSION FONDAMENTALE 1

Mercredi 18 Novembre · 15h00 - 16h00

Modération : Joana Esteves de Lima, Paris
& Capucine Trollet, Paris

SESSION FONDAMENTALE 1*

Eline LEMERLE[1], e.lemerle@institut-myologie.org

Guiraud Simon[2], Moparthi Satish[1], Benoist Marion[1], Lainé Jeanne[1], Miagoux Quentin[3], Mamchaoui Kamel[1], Labella Béatrice[4], Evangelista Teresinha[4], Nissan Xavier[3], Amthor Helge[2], Garcia Luis[2], Vassilopoulos Stéphane1

1. Sorbonne Université, INSERM, Institute of Myology, Centre of Research in Myology, Paris, France.
2. SQY Therapeutics, UVSQ, 78180 Montigny le Bretonneux, France
3. iStem, CECS, Corbeil-Essonnes, France.
4. Neuromuscular Morphology Unit, Institute of Myology, Pitié-Salpêtrière Hospital, Paris, France.

Dystrophin controls clathrin-mediated endocytosis and endolysosomal homeostasis

Dystrophin is a key cytoskeletal scaffold linking actin to the extracellular matrix in skeletal muscle, yet its role in organizing membrane trafficking remains poorly understood. Notably, recent studies report defects in endolysosomal trafficking in Duchenne muscular dystrophy, including altered endosome dynamics, lysosomal stress, and impaired autophagic flux, but how dystrophin loss causes these defects remains unclear.

To address this, we combined correlative fluorescence microscopy and platinum replica electron microscopy on unroofed dystrophin-GFP engineered myotubes to resolve its nanoscale organization at the plasma membrane. We found that dystrophin is organized into discrete circular domains forming cortical "clearings" that encircle large, flat clathrin lattices, termed clathrin plaques, which function as adhesion platforms rather than endocytic structures. These plaques are enriched in integrin β5 and embedded within branched actin networks, forming stable membrane-ECM anchoring sites. Dystrophin localizes at the periphery of these adhesive domains, where it cooperates with the cortical cytoskeleton to spatially confine and mechanically stabilize clathrin plaques, reinforcing membrane adhesion and resistance to contractile stress.

In contrast, ultrastructural analysis in DMD patient myotubes lacking dystrophin, reveals clathrin plaques, lost and replaced by numerous clathrin-coated dome-shaped pits and vesicles. This transition is accompanied by pronounced adhesion defects, with reduced cell-substrate attachment and impaired cortical stability. Consistently, functional assays show increased endocytosis in dystrophin-deficient cells, indicating that dystrophin-dependent clathrin plaques act as adhesive platforms whose loss weakens membrane anchorage and unleashes endocytic activity.

Mechanistically, we show that the clathrin machinery is upregulated in DMD, with increased expression of key endocytic components in patient-derived myotubes and muscle biopsies. Importantly, antisense oligonucleotide-mediated dystrophin restoration normalizes clathrin machinery expression in patients and rescues endocytosis rates in isogenic corrected myotubes.

Together, these findings identify a dystrophin-dependent membrane architecture that controls clathrin organization and endocytosis, linking cytoskeletal defects to membrane trafficking dysregulation in DMD.

SESSION FONDAMENTALE 1*

Tom DEL BEN[1], tom.del-ben@umontpellier.fr

J Miro[1], F Rivier[1], A David[2], A Attina[3], M Cossee[1], C Notarnicola[1], S Tuffery-Giraud[1]

1. PhyMedExp, Univ Montpellier, INSERM, CNRS, Montpellier, France
2. IRCM, Univ Montpellier, ICM, INSERM, Montpellier, France
3. IRMB-PPC, Univ Montpellier, INSERM, CHU Montpellier, CNRS, Montpellier, France.

Role of epitranscriptomics in the regulation of gene expression during myogenic differentiation under normal condition and in patients with DMD

Epitranscriptomics is an emerging field that refers to post-transcriptional RNA modifications (marks) that regulate all aspects of RNA metabolism, including RNA processing, export, translation, and stability, thus representing an additional layer of gene regulation. These reversible RNA modifications suggest dynamic regulation in response to environmental, developmental or stress signals that influence many physiological and pathophysiological processes. To date, the role of epitranscriptomics in human myogenic processes remains poorly understood.

Our project aims to profile the dynamic changes in epitranscriptomic marks during the myogenic program (quiescence and differentiation), and to establish whether the RNA modification patterns are altered in the context of DMD and contribute to, or reflect, the pathomechanisms.
We first profiled the pattern of 30 different RNA modifications by mass spectrometry at three key stages of human myogenic differentiation (reserve cells, myoblasts, and myotubes) in both healthy and DMD muscle cells. RNA modifications whose levels varied significantly during myogenic differentiation were prioritized for functional investigations.

Specifically, we knocked down by siRNA the effectors (writers, erasers, readers) of the m6A mark at both the proliferative and differentiating stages of human primary muscle cells. We found that inhibition of the writer WTAP, the eraser FTO and the readers YTHDC1 and IGF2BP1 markedly impaired myotube formation, as shown by reduced troponin T staining and a lower fusion index. These findings were further supported by altered expression of myogenic differentiation markers at the mRNA and protein levels suggesting a defect in myogenic differentiation.
The downstream fate of m6A-modified RNAs depends on the reader that recognizes the mark. Despite their distinct functions, with IGF2BP1 promoting mRNA stability and translation and YTHDC1 contributing to the nuclear export and splicing of target transcripts, depletion of either factor impaired myotube formation. This suggests that m6A controls myogenic differentiation through reader-specific regulatory mechanisms, possibly acting on distinct sets of target genes.

In conclusion, our work provides new insights into epitranscriptomic regulation in human myogenic differentiation.

SESSION FONDAMENTALE 1*

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Philippos Mourikis

Institut Necker Enfants Malades,Paris, France

Inducible CRISPR/Cas9-mediated gene targeting in vivo: a versatile model for screening of muscle stem cell regulators.

Muscle stem cells (MuSCs) are indispensable for tissue regeneration. Previous studies have established that, in addition to intrinsic factors, components of the microenvironment are essential for quiescent MuSCs fate. Indeed, manipulation of niche components or signaling pathways can lead to diverse flavors of MuSCs activation, ranging from ectopic proliferation to spontaneous differentiation/fusion or cell death. Therefore, dissecting the interacting pathways between MuSCs and their niche is of great biological interest and essential for the development of regenerative therapies. Analysis of gene expression profiles of quiescent and early-activated MuSCs identified several novel potential regulators of MuSCs quiescence. However, generating MuSC-specific knock-out mice for each candidate gene faces practical, financial, and ethical limitations. To address these challenges, we have developed a MuSC-specific inducible Cas9 mouse model that enables in vivo targeting of any gene of interest. In our system, short-guide RNAs are delivered using adeno-associated viruses that also express a fluorescent marker for cell identification and downstream analyses. To ensure stable transgene expression and circumvent episomal AAV dilution, we incorporated transposase-mediated genomic integration. Using this strategy, we have investigated the role of multiple target genes in the maintenance of MuSCs quiescence, their return to quiescence following injury, or their initial entry to quiescence during postnatal development. Focusing on Sema6a, Plxna2, Sparc, and PcdhgC3 Cas9-cKO mice, our data uncover gene-specific modes of MuSC regulation, ranging from changes in MuSCs number residing under the basal lamina, to the ectopic presence of single MuSCs in the interstitial space or accumulation of several MuSCs between muscle fibers. Altogether, our data unmask novel players of MuSCs complex quiescent state and confirm the strength of our model for rapid and reliable gene screening in quiescent MuSCs, directly in vivo.

SESSION FONDAMENTALE 1*

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Margot Issertine[1,2], Klara Cigosova[1], Jade Bouirel[1,2], Inessa Gibaut[1,2], Lucas Bernard[1], Valerie Montel[3], Laurence Stevens[3], Angèle Chopard[1,2], Thomas Brioche[1,2]

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3. APMS (Activité Physique Muscle et Santé) team, URePSSS, URL 7369, University of Lille, France

Combined exercise and nutrition countermeasures against severe inactivity muscle loss in rodents

Muscle deconditioning occurs during hospitalization and spaceflight, and is characterized by rapid losses in muscle strength, mass and oxidative capacity. These changes impair performance and quality of life, challenging the return to Earth or to active life. Recovery strategies are therefore essential and currently rely on intensive postflight or postoperative reconditioning.
Human bedrest studies suggest that the first days of severe inactivity are critical for muscle deconditioning and countermeasure efficacy. Lunar transit lasts approximately 4–6 days, making this early phase a key intervention window. Similarly, some surgical procedures involve a few days of inactivity followed by rehabilitation under partial weight-bearing conditions.
Building on previous studies in mice, we investigated combined exercise (endurance and resistance training) and nutritional supplementation (HMB, ergothioneine and nacre powder) in Wistar rats undergoing severe inactivity with simulated microgravity followed by partial gravity (0.2g).
70 rats were assigned to a ground control group (GC) without unloading or countermeasures, a control group without countermeasures (C), or an exercise-nutrition group (EN). C and EN underwent 7 days of hindlimb unloading (HU), followed by 15 days of partial weight bearing at 20% body weight (PWB). EN performed 3 weeks of exercise preconditioning before HU and resumed training during PWB. EN received the nutritional supplementation throughout the entire protocol. Animals were euthanized after each experimental stage.
After HU, maximal aerobic velocity and maximal climbing load decreased in both unloaded groups; however, EN maintained higher functional performance and recovered during PWB, exceeding GC performance. The intervention also preserved triceps surae cross-sectional area (CSA) during HU, whereas CSA decreased in C. However, triceps surae mass and CSA declined during PWB in both groups. The MyHC-I proportion decreased in C, with these fibers transitioning toward a faster phenotype, but was maintained in EN.
This study represents the first animal model assessing exercise countermeasures under partial gravity. Beyond its relevance to lunar missions, this sequence parallels clinical pathways: preconditioning before unloading mirrors prehabilitation before postoperative inactivity, and partial reloading at simulated lunar gravity offers a framework for progressive rehabilitation using bodyweight support, such as AlterG treadmills.

SESSION CLINIQUE 1

Mercredi 18 Novembre · 17h00 - 18h30

Modération : Jean-Baptiste Davion, Lille
& Ulrike Walther-Louvier, Montpellier

SESSION CLINIQUE 1

Christine BARNERIAS[1], christine.barnerias@aphp.fr

Julien Durigneux[2*], et l'ensemble des participants de la RCP SFNP-FILNEMUS

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**Auteur principal*

Un an de dépistage néonatal de l'amyotrophie spinale en France

Après l'étude pilote DEPISMA réalisée dans 2 régions française (Grand Est et Nouvelle Aquitaine) débutée en janvier 2023, le dépistage de l'amyotrophie spinale infantile a été étendu à l'ensemble du territoire français à partir du 01/09/2025. Nous rapportons les résultats de cette première année du dépistage pour l'amyotrophie spinale (SMA).

Méthode : Nous avons analysé les données des nouveau-nés dépistés entre le 1er septembre 2025 et le 31 août 2026. Pour chaque patient, nous avons recueilli le nombre de copies du gène SMN2, ainsi que les délais (en jours de vie) de retour des résultats du test de Guthrie, de la première consultation, de la réponse de la réunion de concertation pluridisciplinaire (RCP) et de l'initiation du traitement.

Résultats : Entre le 01/09/2025 et le 01/09/2026, 70 patients ont été dépistés pour l'amyotrophie spinale infantile. Parmi ces 70 patients, 68 ont été confirmés comme ayant une amyotrophie spinale avec zéro copie de SMN1, 2 patients étant des faux positifs. Pour les 68 patients confirmés, le nombre de copies de SMN2 étaient de 1 copie pour 1 cas, 2 copies pour 32 cas (47%), 3 copies dans 21 cas (30%) et 4 copies dans 14 cas (20%). 14 patients avaient des symptômes moteurs au moment du dépistages (20%) et 54 patients (80%) n'avaient pas de symptômes moteurs. Le délai médian de résultat du test sur buvard était de 8 jours (J5–J12), celui de la première consultation de 9 jours (J1–J13), celui de la réponse de la RCP de 10,5 jours (J6–J16). 58 patients ont reçu une thérapie innovante, avec un délai médian de 18 jours (J10-J32). Pour 10 enfants, il a été décidé une prise en charge palliative, du fait de symptômes sévères au moment du dépistage (atteinte paralytique majeure, atteinte des fonctions respiratoires et/ou bulbaires).

En Parallèle, il y a eu 1 faux négatif ; il s'agit d'un patient avec un génotype composite (une délétion et une mutation ponctuelle), n'ayant donc pas pu être dépisté. Ce patient s'est présenté à J28 de vie avec une atteinte motrice sévère, SMA type 1a.

Conclusion : Cette étude a mis en évidence la rapidité de la prise en charge des patients dépistés, rendant possible l'initiation d'un traitement dans le premier mois de vie. Elle retrouve une incidence plus élevée des 4 copies de SMN2 que celle décrite classiquement dans les registres de patients. Enfin cette étude souligne la fréquence significative de patients déjà symptomatiques lors de la première consultation.

SESSION CLINIQUE 1*

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Tamara Dangouloff[1,2], Eléonore Goffioul[1,3], Camille Bisson[4], Diane d'Haultfoeuille[4], Damien Eggenspieler[4], Laurent Servais[1,2,5]

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Active NBS: A Remote Study for Longitudinal Motor Monitoring in Infants with Spinal Muscular Atrophy (SMA) Identified by Newborn Screening: First Results

Background: Although newborn screening followed by early treatment has dramatically altered the clinical course of spinal muscular atrophy (SMA), subtle motor impairments may persist and can be difficult to quantify and follow with currently available standardized measures.
Objective: To monitor motor development in children with SMA identified through newborn screening using digital tools in their everyday environment.

Methods: Active NBS is an academic, multicenter, fully remote observational study launched in December 2025. The study includes children with SMA identified through newborn or family screening. Patients are consented remotely and provide clinical information from standard of care. Patients are assessed using two wearable technologies: the MAIJU and the SYDE. The MAIJU is a pyjama-like garment, equipped with 4 sensors, that records the quantity and quality of movement. It is used in children who have not yet achieved independent walking. Recordings are used to generate the Baby Motor Score (BIMS), an objective measure of motor development. Ambulatory children are monitored using Syde® wearable sensors, worn on both ankles. One of the parameters collected is the SV95C, corresponding to the speed of the fastest 5% of recorded strides.

Results: Since December 2025, 25 children have been enrolled: 7 with 2 SMN2 copies, 13 with 3 copies, and 5 with 4 copies. Median age at inclusion was 26 months (P25: 15; P75: 42). Initial treatment consisted of risdiplam (40%), nusinersen (8%), onasemnogene abeparvovec (48%) or follow-up (4%). At study inclusion, 11 (44%) were considered symptomatic by their parents.
Among 22 children who achieved independent walking, mean age at walking was 16.4 months (SD 6.5). Walking age differed according to SMN2 copy number (Kruskal-Wallis $\chi^2 = 9.21$, $p<0.05$).
The first 7 children who completed one-month Syde® monitoring period all recorded ⩾50h of data, required to derive the digital measures. Median SV95C was 1.44 m/s (P25: 1.30; P75: 2.20), compared with 2.14 m/s (P25: 1.80; P75: 2.40) in control children aged 1 to 8 years. At baseline, intra-class correlation coefficients for SV95C is 0.98.

Conclusion: These preliminary results demonstrate the feasibility and acceptability of remote real-world motor monitoring using wearable devices in children with SMA identified through newborn screening. Data collection is ongoing to assess patients' evolution over years.

SESSION CLINIQUE 1

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Metabolomics reveals multiple metabolic alterations and biomarkers of disease severity in facioscapulohumeral muscle dystrophy

Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common adult-onset myopathies and is causally associated with contraction of the D4Z4 macrosatellite repeat array on chromosome 4. It presents with a variable pattern of progressive muscle weakness affecting the face, shoulder girdle, and lower limbs. The pathophysiological mechanisms underlying the disease remain incompletely understood, and no effective treatments are currently available. Moreover, the lack of validated biomarkers limits the assessment of disease progression and therapeutic effects in clinical trials. Metabolic dysfunction has been hypothesized as a contributing factor, yet this hypothesis has been explored in only a limited number of studies.

In this multicenter, observational, cross-sectional case-control study, we conducted quantitative plasma metabolomics using mass spectrometry in 57 patients with mild-to-moderate FSHD and 63 age- and sex-matched controls. Data were analyzed using an integrative approach combining univariate and multivariate analyses to discriminate the metabolic profiles of patients from those of controls.

We identified 57 discriminant metabolites distinguishing patients from controls and revealing dysregulation of several metabolic pathways converging on mitochondrial dysfunction. Two metabolites strongly correlated with clinical measures of disease severity. These findings reveal substantial systemic metabolic disturbances in the early stages of FSHD, improving our understanding of disease pathogenesis and identifying potential new avenues for biomarker development.

SESSION CLINIQUE 1*

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Inputs and pitfalls of muscle biopsy and dermal fibroblast culture in diagnosing COL6-related dystrophies: insights from 295 suspected cases

Context. Collagen VI-related dystrophies (COL6-RD) definite diagnosis can be challenging as variants of unknown significance (VUS) are frequently found. Muscle imaging, biopsy, and dermal fibroblast culture (DFC) can offer supporting clues for a collagenopathy. Their respective utility and limitations remain to be characterized.
Objective. We aimed to evaluate sensitivity (Se) and specificity (Sp) of COL6 expression in muscle biopsies and DFC in COL6-RD.
Methods. Retrospective review (2011–2021) at Hospices Civils de Lyon of all patients with clinically suspected COL6-RD, of all requisitions for anti-COL6 immunostaining on muscle cryosection, and of all requisitions for a collagen synthesis and deposition assay on DFC. Definite COL6-RD was defined by pathogenic COL6 variants.
Results. We included 295 cases, with anti-COL6 immunostaining on muscle biopsy (n=244) and/or on DFC (n=193). 49% of patients remained without final diagnosis (n=144/295), including suspicion of COL6-RD without identified pathogenic variants in n=6. Diagnosis other than COL6-RD was found in 46% (n=135/295) of cases, including genetic neuromuscular disorders (NMD) in n=105, non-NMD in n=20, and acquired NMD in n=10. Finally, definite COL6-RD was confirmed in 5% (n=16/295).

Sixteen patients had definite COL6-RD; muscle COL6 immunostaining was available in n=11/16; DFC was available in n=14/16. Of definite COL6-RD patients, n=6/11 showed abnormal muscle COL6 expression (Se=55%), n=11/14 had abnormal DFC (Se=79%).
In the 132 cases with an available final diagnosis and muscle COL6 immunostaining, abnormal muscle COL6 expression was observed in n=11/132 cases, including n=6/11 definite COL6-RD (Sp=96%). Among all cases showing abnormal muscle COL6 expression (n=22), 27% (n=6/22) had definite COL6-RD, 9% (n=2/22) had clinical suspicion without identified pathogenic variants in collagen genes, and 23% (n=5/22) had alternate diagnoses.

In the 92 cases with an available final diagnosis and DFC, DFC abnormalities were found in 21/92 cases including n=11/21 definite COL6-RD (Sp=87%).
Among all cases showing DFC abnormalities (n=39), 28% (n=11/39) had definite COL6-RD, 13% (n=5/39) had clinical suspicion of COL6-RD without identified pathogenic variants in collagen genes, and 26% (n=10/39) had alternate diagnoses.

Conclusion. The present work highlights the potential pitfalls of muscle and skin collagen labelling in diagnosing COL6-RD.

SESSION CLINIQUE 1

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CHU de Montpellier, Institut Genomique Fonctionnelle, APHP, Centre de Recherche en Myologie

Les anti-agrine dans la myasthénie auto-immune

Environ 9 % des patients atteints de myasthénie auto-immune présentent une double séronégativité (dSN-MG), soit l'absence d'anticorps dirigés contre le récepteur de l'acétylcholine (AChR) et la Muscle-specific tyrosine kinase (MuSK). Les protéines LRP4 et agrine sont apparues comme des cibles antigéniques potentielles ces dernières années mais leurs fréquences rapportées varient considérablement selon les études et les méthodes. Notre objectif était de mettre au point un test d'identification des anticorps anti-LRP4 et anti-agrine au sein d'une cohorte française multicentrique. Les sérums de 103 patients atteints de myasthénie (24 AChR-MG, 79 dSN-MG), de 104 patients atteints d'autres affections neurologiques [Maladie de Charcot-Marie-Tooth (N=20), sclérose latérale amyotrophique (N=22), polyradiculoneuropathie inflammatoire démyélinisante chronique (N=20), nodopathie auto-immune (N=22) et 20 patients atteints de gammapathie monoclonale (GAM]) et de 22 témoins sains ont été analysés. Les anticorps anti-LRP4 ont été recherchés à l'aide d'un cell based assay (CBA) analysé en cytométrie en flux. Les anticorps anti-agrine et leurs isotypes ont été identifiés par ELISA. Des anticorps anti-agrine ont été détectés chez 16 des 103 patients atteints de myasthénie (15,5 %), dont 11 des 79 patients dSN-MG (13,9 %) et 5 des 24 patients AChR-MG (20,8 %), ainsi que chez 5 des 104 patients atteints d'autres pathologies neurologiques (4,8 %). Il s'agissait principalement d'IgG1/IgG2 et la majorité des patients anti-agrine séropositifs présentaient une forme généralisée de la maladie (12/15). Le CBA n'a pas pu être validé par notre laboratoire devant un signal trop faible des contrôles positifs anti-LRP4. Des anticorps anti-agrine ont été mis en évidence chez certains patients dSN-MG et coexistaient fréquemment avec des anticorps anti-AChR, ce qui conforte l'hypothèse de l'agrine comme cible antigénique potentielle. Toutefois, leur spécificité pour la myasthénie est limitée, puisqu'ils ont également été détectés chez des patients atteints d'autres atteintes neurologiques. Il est probable qu'une positivité pour les anticorps anti-agrine ne suffise pas, à elle seule, à poser le diagnostic de myasthénie.

SESSION CLINIQUE 1*

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4. Centre de Recherche en Myologie, Institut de Myologie, Sorbonne Université, Inserm UMRS974, 75013 Paris, France

The Radiological Pattern of Mitochondrial Myopathies

Objective: To characterize whole-body intramuscular fat distribution pattern in patients with mitochondrial myopathies and explore correlations with disease type, duration and genetic findings.

Methods: Retrospective, cross-sectional, bicentric study enrolling patients with genetically confirmed mitochondrial myopathy who underwent whole-body or lower limb muscle MRI. Intramuscular fatty replacement was evaluated on T1-weighted images and represented by a heatmap. A second group of suspected mitochondrial myopathy based on clinical and muscle biopsy findings was enrolled.

Results: MRI scans from 39 patients covering 1468 muscles were analyzed using the Mercuri score. Patients with genetically confirmed mitochondrial myopathy (n=27, 70% female) had a mean age of 44.26 ± 15.8 years at MRI and 24.52 ± 15.87 years at symptom onset (mean interval onset-MRI, 19.74 ± 12.49 years). Genetic diagnoses included nuclear DNA mutations (n=13), mtDNA point mutations (n=9), including 6 MELAS and 1 MERRF, and large mtDNA deletions (n=5). Abnormal muscle involvement on MRI was observed in 19/27 (70.4%) patients and was similar across genetic groups, most frequently involving the gluteus medius (63%), semitendinosus (59%), lumbar erector (56%), and semimembranosus (52%) muscles. Patients with genetically confirmed mitochondrial myopathy (n=27) were then compared with patients with suspected mitochondrial myopathy (n=12). In this last group, 50% were female, with a mean age of 49.75 ± 13.92 years at MRI and 36 ± 20.21 years at symptom onset (mean interval onset-MRI, 13.75 ± 10.81 years). Patients with suspected mitochondrial myopathy had less frequently abnormal muscle involvement on MRI compared to the genetically confirmed group (5/12, 41.7% vs 19/27, 70.4%), although this difference was not significant (Fisher's exact test, p=0.115). Muscle involvement was also different, with more heterogeneous involvement in patients with suspected myopathy, which included gastrocnemius medialis muscle (41.6%) and the anterior, medial, and posterior compartments of the thigh (33%).

Conclusion: This preliminary study shows that patients with genetically confirmed mitochondrial myopathy have frequent muscle involvement on MRI which predominantly involves axial, glutei and posterior thigh muscles. Muscle involvement on MRI seemed different than that of a group with suspected mitochondrial myopathy. The inclusion of patients from other centers will help us confirm these findings.

SESSION FONDAMENTALE 2

Mercredi 18 Novembre · 17h00 - 18h30

Modération : Alicia Mayeuf-Louchart, Lille
& Anita Kneppers, Lyon

SESSION FONDAMENTALE 2*

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A novel human 3D muscle-FAPs organoid platform recapitulates OPMD-associated fibrosis and enables anti-fibrotic drug screening

Muscle fibrosis, characterized by the excessive accumulation of extracellular matrix (ECM) components around muscle fibers, is a major clinical feature of Oculopharyngeal muscular dystrophy (OPMD) and leads to impaired muscle function. Today, no treatment is available to target fibrosis in OPMD. In this study, we developed complementary human 2D and 3D co-culture systems combining myoblasts and fibro-adipogenic progenitors (FAPs) to model the OPMD fibrotic microenvironment, study intracellular communication and identify anti-fibrotic drugs targeting FAPs.

In 2D cultures, we identified Bosentan (a specific inhibitor of the endothelin receptor type B, EDNRB), as a potent modulator of the OPMD fibrotic phenotype, capable of reducing OPMD FAPs proliferation and excessive ECM deposition. To better mimic physiological conditions, we established 3D skeletal muscle organoids combining myoblasts and FAPs. These human-derived constructs feature mature multinucleated myofibers expressing dystrophin with organized sarcomeric structures, produce ECM components and exhibit spontaneous contractile activity.

The 3D organoids recapitulate key pathological features of OPMD including increased FAPs proliferation, enhanced ECM deposition (notably COL1A1) and an increased number of Pax7+ satellite cells. We further demonstrated that the anti-fibrotic effect of Bosentan is maintained in the 3D environment, confirming the model's relevance for pharmacological testing. By combining 2D discovery and 3D validation, this platform provides a relevant experimental tool to investigate cellular interactions and identify and validate novel therapeutic strategies targeting fibrosis in OPMD and related muscular diseases.

SESSION FONDAMENTALE 2*

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AMPK activation enhances Pax7 expression in human muscle reserve cells via fatty acid metabolism

Skeletal muscle regeneration is driven by muscle stem cells (MuSCs), a heterogeneous population endowed with self-renewal and differentiation capacities. However, their therapeutic potential is limited by the rapid loss of regenerative capacity during in vitro expansion. Our previous work demonstrated that human muscle reserve cells (MuRCs) closely resemble quiescent MuSCs and have enhanced regenerative capacity in vivo. Transcriptomic analyses further revealed heterogeneity within the MuRC population, particularly in Pax7 expression. Single-cell RNA sequencing of MuRCs from four biological replicates identified a continuum of cellular states, including a distinct Pax7-High subpopulation characterized by transcriptional features of deep quiescence and reduced myogenic priming. Building on these findings, we tested pharmacological modulation of AMPK using the activator compound 991 and the inhibitor BAY3827, together with etomoxir and culture conditions designed to promote fatty-acid oxidation (FAO). We assessed their effects on AMPK activity, Pax7 expression, myogenic differentiation, and MuRC reactivation kinetics. AMPK activation with compound 991 significantly increased the proportion of Pax7-High MuRCs without impairing their myogenic differentiation capacity. This effect was abolished by co-treatment with etomoxir, supporting a requirement for mitochondrial FAO in the AMPK-dependent enrichment of Pax7-High cells. Consistently, combining compound 991 with L-carnitine and lipid supplementation further enhanced Pax7 expression, with a trend toward a 1.6-fold increase compared with control conditions. Moreover, compound 991 delayed MuRC reactivation, as indicated by a reduced proportion of Ki67-positive cells 24 hours after re-exposure to growth medium. Together, these findings identify metabolic and pharmacological conditions that favor a deeply quiescent Pax7-High human MuRC state while preserving myogenic potential. They further suggest that coordinated modulation of AMPK signaling and FAO represents a promising strategy to promote stemness and maintain regenerative potential during the in vitro generation of human MuRCs.

SESSION FONDAMENTALE 2*

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**equal contribution*

Loss of SETDB1 in myofibers alters the extracellular matrix niche and the muscle stem cell dynamic during muscle regeneration

Skeletal muscle regeneration relies on extrinsic and intrinsic signals in muscle stem cells (MuSCs). Indeed, MuSCs interacts extrinsically with surrounding cells and matrix components of their local microenvironment. Intrinsically, MuSCs are regulated by tightly orchestrated signaling pathways, and genetic and epigenetic regulators. Recent advances suggest a crosstalk between these different levels of regulation. Although epigenetic regulation within MuSCs is well documented, how chromatin regulators in remaining myofibers influence the regenerative niche remains poorly understood. Here, we investigated the role of the histone methyltransferase SETDB1 using an inducible, myofiber-specific Setdb1 knockout mouse model.

Following partial muscle injury, Setdb1-deficient muscles exhibited increased numbers of PAX7+ MuSCs at the interface between injured and uninjured regions. Ex vivo cultures of isolated myofibers revealed enhanced MuSC activation and proliferation, supporting a non-cell-autonomous influence of myofiber-Setdb1 Knockout on MuSC behavior.

Spatial transcriptomics at four days post-injury identified an altered transcriptional landscape, with enrichment of extracellular matrix remodeling and stress-associated programs in myofiber-associated regions. Computational prediction of Setdb1 loss using independent single-nucleus RNA sequencing data converged with these findings, further prioritizing extracellular matrix components as candidate mediators. Initial investigations of collagen I did not reveal significant changes in protein abundance, and preliminary functional assays did not support a contribution through DDR1/DDR2 signaling. In contrast, immunostaining revealed increased collagen VI abundance in the uninjured region of Setdb1-deficient muscles at four days post-injury, identifying collagen VI as a candidate associated with the altered regenerative niche. Decellularization–recellularization experiments using muscle-derived matrices and primary myoblasts are ongoing to isolate the contribution of the extracellular matrix to myogenic cell behavior.

Together, these findings support a role for SETDB1 from myofiber in regulating the regenerative microenvironment. They associate enhanced MuSC activation and expansion with extracellular matrix changes and nominate collagen VI for further functional investigation as a potential mediator linking myofiber chromatin regulation to stem cell responses.

SESSION FONDAMENTALE 2*

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Unravelling Cellular and Molecular Defects in Congenital Myotonic Dystrophy Using Human Neuromuscular Organoids

Context : Congenital myotonic dystrophy (CDM) is the most severe infantile form of myotonic dystrophy type 1, caused by massive CTG expansions in DMPK gene. Although traditionally attributed to MBNL loss-of-function through toxic RNA sequestration, the early CDM pathological mechanisms leading to altered neuromuscular system development remain poorly understood. To evaluate these consequences, human neuromuscular organoids (NMOs) provide a physiological model to study the early steps of the human neuromuscular development in healthy and pathological conditions.

Methods: We generated NMOs from control and CDM patient-derived human induced pluripotent stem cells (hiPSC), as well as MBNL1/2 double-knockout (DKO) cell lines and differentiated for up to 100 days. Organoids were assessed by immunofluorescence, electron microscopy, calcium imaging, single-nucleus RNA sequencing (snRNA-seq), and ATAC-seq.

Results: Control and CDM NMOs generate myogenic and neuronal progenitors by day 10 and develop organized sarcomeres and synaptic contacts by day 50. SnRNA-seq analysis in day 50 NMOs revealed marked transcriptional alterations. Neuronal clusters showed increased glutamatergic signalling, including GRM7, RELN, and GRM5. In the muscle compartment, CDM NMOs displayed increased extracellular matrix gene expression (COL1A2, COL4A1, COL3A1) and reduced expression of myogenic regulators (MYOD, MYOG, SIX1). Immunofluorescences confirmed reduced MYOD and MYOG protein levels, indicating impaired myogenic program. Strikingly, transcriptional alterations observed in CDM organoids were not recapitulated in MBNL1/2 DKO organoids, several gene deregulations showing CDM-specific deregulation. These findings suggest MBNL-independent mechanisms in early CDM pathophysiology. Given the developmental stage modelled by NMOs and the predominant role of CELF1 during early neuromuscular development, we are investigating CELF1 stability and phosphorylation status, as well as transcriptional alterations potentially driven by CELF1 deregulation.

Conclusion: NMOs model recapitulates key features of CDM and reveals impaired myogenic differentiation associated with MBNL-independent MYOD/MYOG dysregulation. These findings point to alternative regulatory mechanisms underlying early CDM pathogenesis. Ongoing studies of CELF1, combined with ATAC-seq analysis of chromatin accessibility, aim to identify upstream transcriptional regulators contributing to CDM-associated molecular defects.

SESSION FONDAMENTALE 2*

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Activation of TGF-βR1/ALK5 Signaling in Adult Mouse Myofibers Rapidly Disrupts Proteostasis and Triggers Progressive Mitochondrial Metabolism Defects

Transforming growth factor-β (TGF-β) cytokines are central mediators of muscle atrophy and fibrosis in neuromuscular diseases, muscle-wasting disorders, and age-related sarcopenia. However, the consequences of chronic, cell-autonomous activation of this signaling pathway in skeletal muscle are yet to be defined, particularly regarding the effects of sustained TGF-β signaling on mitochondrial metabolism, a key determinant of muscle mass and function. To address this, we developed a mouse model with inducible, muscle-specific expression of a constitutively active ALK5/TGFβRI receptor in adult myofibers. ALK5 activation in adult mice rapidly induces muscle atrophy, reduces force production, and shifts fiber composition toward a slow-twitch phenotype while impairing mitochondrial metabolism. This reveals a previously unrecognized axis linking TGF-β signaling to metabolic regulation. Transcriptomic and functional analyses show that ALK5 activation rapidly triggers TGF-β/SMAD2/3 and TNF-α/NF-κB pathways alongside ubiquitin-proteasome system (UPS)-mediated proteolysis. Despite increased UPS activity, autophagic flux is impaired, compromising proteostasis. Mechanistically, ALK5 signaling suppresses the ERRα/PGC-1α/PERM1 axis, downregulating genes involved in mitochondrial biogenesis and oxidative metabolism. Prolonged ALK5 activation leads to impaired oxidative phosphorylation, reduced ATP synthesis, and accumulation of enlarged, dysfunctional mitochondria. These findings establish TGF-β/ALK5 signaling as a central regulator of mitochondrial dysfunction and proteostasis failure in muscle atrophy.

SESSION FONDAMENTALE 2

Gabriele GUARNACCIA[1,2],

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Tumor-derived SAA1-TLR4 signaling drives tumor-to-muscle communication in pancreatic cancer cachexia

Cancer cachexia limits treatment tolerance and survival in pancreatic ductal adenocarcinoma (PDAC), yet the tumor-derived signals driving tissue dysfunction remain poorly understood. Here, we identify serum amyloid A1 (SAA1) as a mediator of tumor- to-host communication acting through Toll-like receptor 4 (TLR4). Tumor-derived SAA1 was elevated in human PDAC and in a mouse PDAC model and disrupted both myofiber and muscle stem cell (MuSC) homeostasis. Genetic reduction of tumor-derived SAA1 uncoupled tumor progression from host wasting, preserving muscle mass and function and prolonging survival without affecting primary tumor growth. Mechanistically, SAA1-
TLR4 signaling drove multicellular remodeling of the skeletal muscle microenvironment. Therapeutic TLR4 inhibition after cachexia onset restored muscle mass, function and MuSC abundance and prolonged survival independently of tumor growth. Conservation of SAA1-TLR4 signaling in human skeletal muscle identifies a therapeutically actionable tumor–host pathway and demonstrates that host deterioration can be targeted independently of tumor progression.

SESSION FONDAMENTALE 3

Jeudi 19 Novembre · 11h00 - 12h00

Modération : Laure Strochlic, Paris
& Bénédicte Chazaud, Lyon

SESSION FONDAMENTALE 3*

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Contribution of Skeletal Muscle Cell Subpopulations to the Pathophysiology of Facioscapulohumeral Muscular Dystrophy (FSHD)

Facioscapulohumeral muscular dystrophy (FSHD) is an inherited neuromuscular disorder characterized by progressive and asymmetric muscle weakness. It is caused by epigenetic alterations leading to aberrant expression of the DUX4 transcription factor, associated with D4Z4 macrosatellite contraction in FSHD1 or SMCHD1 variants in FSHD2. However, the primate-specific nature of the D4Z4 macrosatellite limits the study of disease pathophysiology.

To overcome this limitation, our team developed an in vitro model based on human induced pluripotent stem cells (hiPSCs) differentiated into muscle fibers innervated by motor neurons, allowing the study of muscle, neuronal, and stromal populations.

We characterized the transcriptomic, cellular, and functional signatures of this model at three key stages of differentiation (D8, D17, and D30).

Transcriptomic analysis showed an overall differentiation profile comparable across conditions but suggested different dynamics in FSHD, with delayed muscle programs, as well as a shift in neuronal programs in FSHD2 compared with FSHD1. Beyond these differences, a DUX4-associated transcriptional signature shared by FSHD1 and FSHD2 was detected, including DUX4-regulated genes also identified in FSHD patient muscle biopsies (Yao et al., 2014). This comparison shows that our model recapitulates part of the molecular signature observed in patient muscle.

In addition, deconvolution analyses using reference single-cell RNA-seq datasets identified the main neuromuscular populations and suggested a lower representation of mature neurons in FSHD2, as well as the presence of mesenchymal populations.

In parallel, flow cytometry revealed the transient emergence, between D8 and D17, of a population displaying a mixed stromal/myogenic profile. Its presence led us to investigate its fibro-adipogenic potential, as these populations may contribute to fibrosis and fatty replacement in neuromuscular disorders. TGFβ induced a fibro-mesenchymal phenotype across all conditions, whereas adipogenic stimulation resulted in lipid accumulation predominantly in FSHD1/2 cells.

Finally, the independent study of motor neurons revealed few morphological differences but earlier electrical activity in FSHD1, suggesting altered cell maturation.

The integration of these data aims to better define the contribution of different skeletal muscle cell subpopulations to disease pathophysiology.

SESSION FONDAMENTALE 3*

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Role of microtubule glutamylation in skeletal muscle formation and function

Striated skeletal muscle are large multinucleated cells where nuclei are spatially organized at the periphery. Disruption of myonuclei positioning is a hallmark of many myopathies, yet underlying molecular mechanisms remain poorly understood. Previous work from the team showed microtubules (MTs), their associated proteins, and tyrosination/detyrosination, a tubulin post-translational modification (PTM) regulate peripheral anchoring of myonuclei. This project aims to decipher the role of additional tubulin-PTMs (t-PTMs) in skeletal muscle formation and function. T-PTMs are regulated by specific enzymes. I conducted a RT-qPCR analysis to profile their expression along myogenesis in differentiated murine primary myoblasts. While expression of most enzymes was downregulated during differentiation phase, members of tubulin tyrosine ligase-like (TTLL, glutamylases) and cytosolic carboxypeptidase (CCP, deglutamylases) families were strongly upregulated. Glutamylation is considered as a potential fine-tuning mechanism of MT functions. Using western-blotting approaches, I showed MT glutamylation was significatively increased in both MT subunits. In adult myofibers, MTs exhibited strong glutamylation level that is also muscle-type dependent. Glutamylation accumulation and maintenance appear to be a key factor for muscle development and homeostasis. It is known in other cells such as neurons, excessive glutamylation impairs cell trafficking and survival. Expression analysis showed the deglutamylase CCP6 was continuously upregulated during myogenesis. CCP6 was the best candidate to test whether modulating glutamylation is required for muscle architecture. I assessed CCP6 depletion consequences through cross-section area distribution analysis and fiber typing in various muscles from the CCP6 knockout mice. These mice exhibited hindlimb muscle hypertrophy associated with more IIA fibers. Data suggest CCP6 removal modifies muscle phenotype. To explain that I am using CCP6 KO muscle stem cells (MuSC) cultures to assess myogenesis. If they showed an increased proliferative capacity, fewer cells were able to commit to differentiation. But they remained able to form contractile myofibers. Data suggest CCP6 helps to control MuSC pool through cell cycle regulation and thereby allows timely progression into differentiation. Altogether, our data point a role for the glutamylation of the microtubule network in muscle formation and in its maintenance and likely in its function.

SESSION FONDAMENTALE 3

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Role of FUBP1 in the transcriptome diversity of human skeletal muscle cells

FUSE-Binding Protein 1 is a single-stranded DNA- and RNA-binding protein well known for its role as a transcription factor and more recently as a key splicing factor. Mostly studied in cancer, its regulatory functions in physiological contexts remain poorly defined. Here, we investigated the role of FUBP1 in regulating the transcriptome in human skeletal muscle.

Transcriptomic analysis in a human muscle cell line depleted of FUBP1 revealed widespread changes in gene expression, splicing, and isoform diversity, particularly in long genes. Selected splicing events were independently validated in human primary muscle cells. We found that differentially expressed and alternatively spliced genes are enriched in pathways related to muscle development, contraction, cell adhesion, actin filament, and extracellular matrix organization in line with the impaired differentiation observed in FUBP1-depleted muscle cells.

High resolution RNA binding profiles generated by iCLIP2 revealed a predominant association with the long introns of large genes, with a specific binding pattern in extra-long introns (> 100 kb), as well as binding to the 3'UTR region, which is the second most frequent target region.

An integrative analysis of iCLIP2 results with transcriptomic data showed that FUBP1-dependent splicing regulation is associated with intronic binding. In addition, FUBP1 binding sites within 3'UTRs were linked to the modulation of alternative polyadenylation and the regulation of gene expression. Altogether, our findings identify FUBP1 as a regulator acting at multiple transcriptomic levels in human skeletal muscle cells, a tissue that expresses a high level of long genes, further illustrating the multifaceted functional roles of this protein.

SESSION FONDAMENTALE 3*

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A Scalable hiPSC-Based Screening Framework for ACTN2-, PYROXD1-, and FHL1-Related Congenital Myopathies

Congenital myopathies represent a heterogeneous group of ultra-rare inherited muscle disorders characterized by early-onset hypotonia and muscle weakness, with an overall prevalence of 1 to 9 per 100,000 individuals and over 30 causative genes identified. Their rarity and the limited availability of patient muscle biopsies represent major barriers to large-scale mechanistic studies and therapeutic discovery. To overcome these limitations, we developed human induced pluripotent stem cells (hiPSCs) -based models of ACTN2-, PYROXD1-, and FHL1-related myopathies, together with CRISPR/Cas9-corrected isogenic controls. Patient and isogenic hiPSCs were differentiated into mature myotubes and used to establish a multiparametric phenotypic platform combining calcium flux kinetics, real-time metabolic profiling, and high-content imaging (HCI) to quantitatively characterize cellular morphology and sarcomeric protein expression. These phenotypic analyses were complemented by RNA sequencing to characterize disease-associated transcriptional alterations and identify molecular pathways underlying the observed cellular and functional defects. Integration of these complementary functional, molecular and phenotypic readouts identified robust pathological signatures suitable for drug screening. As a proof of concept, screening a medium-size drug library demonstrated the scalability of the platform and identified several promising candidate compounds improving disease-associated phenotypes. Overall, these results establish a scalable human iPSC-based framework for phenotypic drug discovery and repurposing across genetically distinct congenital myopathies, providing a strategy to accelerate therapeutic development for these ultra-rare neuromuscular diseases.

SESSION FONDAMENTALE 4

Vendredi 20 Novembre · 11h00 - 12h00

Modération : Thomas Laumonier, Genève
& Alexis Boulinguiez, Paris

SESSION FONDAMENTALE 4*

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LAMA2-related Muscular Dystrophy: How Nonsense-Associated Alternative Splicing Offers Cellular Protection

Cells activate various mechanisms to counteract the detrimental effect of nonsense mutations, one being nonsense-associated alternative splicing (NAS). While working in concert with nonsense-mediated decay, which degrades premature termination codons (PTC)-bearing transcripts, NAS bypasses the PTC by splicing out the mutated exon. NAS is a protective mechanism observed across multiple disorders, generally associated with a milder phenotype. Notably, in Duchenne muscular dystrophy, NAS can result in the milder Becker muscular dystrophy phenotype, providing a rationale for emerging therapeutic strategies. In LAMA2-related muscular dystrophies (LAMA2-MD), a rare disease caused by LAMA2 mutations, NAS remains largely unexplored, reported only once in 2001. We investigated NAS in cellular models derived from patients who, despite carrying PTC mutations, display a limb girdle-like phenotype rather than a severe congenital form. Across myogenic and fibroblast cells from five patients, three homozygous and two compound heterozygous, we found that NAS occurred exclusively in homozygous cells, and only when exon skipping preserves the reading frame. Surprisingly, no alternative splicing was detected in iPSC-derived myotubes from these patients, a possible consequence of cells' reprograming. To test this hypothesis, we will assess NAS in the original patients' PBMCs and from thirteen additional patients. Beyond its therapeutical potential, we believe NAS to be an easily accessible treatment efficacy readout for a PTC-correcting therapy we are developing. Hence, understanding the genetic context required for NAS should provide refined genotype-phenotype correlations and enable patients' stratification. This knowledge is essential for successful future clinical trials and will pave the way towards personalized treatment strategies.

SESSION FONDAMENTALE 4*

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First multi-scale profiling of the musculoskeletal fascia in aging: from resident stromal cell signatures to in vivo ultrasound biomarkers

Musculoskeletal aging research has primarily focused on muscle fiber atrophy, often overlooking the surrounding connective microenvironment. The deep musculoskeletal fascia is a dynamic structure involved in lateral force transmission, proprioceptive feedback, and cellular cross-talk. It also contains recently identified resident fascial mesenchymal stromal cells (FSCs) that, like their counterparts in muscle (FAPs) and adipose tissue (ASCs), may contribute to tissue homeostasis and regeneration. While sarcopenia is well documented, fascial dynamics remain poorly understood. We hypothesized that age-dependent fascial remodeling closely reflects, or may contribute to, musculoskeletal decline.

Using an exploratory multi-scale approach in C57BL/6 mice across three life stages (Young: 3 months, Middle-aged: 12 months, Elderly: 23 months), we investigated structural, cellular, and functional adaptations of the fascia lata. Physical performance was evaluated via grip strength and dynamic gait analysis. Non-invasive fascial imaging was explored using high-frequency ultrasound, complemented by Second Harmonic Generation (SHG) microscopy. Resident FSCs were isolated by FACS based on the Sca-1+/CD45-/CD31- phenotype and profiled by bulk RNA sequencing to characterize their molecular profile.

At the cellular level, transcriptomic analysis showed that FSCs have a distinct signature compared to FAPs and ASCs, with an inflammaging profile during aging. Importantly, these biological changes were linked to physical performance: elderly mice with motor decline showed higher expression of inflammatory factors and matrix-degrading enzymes (such as Mmp13, Cxcl3, Cxcl5, Tnf). At the tissue level, this remodeling was associated with disorganized collagen fibers on SHG imaging. In vivo, high-frequency ultrasound captured these structural alterations, showing a trend toward increased echogenicity with age while supporting the feasibility of assessing this micrometric system. Clinically, this fascial remodeling coincided with reduced grip strength and a widened rear base of support during gait.

Overall, these findings in mice suggest that fascial stromal cells and matrix alterations are associated with locomotor decline. This work provides a translational proof-of-concept that the deep fascia could serve as a promising non-invasive biomarker and a new therapeutic target to preserve mobility, not only in aging, but also in neuromuscular disorders.

SESSION FONDAMENTALE 4*

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Neuromuscular electrical stimulation training minimizes sepsis-induced skeletal muscle dysfunctions

Sepsis is an acute inflammatory response to infection that often requires intensive care, prolonged bed rest, and sedation, leading to severe skeletal muscle loss and weakness. These alterations are associated with cellular disturbances, including myofiber atrophy, altered muscle satellite cell (MuSC) regulation and inflammatory cell infiltration. Currently, no effective therapy exists for sepsis-induced skeletal muscle dysfunction. Neuromuscular Electrical Stimulation (NMES), which increases contractile activity through electrical pulses, emerges as a promising non-pharmacological approach, although its efficacy remains debated, mainly due to uncontrolled force output.

Our lab developed a standardized force-controlled NMES protocol that enhances MuSC number and status, macrophage abundance, and myofiber size in healthy muscle. We aimed to investigate whether NMES could attenuate sepsis-induced skeletal muscle dysfunction in a murine model of sepsis induced by cecal ligation and puncture (CLP). Mice underwent CLP or sham surgery. From day 1 post-surgery, CLP mice received either six NMES sessions at 15% of maximal force over a seven-day period or a control intervention. Plantar flexion force was measured until day 8 post-surgery while gastrocnemius muscle was harvested for immunostaining.

CLP induced severe muscle mass and strength loss, accompanied by an increase in the number of MuSCs and fibro-adipogenic precursors. NMES attenuated muscle force loss and increased myofiber size, myonuclei content and macrophage abundance in CLP mice.

Thus, contractile activity promotes beneficial adaptations in multiple cellular components of skeletal muscle during sepsis, involving both muscle fibers and the muscle cellular environment. These findings support further investigation of contractile activity-induced myokines as potential mediators of these adaptations.

SESSION FONDAMENTALE 4*

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Unlocking Muscular Dystrophies Using Patients' Induced Pluripotent Stem Cells

Muscular dystrophy (MD) encompasses genetic disorders marked by progressive muscle weakness and impacting mobility. Despite over 100 MD-associated genes identified, many cases remain undiagnosed. This study focuses on a 48-year-old patient with undiagnosed MD, carrying a homozygous variant of unknown significance in the PLEC1 gene, encoding for P1f protein. Using hiPSC-derived skeletal muscle cells (SkMCs) and innervated muscle fibers (iMFs), we aim to explore the pathogenicity of the PLEC1 mutation.

HiPSCs from the MD patient, healthy controls and control lines with known MDs (DM1, DMD, SMA) were used in this study. Transcriptomic analysis identified significant downregulation of the mitochondrial genes CHCHD2 and SLC15A4, and the metabolic gene NAPRT in the patient's hiPSC-iMFS, indicating potential mitochondrial and metabolic dysfunctions. Consistently, Seahorse Mito Stress Test revealed reduced mitochondrial respiration in patient hiPSC- SkMCs, despite a preserved mitochondrial mass and respiratory chain components. Elevated mtDNA copy number were also observed in the patient's hiPSC-SkMCs compared to his unaffected sibling, confirming impaired mitochondrial function. Using a custom MATLAB algorithm, functional analysis revealed calcium signaling defects in the patient's hiPSC-iMFs.

Our study provides insights into the pathogenesis of an undiagnosed MD. The discovery of the PLEC1 variant expands knowledge of MD-related genetic factors. Our MATLAB algorithm for calcium flux analysis offers a useful tool for studying contractile function. Additionally, mitochondrial respiration defects suggest new molecular mechanisms to explore. Rescue experiments restoring P1f expression in the patient's cells will be performed and are anticipated to reverse the cellular defects, thereby establishing a direct genotype–phenotype correlation. This integrative approach enhances our understanding of MD and may guide future therapeutic strategies and diagnostic improvements.

SESSION CLINIQUE 2

Vendredi 20 Novembre · 12h00 - 13h00

Modération : John Rendu, Grenoble
& Pascal Cintas, Toulouse

SESSION CLINIQUE 2

François-Jérôme AUTHIER, francois-jerome.authier@aphp.fr

Ana Šarić, Cyrielle Hou, Baptiste Periou, Charlotte Gressier, Sarah Souvannanorath, Edoardo Malfatti, Fred Relaix, Nadia Oubaya, Ludovic Martin

CHU Henri Mondor (APHP); INSERM U955, Eq. Musk ether; Université Paris Est-Créteil,

Valeur prédictive de l'expression musculaire d'ISG15 (Interferon-Stimulated Gene 15) pour le diagnostic de la dermatomyosite

La dermatomyosite (DM) se distingue immunologiquement des autres myopathies inflammatoires idiopathiques (MII) par sa signature interféron (IFN) de type I, attestée par l'induction de l'expression du gène ISG15 (interferon-stimulated gene 15) dans le tissu musculaire. Nous avons évalué la valeur prédictive de l'expression musculaire d'ISG15 pour le diagnostic de DM de manière rétrospective (étude monocentrique).

Deux cent vingt-sept patients consécutifs ont été inclus. La classification diagnostique incluait les données cliniques, immunologiques et histopathologiques, et les patients ont été répartis en trois groupes : (i) myopathies inflammatoires idiopathiques (MII, n=75 dont 21 DM) ; (ii) pathologies non inflammatoires (PNI, n=123) ; et (iii) patients sans pathologie musculaire définie, désignés comme contrôles (CTL, n=29). L'expression musculaire d'ISG15 a été quantifiée par qPCR sur tissu congelé. L'expression musculaire d'ISG15 était plus élevée dans les muscles des patients atteints de DM par rapport aux autres myopathies inflammatoires idiopathiques (MII), aux myopathies non inflammatoires (MNI) et aux témoins (CTL) ($p < 0,0001$). Le seuil optimal pour le diagnostic de DM parmi les MII a été évalué à 13,603, avec une sensibilité de 90,48 % (IC 95 % : 69,62 ; 98,83) et une spécificité de 92,16 % (IC 95 % : 81,12 ; 97,82), les taux d'ISG15 étant inférieurs à ce seuil chez seulement deux patients atteints de DM. Des taux d'ISG15 supérieurs au seuil ont été observés chez 17 des 227 patients (7,48 %), incluant 1 témoin, 11 patients PNI et 5 patients avec MII non-DM.

Notre étude a confirmé l'association spécifique de la DM à une signature interféron de type I au niveau musculaire. Dans une optique d'optimisation diagnostique, cette étude de cohorte met en évidence l'intérêt potentiel de la quantification de l'ISG15 musculaire pour le diagnostic de la DM.

SESSION CLINIQUE 2*

Béatrice LABELLA[1], b.labella@institut-myologie.org

Sami Tayb-Boulahfa[2], Teresinha Evangelista1,[3], Hortense Chassepot[4], Marie Bretagne[5], Aude Rigolet[6], Nicolas Champtiaux[6], Samuel Malartre[6], François Fer[6], Olivier Benveniste[6], Joe-Elie Salem[5], Sarah Léonard-Louis[1], Yves Allenbach

1. Department of Neuropathology, Hôpital Pitié-Salpêtrière, Assistance Publique–Hôpitaux de Paris (AP-HP), Paris, France.
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4. Department of Internal Medicine, Hôpital Henri-Mondor, AP-HP, Créteil, France.
5. Department of Pharmacology, Clinical Investigation Center and Cardio-Oncology Unit, Hôpital Pitié-Salpêtrière, AP-HP, Sorbonne Université, Paris, France.
6. Department of Internal Medicine and Clinical Immunology, Hôpital Pitié-Salpêtrière, AP-HP, Sorbonne Université, Paris, France.

Defining the Histopathological Spectrum of Immune Checkpoint Inhibitor-Related Myositis: Development and Validation of a Diagnostic Score

Immune checkpoint inhibitor (ICI)-related myositis is a potentially severe immune-related adverse event for which validated histopathological diagnostic criteria are lacking. This study aimed to characterize the histopathological spectrum of ICI-myositis and to develop and independently validate a simple, reproducible muscle biopsy-based diagnostic score.

We conducted a monocentric cohort study including adults with suspected ICI-myositis. The development cohort comprised 100 patients evaluated between January 2017 and December 2023, including 73 patients with ICI-myositis and 27 controls, classified according to multidisciplinary expert consensus. Muscle biopsies were assessed using 47 histopathological variables across muscle fiber, inflammatory, vascular, and interstitial domains. Histological evaluation included hematoxylin and eosin staining, MHC class I and II immunostaining, and C5b9 staining. Variables were evaluated for diagnostic discrimination and interobserver agreement, and a simplified diagnostic score was developed. Its performance was subsequently assessed in an independent validation cohort of 54 patients (January 2024–August 2026).

ICI-myositis exhibited a predominantly inflammatory-necrotizing histopathological pattern. Endomysial inflammatory infiltrates were observed in 94% of ICI-myositis cases versus 8% of controls (OR 149, 95% CI 29.2–763), clustered necrosis in 73% versus 4% (OR 46.1, 95% CI 8.11–262), and focal clustered MHC-II expression in 85% versus 8% (OR 48.4, 95% CI 11.0–212). Interobserver agreement was excellent for endomysial inflammation and clustered necrosis (κ=0.95 for both).

A three-item diagnostic score was developed, assigning one point each for endomysial inflammation, clustered necrosis, and clustered MHC-II expression. A threshold of ⩾2 points yielded 88% sensitivity (95% CI 78–94%) and 100% specificity (95% CI 86–100%) in the development cohort. In the independent validation cohort, the same threshold achieved 80% sensitivity (95% CI 66–89%) and 100% specificity (95% CI 72–100%).

ICI-myositis displays a recognizable inflammatory-necrotizing histopathological phenotype. A simple three-item diagnostic score demonstrated excellent specificity and good sensitivity in both development and independent validation cohorts. This reproducible approach may help standardize muscle biopsy interpretation and support multidisciplinary diagnosis of ICI-related myositis.

SESSION CLINIQUE 2

Marion MASINGUE[1], marion.masingue@aphp.fr

Edouard Januel[2], Marianne Hezode[1], Damien Sternebeg[3]

1. Centre de référence neuromusculaire NEIDF, Neuromyologie, Hôpital Universitaire Pitié-Salpêtrière, APHP, Sorbonne Université, Paris, France.
2. Service de neurologie et service de recherche clinique, Hôpital Fondation Adolphe-de-Rothschild, Paris, France.
3. Service de Biochimie Métabolique, Hopital Universitaire Pitié Salpétrière, APHP, Sorbonne Université, Paris, France.

Une Myasthénie du sujet âgé

Un homme, né au Cameroun, de parents non consanguins et sans antécédent familial, est vu en centre de référence neuromusculaire à l'âge de 72 ans pour une tête tombante.
Les acquisitions motrices ont été normales, mais il a fait un épisode de tétanos à 8 ans pour lequel il a été hospitalisé plusieurs semaines, puis a dû réapprendre à marcher, mais il a par la suite été très sportif.
Il décrit à partir de l'âge de 63 ans une baisse de force généralisée, de début peut-être brutal, et 3 ans plus tard une tête tombante. Les bilans avaient montré : IRM cérébrale, médullaire, 2 EMG normaux, CPK 356, anti-RACh, anti-Musk, dot-myosite négatifs.
À l'examen clinique, on notait une tête tombante avec hyperlordose, pas d'atteinte faciale, de trouble bulbaire ou oculomoteur, pas de déficit abdominal, Mingazzini et Barré complets. Un nouvel EMG retrouvait des décréments avec cupules autour de 15-20% aux 4 membres. Le scanner ne montrait pas de lésion thymique.
Dans l'hypothèse d'une myasthénie séronégative un traitement par anticholinestérasiques, corticoïdes et Cellcept est débuté. Rapidement, le patient s'aggrave avec une faiblesse motrice et l'apparition d'une dysphonie (Garches 41.5/100). Il reçoit 3 cures d'IgIV qui l'améliorent mais seulement transitoirement, puis est hospitalisé et intubé en réanimation pour une crise myasthénique, d'évolution favorable après des échanges plasmatiques (EP). Le contrôle de l'EMG au décours retrouve le syndrome myasthénique, sans argument pour une atteinte motoneuronale, l'effort bref est normal.
Le Cellcept est majoré à 3g/j, les EP sont maintenus toutes les 3-4 semaines, mais la myasthénie reste mal équilibrée avec une fatigabilité majeure et des troubles bulbaires entraînant une altération de l'état général.
Le panel des myasthénies congénitales est alors réalisé. Le logiciel de lecture n'identifie pas de variant, mais la relecture visuelle systématique par le généticien identifie une délétion homozygote dans l'intron 1 de DOK7. Le diagnostic est porté avec un délai de 2 ans par rapport à la première consultation en CRMR, et permet l'arrêt de tous les traitements : corticoïdes, immunosuppresseurs et anticholinestérasiques qui aggravent les SMC DOK7.

Ce cas illustre l'importance (1) d'envisager une cause génétique devant un syndrome myasthénique séronégatif résistant aux traitements standards, même après 60 ans, car les traitements peuvent être délétères, et (2) de la lecture des analyses par des généticiens experts.

SESSION FONDAMENTALE 5

Vendredi 20 Novembre · 12h00 - 13h00

Modération : Julien Gondin, Lyon
& Laure Weill, Paris

SESSION FONDAMENTALE 5*

Alizée DANGREAUX, alizee.dangreaux@univ-amu.fr

MS. Felix, O. Ballouhey, N. Da Silva, S. Courrier, M. Bartoli

Aix Marseille Univ, INSERM, MMG U1251, 13005 Marseille, France

Gene therapy for dysferlinopathies: from minigene strategy using muscle specific viruses to naked DNA sonodelivery

Dysferlinopathies are rare and progressive diseases that exist in two main forms: the Miyoshi Myopathy (MM) and the LGMDR2 (2B). These pathologies appear in the late childhood or early adulthood and both are caused by recessive mutations in the DYSF gene and are characterized by muscular weakness, atrophy, and high levels of creatine kinase in the blood. Patients affected by dysferlinopathies have difficulties carrying objects, climbing stairs, or even just walking. Dysferlin is a large transmembrane protein whose key function is membrane repair in muscle cells. There is currently no etiological treatment for them, only supportive care.

Fifteen years ago, a large homozygous deletion in the gene was observed in a female patient with a late onset presentation and very moderate dysferlinopathy. This mini-gene enables the production of a truncated but partially functional protein. Given the limited encapsidation capacity of AAVs, this mini-gene would enable a gene therapy approach with only the part of the gene required for membrane repair. Following the discovery of this patient, we tested an enlarged mini-gene construct both in vitro and in vivo. We performed systemic injections in dysferlin-deficient mouse model using muscle-specific AAV and we observed a good targeting in the quadriceps. The other organs have yet to be analyzed, and hepatotoxicity tests need to be conducted. However, although we were able to restore several functions of the full protein, we could not fully rescue all dysferlin associated function.

Therefore, we decided to develop an innovative alternative approach based on ultrasound-mediated delivery as a safe method to administer naked DNA coding the full dysferlin protein. This technique avoids the use of viruses, which can be toxic in gene therapy trials. This is based on a systemic injection of microbubbles and plasmid DNA encoding dysferlin and applying ultrasound to muscles, this combination will allow the genetic material to pass through the vessel barriers. Since the initial results are very promising, we will administer the full-length dysferlin in a deficient mouse, enabling the restoration of all dysferlin functions. If this technique is proven effective, it could be developed for conditions with other genes involved whether they are small or large.

SESSION FONDAMENTALE 5*

Marine LECONTE, m.leconte@institut-myologie.org

Lucas Ratelet, Zoheir Guesmia, Gisèle Bonne and Anne Bertrand

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

DNA damage in LMNA-related congenital muscular dystrophy

Repair of DNA double-strand breaks via the non-homologous end joining involves a cascade of histone modifications, starting with phosphorylation of H2AX (γH2AX), followed by histone H2AK15 ubiquitylation and H4K16 deacetylation that are both required for 53BP1 recruitment at DNA breaks, forming foci necessary to allow DNA repair. Recent studies have shown an accumulation of DNA breaks in a group of neuromuscular pathologies linked to mutations in the LMNA gene, and more particularly in its most severe form, the LMNA-related congenital muscular dystrophy (L-CMD). The LMNA gene codes for lamins A/C, proteins organized in a network at the nuclear membrane called the nuclear lamina, involved in nuclear resistance to mechanical stress. Lamins A/C interact with numerous proteins, including 53BP1, protecting it from degradation in absence of DNA damage and facilitating its recruitment to break sites. Although increased nuclear fragility is likely to trigger DNA damage in L-CMD, we hypothesize that the accumulation of DNA breaks might be due to DNA damage repair defect in presence of mutated lamins A/C.
We report here for the first time that primary myotubes derived from L-CMD patients have increased DSB due to defects in 53BP1 foci formation link to an upregulation of H4K16ac. Treatment of L-CMD myotubes with a drug specifically inhibiting KAT8 activity, the lysine acetyl transferase responsible for histone H4K16 acetylation, restore 53BP1 foci formation, thus allowing DSB repair. Altogether, our data might open new therapeutic avenues through a modulation of KAT8 activity for LMNA-related muscular disorders, for which no therapies are yet available.

SESSION FONDAMENTALE 5*

Minh Ngoc KONG[1], mkhong@istem.fr

Jérôme Polentes[1], Noémie Bérenger-Currias[1], Denis Furling[2], Cécile Martinat[1], Lise Morizur[1]

1. I-STEM, CECS / Inserm UMR861 / UEVE - Corbeil-Essonnes (France)
2. Centre de Recherche en Myologie, Sorbonne Université, Inserm, Institut de Myologie, Paris (France)

Engineered human myobundles as a proof-of-concept preclinical platform for therapeutic testing in Myotonic Dystrophy Type 1

Myotonic dystrophy type 1 (DM1) is the most common adult-onset muscular dystrophy. Despite identifying the causal mutation three decades ago, incomplete understanding of disease mechanisms hinders progress in treatment development. This underscores the need for innovative strategies and more predictive translational models. Recent advances in 3D cell culture techniques using human pluripotent stem cells (hPSCs) have enabled the development of functional human skeletal muscle constructs. We implemented a transgene-free protocol to differentiate distinct hPSC lines into a homogeneous and expandable population of myogenic progenitor cells. In 2D culture, these progenitors fused to form myotubes with a high fusion index, well-organized sarcomeric architecture, and spontaneous contractile activity. Notably, a small fraction of cells expressed Pax7 adjacent to muscle fibers. To generate functional skeletal muscle tissue, progenitors were embedded within 3D hydrogel scaffolds anchored between flexible pillars. Myobundles derived from DM1 cells were subsequently used to evaluate multiple therapeutic strategies. Engineered myobundles reproducibly formed cross-striated myotubes capable of generating active twitches in response to acetylcholine or electrical stimulation after 7 days. Contractile activity correlated with robust calcium transients after exposure to acetylcholine. We applied this 3D skeletal muscle platform to hPSCs carrying mutations in the DMPK gene. We validated the pathological relevance of the model by observing known molecular hallmarks of the disease, including nuclear RNA foci and splicing defects. DM1 myobundles also displayed functional impairments, with reduced contractile force at day 7 and day 14, and delayed relaxation kinetics. Notably, we observed reversal of key disease hallmarks following treatment with multiple therapeutic modalities, including small molecules and gene therapy-based approaches. We developed a robust 3D human skeletal muscle platform that recapitulates molecular and functional features of DM1. The model enables quantitative assessment of disease-associated contractile deficits alongside molecular hallmarks. It establishes a proof-of-concept functional preclinical platform to evaluate therapeutic candidates.

SESSION FONDAMENTALE 5*

Liudmila AFANASEVA, liudmila.afanaseva@univ-lyon1.fr

Nicolas Lacoste, Laurent Schaeffer, Edwige Belotti

Pathophysiology and Genetics of Neuron and Muscle (PGNM), Institut NeuroMyoGène, Université Claude Bernard Lyon 1, CNRS UMR5261, INSERM U1315, Faculté de Médecine Rockefeller, France

Nucleus-mitochondria cross-talk in a mouse model of premature skeletal muscle aging

Skeletal muscle aging is characterized by the progressive accumulation of DNA damage, mitochondrial dysfunction, oxidative stress, and muscle atrophy. Increasing evidence suggests that bidirectional communication between the nucleus and mitochondria is critical for coordinating stress responses, preserving genome integrity, and maintaining metabolic and cellular homeostasis. To investigate the molecular mechanisms underlying this cross-talk, we used a skeletal muscle-specific H2A.Z knockout mouse model (H2A.Z mdKO), which recapitulates several hallmarks of skeletal muscle aging, including DNA damage accumulation, oxidative stress, mitochondrial dysfunction, and muscle atrophy.

Analysis of H2A.Z-deficient skeletal muscle revealed alterations in several regulators of nucleus–mitochondria communication, including PARP1, p53 and sirtuins, together with reduced NAD^+ levels. Transcriptomic analyses further identified methylenetetrahydrofolate dehydrogenase 2 (MTHFD2) as one of the most strongly induced genes. Beyond its established role in mitochondrial one-carbon metabolism, recent studies have shown that MTHFD2 can translocate to the nucleus and influence epigenetics, transcriptional regulation and chromatin remodeling. Consistent with this, we observed increased nuclear MTHFD2 in H2A.Z-deficient muscle, suggesting a potential role in stress-induced genome maintenance and DNA repair pathways.

These findings define two complementary lines of investigation. First, we are testing whether MTHFD2 contributes to the maintenance of genome stability and nucleus–mitochondria communication in skeletal muscle under conditions of chronic cellular stress. Second, we are evaluating whether long-term restoration of NAD^+ levels through precursor supplementation can alleviate the muscle atrophy, DNA damage accumulation, mitochondrial dysfunction, and associated alterations in nucleus–mitochondria signaling observed in H2A.Z-deficient muscle. Together, these studies will provide new insights into the molecular mechanisms linking genome maintenance, mitochondrial homeostasis, and skeletal muscle aging.

POSTERS

SESSION POSTERS 1

Mercredi 18 Novembre
16h00 - 17h00

LISTE POSTERS - SESSION 1

Mercredi 18 novembre de 16h00 à 17h00

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7	*	AKAN	Melisa	Exercise-induced irisin release: a robust phenomenon or a context-dependent response?
13		ALCAIN	Romain	Decreased skeletal muscle fatigability under cold exposure is a consequence of limited initial contractile capacity
19		GOUTTEFARDE	Antonin	Etude in vitro de la pharmacocinétique et de la pharmacodynamie d'un oligonucléotide antisens tricyclo-DNA en utilisant un système hybride homme-murine
25	*	ARSLAN	Aybüke	Mitochondrial and autophagic remodeling in quiescent and reactivated human muscle reserve cells
31		AUGUSTE	Anne	Efficacité et tolérance de l'efgartigimod PH20 par voie sous-cutanée chez les adultes atteints de MGo : Résultats intermédiaires de l'étude ADAPT OCULUS
37		BARBAROT	Nicolas	Understanding the impact of the systemic environment on ICU-acquired muscle weakness : study protocol of the REAMUS translational project
43	*	BARQUISSAU	Valentin	Catalytically inactive MTM1 recapitulates XLCNM and impairs mitochondrial function
49		BÂRSAN	Ioana Cristina	Myosite à inclusions : présentation atypique par atteinte inaugurale de loge postérieure de jambe, à propos de deux cas cliniques
55		BASSEZ	Guillaume	TRACK DM: Design of longitudinal natural history study in people with myotonic dystrophy linking retrospective data with prospective follow-up
61	*	BASTARD	Damien	Torpor and hibernation: Regulation of circulating factors involved in muscle protein balance
67		BAUCHE	Stéphanie	Nesprin-1 Dysfunction Reveals a Role for Nuclear Envelope Proteins in Congenital Myasthenic Syndromes and Neuromuscular Synaptopathy
73	*	BERGAMASCHI	Mauro	Analysis of new therapeutic targets involved in the modulation of the inflammatory response in Fibrodysplasia Ossificans Progressiva
79	*	BLAECKE	Camille	Characterization of TRPV1 in the pathophysiology of exertional heat stroke
85		BLERVAQUE	Léo	Wearable actigraphy for early risk stratification at the initiation of first-line systemic anticancer therapy: preliminary results of a prospective cohort study
91	*	BOBE	Elio	Modeling TTN-Related Muscle Diseases Using Human 3D MYOrganoids
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LISTE POSTERS - SESSION 1

Mercredi 18 novembre de 16h00 à 17h00

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108		BOULINGUIEZ	Alexis	Targeting endoplasmic reticulum and mitochondria to alleviate protein aggregation in oculopharyngeal muscular dystrophy
111		BOWEN	Maximilien	Force-Velocity-Endurance (FoVE) Mapping of the Adductor Pollicis: Independence of Muscle Capacities
114	*	BROCKER	Noé	Lactylation, Epigenetic Regulation and in skeletal muscle adaptation
117	*	BRUN	Ambre	Innervation of Amyotrophic Lateral Sclerosis Muscles: Role of PS
120		BRUREAU	Anthony	A translational rat model and composite efficacy score to evaluate CAPN3 gene therapy
123		BUON	Céline	Is skeletal muscle metabolically reprogrammed in asymptomatic ALS gene mutation carriers?
126		CADOT	Bruno	Nesprin-1 mutations trigger nuclear envelope deformations in muscle cells
129		CARTHE	Louann	Distinct slow-to-fast contractile transcriptional remodelling in the mouse soleus and gastrocnemius muscles after 30 days of hindlimb unloading
132		CASAS	François	Furan fatty acid supplementation protects against muscle atrophy during cancer cachexia
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147		DI GALLO	Maxime	Releasing the Brake on Fast Fibers: Sortilin Inhibition Unlocks Type IIB Muscle Growth
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SESSION POSTERS 1 - 1

Maria ABOU SAMRA[1], mabousamra@genethon.fr

John Vissing[2], Tanya Stojkovic[3], Claire Colpin[1], Céline Vaint[1], Damien Stalin[1], Emmanuel Thevenot[1], Isabelle Richard[1], Sophie Olivier[1]

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2. Rigshospitalet, University of Copenhagen, Copenhagen, Denmark.
3. Neuromuscular Reference Center, Institute of Myology, Pitié-Salpêtrière Hospital (AP-HP), Paris, France

ATA-001-FKRP study: Safety of ATA-100 an AAV-based gene therapy in patients with FKRP-related limb-girdle muscular dystophy enrolled in the dose escalation phase

Limb-girdle muscular dystrophy type R9 (LGMDR9) is an autosomal recessive disorder caused by mutations in the FKRP gene and characterized by progressive proximal muscle weakness. No curative treatment is currently available. ATA-100 is a recombinant adeno-associated virus serotype 9 (AAV9)-based gene therapy carrying a codon-optimized human FKRP transgene under the control of a muscle-specific desmin promoter. A cardiac-specific microRNA target sequence was incorporated to limit cardiac expression and reduce the risk of cardiac toxicity.
This analysis assessed the safety of ATA-100 in the dose-escalation phase of the ATA-001-FKRP study. Six ambulant adults with genetically confirmed LGMDR9, aged 29-44 years and negative for anti-AAV9 antibodies, received a single intravenous administration of ATA-100, including three patients in Cohort 1 (9.0E+12vg/Kg) and three patients in Cohort 2 (2.7E+13vg/Kg). All patients received prophylactic corticosteroids starting on the day of infusion at 1 mg/kg/day for 4 weeks followed by tapering; sirolimus could be initiated in case of significant transaminase elevation.
As of August 2026, follow-up ranged from 1 to 3 years post-treatment. Early adverse events were predominantly mild and consisted mainly of gastrointestinal disorders, palpitations, insomnia, and somnolence. The most common finding beyond Day 30 was clinically significant elevation of hepatic transaminases, observed in four patients. These elevations were mainly mild to moderate, with only two severe elevations reported in two patients. All events were asymptomatic and resolved with treatment. Transaminase elevations occurred approximately 3 months after dosing in Cohort 1 and around 1 month in Cohort 2. In Cohort 1, two patients experienced transaminase elevations at the end of corticosteroid tapering, requiring corticosteroid re-escalation and sirolimus. In Cohort 2, elevations tended to occur earlier during the tapering phase, requiring prolonged corticosteroid and sirolimus. Five patients received sirolimus for a mean duration of 19 weeks (range 9-36 weeks). No serious adverse drug reactions were reported in the study.
ATA-100 demonstrated an acceptable safety profile in ambulant adults with LGMDR9. The main treatment-emergent finding was manageable and reversible transaminase elevation, consistent with expected immune responses following systemic AAV gene therapy. Follow-up is ongoing to further characterize the long-term safety profile of ATA-100.

SESSION POSTERS 1 - 7*

Melisa AKAN[1,2], melisa.akan@umons.ac.be

Antoine Delpierre[1], Vincianne Jenart[1], Alexandre Legrand[1], Agnès Villers[2], Alexandra Tassin[1]

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2. Neuroscience Unit, University of Mons, Mons, Belgium.

Exercise-induced irisin release: a robust phenomenon or a context-dependent response?

Introduction: Exercise training (ET)-mediated systemic effects are largely driven by exerkines secreted by skeletal muscles. Among these, irisin is a peptide hormone released into circulation following cleavage of the transmembrane protein FNDC5. This process is notably triggered during ET. However, the mechanisms and extent to which different types and contexts of exercise modulate irisin release, and whether muscle-derived irisin directly contributes to ET response, remain controversial.

Methods: We investigated circulating irisin levels across different exercise contexts and experimental models in humans and mice. A pilot study was conducted in a population of 56 volunteers aged 20–25 years (44.5% females, 55.5% males). The ET protocol consisted of six 100 m sprints / 10 min recovery periods followed by 1 h of rest. For the in vivo study, 32 male C57BL/6J mice were randomized into trained (n=16) and untrained (n=16) groups. Trained mice underwent treadmill running 5 days/week for 8 weeks (not-volontary (NV) - or voluntary (V) – ET) in an enriched environment. NV and V- ET achieved a similar workout. In the in vitro study, C2C12 cells were differentiated for 6 days and submitted to EPS (Electrical Pulse Stimulation, 1 Hz, 2 ms, 20 V) for 6 h.

Results: In humans, anaerobic ET increases irisin plasma levels (Irisinpl) with a fold change of 1.09. Interestingly, in male subjects, Irisinpl post-ET is positively correlated with BMI and hamstring muscle force. In male mice, V-ET, but not NV-ET, increases FNDC5 protein levels in the gastrocnemius muscle. However, Irisinpl increases both in V and NV-ET groups compared to untrained mice, with fold changes of 1.11 and 1.12, respectively. Finally, in the culture medium of EPS - C2C12 cells, irisin levels increased after 5 and 6h compared to controls, with fold changes of 1.24 and 1.29, respectively.

Conclusions: ET induces moderately but significantly Irisin secretion, and in a robust manner across different contexts and experimental models. Our preliminary data in humans suggest that BMI and muscle mass could influence Irisinpl. In mice, our findings suggest a differential regulation of FNDC5 expression, location, or cleavage into Irisin according to ET modality. ET-mediated Irisin secretion can be mimicked in vitro using EPS apply on myotubes, allowing further mechanistic studies.

SESSION POSTERS 1 - 13

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Decreased skeletal muscle fatigability under cold exposure is a consequence of limited initial contractile capacity

Introduction. Skeletal muscle function is highly dependent on muscle temperature. Cooling typically results in a marked reduction of maximal force, velocity, and power capabilities. Previous research indicates that muscle fatigue is less pronounced at lower temperatures. However, muscle fatigability is determined by the combination of two underlying parameters. The first is critical intensity, which acts as a threshold above which the muscle fatigues. The second is a fatigability coefficient, which defines the rate of performance decline once this threshold is exceeded. To date, these two distinct parameters have not been dissociated to fully understand how cold exposure affects muscular function.

Methods. The study (n=10 participants; two thermal conditions: cold vs. neutral) investigated the adductor pollicis muscle using a motorized ergometer synchronized with percutaneous electrical stimulation of the ulnar nerve. This approach ensured involuntary contractions, completely eliminating central fatigue factors. After initial forearm immersion in a water bath (17°C), a flexible water-circulating sleeve was placed over the muscle to maintain specific thermal conditions during the evaluation. This procedure achieved a target skin temperature of 23°C for the cold condition and 36°C for the neutral condition. Participants completed a Force-Velocity-Endurance (FoVE) protocol. This method allowed the extraction of Tau, representing the fatigability time constant, alongside the critical intensities for force, velocity, and power.

Results. Cooling the muscle significantly impaired initial contractile properties. Maximal capacities decreased by 31, 49 and 70% for the force, velocity and power capacities, respectively. Critical capacities remained unchanged for both force and velocity between the two thermal conditions. Furthermore, the fatigability time constant, Tau, showed no significant differences between the cold and neutral temperature conditions.

Conclusions. The attenuated fatigability previously observed in cold conditions does not primarily originate from alterations in the fatigability threshold or the rate of fatigue. The initial reduction in maximal capacity constrains the muscle to operate at lower absolute intensities, leading to less supra-critical work and thus reduced overall fatigue accumulation. Therefore, cold exposure limits initial functional capacity rather than fundamentally modifying intrinsic muscle fatigability mechanisms.

SESSION POSTERS 1 - 19

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Etude in vitro de la pharmacocinétique et de la pharmacodynamie d'un oligonucléotide antisens tricyclo-DNA en utilisant un système hybride homme-murine

Le SQY 51 est un oligonucléotide antisens tricyclo-DNA (ASO-tcDNA) utilisé pour traiter la Dystrophie Musculaire de Duchenne, une maladie neuromusculaire entraînant une dégénérescence musculaire au fil des années. Cette maladie est causée par une mutation du gène DMD causant une absence d'expression de la dystrophine, entraînant nécrose, inflammation et fibrose musculaire.
Le SQY 51 va cibler l'exon 51 muté au niveau du pré-ARNm de la DMD permettant un saut d'exon et la restauration d'un cadre de lecture fonctionnel et l'expression d'une dystrophine tronquée mais active.
Afin de restaurer l'expression de la dystrophine, l'ASO-tcDNA doit pouvoir atteindre le noyau afin de se fixer sur sa cible. Cet ASO-tcDNA est conjugué à une queue palmitoyl permettant une grande affinité avec l'albumine sérique.
C'est dans cette perspective que nous nous intéressons, dans le cadre de nos études, aux différentes étapes de l'internalisation et de la compartimentalisation du SQY 51 au sein des fibres musculaires, ainsi qu'à l'impact de sa liaison à l'albumine humaine.
Afin de caractériser ceci, des fibres musculaires d'EDL de souris C57BL10 sont isolées et mise en culture avec l'ASO-tcDNA et de l'albumine humaine/sérum humain. Des méthodes d'immunofluorescence sont ensuite effectuées avec différents marqueurs.

Les résultats préliminaires montrent que le SQY 51 est internalisé en grande partie par la voie d'endocytose clathrine dépendante et que cette internalisation est d'autant plus importante en présence d'albumine humaine.
Les résultats montrent également que le SQY 51, après endocytose, se stock de manière importante dans les lysosomes.
Ces recherches ont pour objectif, à long terme, de trouver des méthodes permettant d'augmenter l'adressage de cet ASO-tcDNA au noyau afin d'améliorer son effet pharmacodynamique.

SESSION POSTERS 1 - 25*

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Mitochondrial and autophagic remodeling in quiescent and reactivated human muscle reserve cells

Human muscle reserve cells(hMuRCs), generated in vitro, closely recapitulate the quiescent state of muscle stem cells(MuSCs) and can be reactivated on demand, providing a powerful model to investigate the mechanisms governing MuSC quiescence and activation.In particular, hMuRCs offer a unique opportunity to dissect how mitochondrial quality control, including mitophagy,is dynamically regulated during the transition from quiescence to activation and proliferation,and how these processes contribute to MuSC function and regenerative capacity. To address this question, we established a human in vitro model allowing the direct comparison of quiescent and activated/proliferating hMuRCs and characterized mitochondrial function by assessing mitochondrial mass and membrane potential using a TMRE/MitoTracker flow cytometry assay validated with the mitochondrial uncoupler CCCP.Compared with quiescent hMuRCs, proliferating hMuRCs(myoblasts) showed an increased mitochondrial membrane potential relative to mitochondrial mass,suggesting a shift in mitochondrial activity associated with the transition from quiescence to proliferative states.This difference was consistently observed across donors and was further supported by live-cell imaging,which showed lower TMRE level in quiescent hMuRCs.In parallel,Western blot analysis showed a progressive increase in the LC3-II/LC3-I ratio during quiescence induction, reaching significantly higher levels in quiescent hMuRCs than in myoblasts.Autophagic flux assays using chloroquine further demonstrated greater LC3-II accumulation in quiescent hMuRCs than in myoblasts, indicating enhanced engagement of the autophagic pathway during quiescence.Finally,bulk RNA-seq analysis revealed significant upregulation of Parkin mRNA in quiescent hMuRCs compared with proliferating myoblasts,accompanied by a slight increase in PINK1 mRNA expression,consistent with a mitophagy-primed state,in which mitochondrial quality-control pathways are poised for engagement.
Together,these findings reveal distinct mitochondrial and autophagic features associated with human MuRC quiescence and suggest a coordinated remodeling of mitochondrial function and autophagy during the transition between quiescent and proliferative states.Elucidating how mitochondrial quality-control mechanisms,particularly PINK1/Parkin-mediated mitophagy,regulate hMuRC fate transitions may provide new insights into the mechanisms underlying the maintenance of MuSC regenerative potential.

SESSION POSTERS 1 - 31

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Efficacité et tolérance de l'efgartigimod PH20 par voie sous-cutanée chez les adultes atteints de MGo : Résultats intermédiaires de l'étude ADAPT OCULUS

Contexte: La myasthénie oculaire (MGo) est une maladie auto-immune médiée par les immunoglobulines G (IgG), caractérisée par une faiblesse des muscles oculaires. L'efgartigimod SC est un fragment Fc d'anticorps IgG1 humain co-formulé avec de l'hyaluronidase humaine recombinante PH20 qui réduit sélectivement les taux d'IgG en bloquant leur recyclage médié par le récepteur Fc néonatal. Les données provenant de patients MG traités par efgartigimod montrent des améliorations des symptômes oculaires. L'étude de phase 3 ADAPT OCULUS (NCT06558279) évalue l'efficacité et la tolérance de l'efgartigimod SC chez les adultes atteints de MGo.

Méthodes: Dans la partie A, les adultes atteints de MGo (classe I MGFA) avec le score MGII PRO ⩾6 sont randomisés 1:1 pour recevoir 4 injections hebdomadaires d'efgartigimod SC ou de placebo, suivies de 4 semaines de suivi. Les participants pouvaient continuer dans la partie B (extension ouverte ⩽2 ans) pour recevoir des cycles de 4 injections hebdomadaires d'efgartigimod SC, suivis de périodes sans traitement. Les 2 premiers cycles de la partie B comprenaient une période de traitement suivie de 4 semaines sans traitement. Les cycles suivants étaient initiés selon l'évaluation clinique, avec un intervalle de ⩾7 jours entre les périodes de traitement.

Résultats: Le critère d'évaluation principal est la variation du MGII PRO entre le début de l'étude et la semaine 4. Les critères d'évaluation secondaires comprennent les changements du MGII (PRO plus examen physique), du score du domaine oculaire sur l'échelle MGADL et du score total MGII entre le début de l'étude et la semaine 4. La tolérance est évaluée par l'incidence et la gravité des événements indésirables. Les résultats préliminaires de l'analyse principale de la partie A seront présentés.

Conclusion: ADAPT OCULUS est le premier essai mondial de phase 3 évaluant la tolérance et l'efficacité de l'efgartigimod SC chez les adultes atteints de MGo.

SESSION POSTERS 1 - 37

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Understanding the impact of the systemic environment on ICU-acquired muscle weakness : study protocol of the REAMUS translational project

Background. Septic Intensive Care Unit (ICU) patients are exposed to prolonged immobility and pro-inflammatory state, contributing to ICU-acquired muscle weakness (ICUAW). Although international guidelines recommend early mobilization in ICU, its effectiveness remains debated. The REAMUS translational project aims therefore to characterize in vitro the extent to which the systemic environment of ICU patients, at different stages of hospitalization and disease severity, (1) contributes to muscle atrophy and metabolic alterations, and (2) affects muscle adaptations in response to contraction.
Methods/design. A prospective cohort study currently conducted in the ICU of Saint Brieuc Hospital follows septic patients respectively ventilated and hospitalized for more than 2 and 7 days (NCT07074028). ICU clinical data, muscle mass and function (ultrasound rectus femoris cross sectional area (RFCSA), MRC score, handgrip test, 6-minute walk test) and circulating inflammatory biomarkers are collected from inclusion up to 3 months post-ICU. Patient sera will then use to investigate the impact of the systemic environment at different time points of hospitalization, on muscle contractile and metabolic phenotype, using a conditioned medium model on the LHCN-M2 human differentiated myotubes. We will next identify the adaptive responses of myotubes to contraction using an in vitro electrical stimulation model combined with similar conditioned medium.
Preliminary results. 34/60 patients are included to date. The ICU mortality rate observed in our cohort is 24%. Exposure to the main risk factors for ICUAW is prolonged : the respective durations of length of ICU stay, mechanical ventilation, sedation, neuromuscular blockade, and corticosteroid therapy are 16, 8, 7, 3, and 4 days. Muscle function and mass are markedly impaired : the MRC score is 45 (ICUAW is defining <48). Handgrip strength is 16 kg in men and 14 kg in women (50% of age- and sex-matched values). The reduction in RFCSA during the first week in the ICU is 9%.
Conclusion. This project could enable 1) to understand how human muscle cells adapt to the systemic environment during ICU stay, according to the patient's clinical and biological status, and 2) to determine the optimal and personalized timing for starting muscle rehabilitation strategies in ICU patients.

SESSION POSTERS 1 - 43*

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Catalytically inactive MTM1 recapitulates XLCNM and impairs mitochondrial function

X-linked centronuclear myopathy (XLCNM) is caused by mutations in the myotubularin gene leading to loss of expression of MTM1. MTM1 is a phosphoinositide phosphatase that hydrolyses PI3P to PI and PI(3,5)P2 to PI5P. Our understanding of the mechanisms involved in the pathophysiology of XLCNM relies mainly on the classical Mtm1-KO mouse model. Using Mtm1-KO mice, studies from the literature identified several functions of MTM1 that depend on its interaction with other proteins, independently of its catalytic activity.
In order to specifically address the role of MTM1 phosphatase activity, we developed a new mouse model expressing a catalytically inactive form of MTM1 (Mtm1C375S) only in skeletal muscle (SkM).
Although they have a longer life expectancy than Mtm1-KO mice (on average, 13 vs 8 weeks), Mtm1C375S mice show, compared with their Mtm1lox/lox controls, a loss of muscle mass and strength associated with muscle fiber atrophy and nuclear internalization, a phenotype similar to that of XLCNM. Analysis of SkM by RNA sequencing (RNAseq) reveals a decrease in mitochondrial biogenesis pathways in Mtm1C375S mice, confirmed by a decreased mtDNA-to-nDNA ratio measured by qPCR. Conversely, electron microscopy reveals an accumulation of mitochondria with altered morphology, pointing to a possible defect in the clearance of dysfunctional mitochondria. This hypothesis is supported by the increased protein expression of autophagy and mitophagy markers in Mtm1C375S muscle. Together with previous studies reporting mitochondrial alterations in Mtm1-KO mice, these results suggest that altered mitochondrial biology is a key feature of XLCNM regulated by MTM1 activity. To determine whether mitochondrial dysfunction plays a direct role in the development of XLCNM, we supplemented the drinking water of 10-week-old Mtm1C375S mice with nicotinamide riboside (NR), a NAD+ precursor capable of improving mitochondrial function in vivo. Compared with untreated Mtm1C375S mice, Mtm1C375S mice treated with NR survive longer and lose less body mass and muscle mass. Histological and molecular analyses are ongoing.
In conclusion, we show that loss of MTM1 phosphatase activity (without loss of expression) in muscle is sufficient to recapitulate XLCNM, and we propose a pharmacological approach targeting mitochondrial function to improve the XLCNM phenotype.

SESSION POSTERS 1 - 49

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Myosite à inclusions : présentation atypique par atteinte inaugurale de loge postérieure de jambe, à propos de deux cas cliniques

Introduction : La myosite à inclusions (IBM) est une myopathie acquise lentement progressive, surtout après 45 ans, associant faiblesse musculaire sélective et anomalies inflammatoires et dégénératives musculaires. Elle atteint typiquement, de façon asymétrique, les quadriceps, les fléchisseurs profonds des doigts et les muscles oropharyngés. Nous rapportons deux cas à début topographique atypique, par atteinte asymétrique prédominant sur les loges postérieures des jambes.

Observations cliniques : Patient 1. Patiente de 61 ans présentant une IBM évoluant depuis six ans, révélée par une atteinte distale asymétrique limitée initialement aux loges postérieures des jambes. L'examen retrouvait un déficit isolé de la flexion plantaire droite à 3/5 MRC et l'IRM, une involution graisseuse des gastrocnémiens en bilatéral et du soléaire droit, avec respect des quadriceps. Le diagnostic était confirmé par la biopsie du gastrocnémien et des Ac anti-CN1A positifs. Après sept ans d'évolution, le tableau s'est enrichi par un déficit asymétrique des fléchisseurs profonds des doigts et dysphagie.
Patient 2. Patiente de 48 ans, évoluant depuis deux ans, avec des difficultés à monter les escaliers, marcher en pente et courir. L'examen initial montrait une impossibilité de marche sur la pointe du pied gauche et un déficit bilatéral prédominant sur les loges postérieures des jambes (4-/5), associé à une atteinte des releveurs des pieds (4/5) et de flexion de la nuque (4/5). Le bilan retrouvait une hyperCKémie modérée, des tracés myogènes à l'ENMG, et une atteinte isolée des gastrocnémiens médiaux au scanner. Deux biopsies musculaires, du gastrocnémien latéral puis du fléchisseur radial du carpe pour confirmation, montraient des anomalies compatibles avec une IBM, confortées par des Ac anti-CN1A positifs. L'évolution vers une atteinte des fléchisseurs profonds des doigts, des quadriceps et des muscles oropharyngés confirmait le phénotype d'IBM.

Conclusion : Une atteinte inaugurale des loges postérieures des jambes clinique et/ou radiologique, est une présentation inhabituelle d'IBM pouvant retarder le diagnostic. La biopsie d'un muscle atteint de la loge postérieure peut être déterminante afin d'intégrer ces données histologiques aux données cliniques, d'imagerie, et sérologiques. Cette présentation atypique doit faire évoquer l'IBM et éliminer les principales myopathies génétiques et inflammatoires évitant des investigations prolongées ou des traitements inadaptés.

SESSION POSTERS 1 - 55

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TRACK DM: Design of longitudinal natural history study in people with myotonic dystrophy linking retrospective data with prospective follow-up

Myotonic dystrophy (DM) is a heterogeneous group of hereditary rare diseases, classified as DM1 and DM2, with a common and defining symptom of myotonia. Knowledge of the daily physiological burden of myotonia and its psychological impact are lacking, including how these aspects can change over time. TRACK DM is a longitudinal non interventional study, linking retrospective data captured from the French DM-Scope Registry with a prospective 24-month follow-up period. The study consists of a detailed retrospective medical history assessment of selected participants over an 18-month period up to the start of the study. This is followed by the prospective study period, with assessment visits at 12 and 24 months. 6 French neuromuscular centers participate in TRACK DM study and recruitment period is due to run from Q3 2026 to Q3 2027.

The primary objective is to study the natural history of DM, focusing on functional tests of the impact of myotonia symptoms, quality of life, and ability to perform daily activities as assessed by patient questionnaires. Other objectives include assessing the prevalence of systemic involvement of DM in relation to cardiopulmonary, gastrointestinal, hepatic and renal organ systems. Additionally, assessment of the pharmacological and non-pharmacological treatments use for myotonia during the data collection period.

Participants genetically diagnosed with DM1 or DM2 will be selected from those within the DM-Scope registry with a confirmed medical history covering ⩾18 months prior to enrolment; they will be ⩾18 years at study entry, with confirmed clinical signs of handgrip myotonia (DM1 participants), or other myotonia subtypes (DM2 participants). The anticipated participant population is N=100 in total (N=90 DM1; N=10 DM2). Descriptive statistics will be used to summarise baseline characteristics, retrospective, and prospective assessments; DM1 and DM2 patients will be analysed separately.

TRACK DM aims to demonstrate the value of enhancing knowledge of the natural history of DM, by providing insight into extramuscular manifestations of DM while symptoms of myotonia and muscle weakness persist.

SESSION POSTERS 1 - 61*

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Torpor and hibernation: Regulation of circulating factors involved in muscle protein balance

Background: Skeletal muscle atrophy is a health problem associated with several pathologies and/or disuse. In nature, hibernating mammals such as the brown bear (Ursus arctos) or the asian ground squirrel (Spermophilus dauricus) are able to preserve their muscle mass during the torpor that can last up to several months, an extended period of starving and lack of mobility. Previous studies have shown that the winter bear serum can modulate the protein balance of human muscle cells, demonstrating that hibernating blood may contain regulatory factors that could act on the signaling pathways controlling the protein cell content.

Objective: We aim at identifying compounds present in bear winter serum that trigger cellular responses through signaling pathways, and to investigate whether they reflect shared regulatory mechanisms in hibernating mammals.

Methods: Human CCL-136 and HFF-1 cells were incubated for 30 min with 5% serum collected during active or hibernation states in both species and the activation of the IGF-1/insulin, BMP and TGF-β pathways was assessed by Western blot through the phosphorylation of AKT Ser473, SMAD1/5/9 and SMAD2/3, respectively.

Results: Analysis of the IGF-1/insulin, BMP, and TGF-βsignaling pathways revealed distinct signaling profiles in response to active and hibernating sera, with a coordinated reduction in both anabolic and catabolic signaling during hibernation in both species. In ground squirrels, serum collected during inter-bout arousal induced an intermediate signaling profile.

Conclusion: The analysis of the effects of the hibernating serum on the three pathways (IGF-1/INS, TGF-β BMP) reveals a similar pattern between the two species, suggesting a conserved mechanism among hibernators. These mechanisms could contribute to the «hibernation-like» effects observed in our previous experiments on human muscle cells. Furthermore, our data suggest that both catabolic and anabolic pathways are involved in controlling the muscle protein balance during torpor.

Perspectives: Future work will explore the impact of winter compounds in other signaling pathways, and how a combination of action on both anabolic and catabolic signaling could preserve the muscle protein. This work paves the way for new therapeutic strategies against muscle atrophy.

SESSION POSTERS 1 - 67

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Nesprin-1 Dysfunction Reveals a Role for Nuclear Envelope Proteins in Congenital Myasthenic Syndromes and Neuromuscular Synaptopathy

Congenital myasthenic syndromes (CMS) are inherited disorders of neuromuscular transmission. Although most known CMS-associated genes encode proteins directly involved in synaptic function, the contribution of nuclear envelope proteins to neuromuscular synaptopathy and subsynaptic myonuclear (SSN) specialization remains poorly understood. We investigated the role of nesprin-1 and other nuclear envelope proteins in neuromuscular junction (NMJ) maintenance and explored the molecular consequences of nuclear envelope dysfunction in distinct myonuclear populations.

We studied a family carrying the SYNE1 splice-site variant, comprising an affected individual and his mildly affected mother. We assessed splicing defects, protein expression, NMJ morphology and myonuclear architecture, and examined agrin-induced acetylcholine receptor (AChR) clustering following depletion of selected nuclear envelope proteins in C2C12 myotubes. To investigate population-specific transcriptional changes, subsynaptic and extrasynaptic myonuclei were isolated from patient muscle biopsies by laser-capture microdissection and analyzed by RNA sequencing, with comparison to a patient with TOR1AIP1-associated disease.

The SYNE1 variant disrupted normal splicing and reduced the expression of giant nesprin-1. The affected individual exhibited marked NMJ remodeling, including partial innervation, fragmented AChR clusters, abnormal nuclear architecture and reduced SSN recruitment, whereas his mother displayed milder abnormalities. Depletion of nesprin-1 and LAP1 impaired agrin-induced AChR clustering in C2C12 myotubes. Transcriptomic profiling revealed altered mitochondrial, translational and proteostasis-related pathways in SSN from severely affected patients. In the mildly affected mother, several stress-associated signatures were more prominent in extrasynaptic nuclei, suggesting distinct distributions of molecular responses across myonuclear populations.

Together, these findings support a role for nuclear envelope dysfunction in NMJ maintenance and neuromuscular synaptopathy, and support SYNE1 as a candidate CMS gene. By combining functional studies with laser-capture microdissection-based transcriptomics, this work provides new insights into the molecular consequences of nuclear envelope defects in subsynaptic and extrasynaptic myonuclei and their potential contribution to clinical variability in CMS.

SESSION POSTERS 1 - 73*

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Analysis of new therapeutic targets involved in the modulation of the inflammatory response in Fibrodysplasia Ossificans Progressiva

Fibrodysplasia Ossificans Progressiva (FOP) is a rare genetic disease characterized by heterotopic ossification (HO), the abnormal formation of bone in soft tissues, such as skeletal muscles. Most patients carry the ACVR1 R206H gain-of-function mutation, which amplifies BMP signalling by increasing sensitivity to Activin-A. In recent years, the immune system has emerged as a crucial modulator of HO. Previous studies showed that immune cells, particularly macrophages (MPs), accumulate in early lesions and influence tissue remodelling, contributing to ossification of fibroadipogenic progenitors (FAPs). Despite these findings, how MPs interact with FAPs to initiate or amplify ossification remains unclear.
Using our conditional knock-in mouse model of FOP, single-cell RNA sequencing was performed, and revealed an altered cell composition after muscle injury, with an increase in MPs and FAPs in FOP mice compared to controls, strengthening the hypothesis that these cells are primed to form an osteogenic niche during HO events. Differential gene expression analysis of MPs cluster identified among the top upregulated genes SPP1, encoding for osteopontin, a protein involved in tissue remodelling and osteogenesis. In addition, in vitro polarization of bone marrow derived MPs (BMDMs) isolated from mice showed that SPP1 is mainly produced by FOP anti-inflammatory MPs.
Both in vitro and in vivo inhibition of SPP1 resulted in reduced osteogenic differentiation of FOP FAPs and decreased ectopic bone formation in FOP mice, identifying SPP1 as a mediator of MP-FAP crosstalk.
To identify new potential therapeutic targets, we investigated the main pathways upregulated in FAPs using Pathway RespOnsive GENes (PROGENy) analysis on our single-cell RNA sequencing data. PI3K and MAPK pathways were upregulated in the FAP cluster of FOP mice, and are also activated by SPP1. Indeed, a time-course experiment in FOP FAPs treated with SPP1 showed an increase in pAKT levels after 3 days of treatment by Western blot analysis.
Regarding MPs, to investigate a possible link between Activin-A and SPP1 production, FOP anti-inflammatory M2 MPs were treated with recombinant Activin-A. Preliminary results showed increased SPP1 production, suggesting that the SMAD1/5 pathway may play a role in SPP1 regulation.
Further in vitro and in vivo studies will help clarify the role of these signalling pathways in FOP, including whether the use of specific inhibitors that can mitigate HO.

SESSION POSTERS 1 - 79*

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Characterization of TRPV1 in the pathophysiology of exertional heat stroke

Exertional Heat Stroke (EHS) is a life-threatening condition that occurs in young, healthy individuals during intense physical activity. It is characterized by extreme hyperthermia (>40 °C), skeletal muscle hypermetabolism, and neurological dysfunction, and is the third leading cause of sudden death in athletes. Although its pathophysiology remains unclear, EHS shares clinical and biological features with malignant hyperthermia (MH), which is associated with mutations in RYR1, CACNA1S, STAC3, and TRPV1. Genetic analysis of a cohort of soldiers who experienced EHS led to identification of a mutation (R772C) in the Transient Receptor Potential Vanilloid 1 (TRPV1) gene. TRPV1 encodes a calcium channel sensitive to temperature and pH, expressed in both sensory neurons and skeletal muscles, where it may contribute to calcium homeostasis. Recently a mitochondrial isoform arising from an alternate transcript of TRPV1 was characterized, and we confirmed its expression in skeletal muscle. Our project aims to investigate the impact of the TRPV1 R772C mutation on skeletal muscle calcium homeostasis, mitochondrial function and the development of EHS and MH. To this end, a knock-in mouse model carrying the R772C mutation was generated. In vitro studies show that the R772C mutation does not appear to impact TRPV1 localization but alters calcium release kinetics. To evaluate the susceptibility of the R772C model to EHS, mice were subjected to exercise under heat and humidity. R772C mutant females exhibit faster exhaustion than their WT counterparts, while no significant difference was observed in males. We also investigated the metabolic profile and mitochondrial function of these animals. Under basal condition, no significant metabolic differences were observed between WT and mutant mice. However, mitochondria from male R772C knock-in mice displayed impaired succinate-stimulated respiration, suggesting a complex II defect that could contribute to a hyper metabolic state during EHS. Further investigation in homozygous mice is required to elicit a more pronounced phenotype. This integrative project may provide new insights into EHS pathophysiology and open perspectives for risk assessment and therapeutic strategies.

SESSION POSTERS 1 - 85

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Wearable actigraphy for early risk stratification at the initiation of first-line systemic anticancer therapy: preliminary results of a prospective cohort study

Functional status predicts clinical trajectory in patients starting anticancer therapy, and ECOG Performance Status scale (PS) is now an eligibility criterion for most regimens. However, PS is clinician-rated and so remain subjective, with only moderate inter-rater reliability and poor patient/physician agreement. Actigraphy has been proposed as an objective surrogate, but standard indices reflect physical behaviour rather than functional capacity, and their link with early outcomes remain unclear. We therefore designed a prospective cohort using novel actigraphy analyses to distinguish behaviour from capacity and assess their prognostic value, particularly in predicting the risk of treatment-related toxicity at baseline.

We report preliminary results from 115 patients starting anticancer therapy, followed for 60 days. Actimetry was performed using wearable devices (ActiGraph GT3X) over the first 28 days of therapy. We measured daily step count (Nstep) and estimate endurance capacity (DBAc ; a correlates of the locomotion speed at fatigability threshold) using a novel approach our team recently validated. (1) Sarcopenia and reported physical activity (GPAQ) was assessed at baseline and toxicities were recorded during follow-up.

Nstep and DBAc were significantly correlated in patients with low DBAc (<0.3g; r=0.73, p<0.001, n=64) but not in those with higher values (r=0.27, p=0.06, n=51). Nstep and DBAc were significantly lower in patients with sarcopenia, low ECOG PS (1 or 2 vs 0) or low reported physical activity (GPAQ) (p<0.01 each). Grade ⩾3 toxicities within the first 60 days of treatment tended to be more frequents in patients with low DBAc (OR 1.68, 95%CI 0.93-3.03; p=0.08) but not with low NStep (OR 1.30, 95%CI 0.81-2.07; p=0.28).

The behavior/capacity relationship appears confined to patients whose capacity is low enough to constrain daily activity. Both indices discriminated PS categories and tracked baseline frailty and inactivity. DBAc may be more sensitive to predict short-term adverse outcomes (toxicity) but it remains to be confirmed beyond this preliminary report. Long-term outcomes (progression-free and overall survival) will be analysed at study completion. If consistent, these results would support actigraphy, emphasizing in particular metrics that isolate capacity from observed behaviour as an objective marker of performance status to guide treatment decisions.

1. Delgado et al. J Exp Biol. 2026 doi: 10.1242/jeb.251129

SESSION POSTERS 1 - 91*

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Modeling TTN-Related Muscle Diseases Using Human 3D MYOrganoids

Titinopathies are rare genetic disorders caused by pathogenic variants in the TTN gene, encoding titin, the largest protein in the human body, a key structural and mechanical component of skeletal and cardiac muscle. Despite the identification of hundreds of disease-associated variants, establishing genotype–phenotype relationships remains challenging due to the size and complexity of TTN and the broad clinical spectrum of associated disorders. Patient-derived muscle organoids offer a promising platform to investigate disease mechanisms and develop personalized therapeutic strategies.

We established induced pluripotent stem cell (iPSC)-derived skeletal muscle organoids from three patients carrying distinct TTN pathogenic variants and presenting heterogeneous clinical phenotypes, including cardiac and respiratory involvement. Structural analyses revealed sarcomeric abnormalities, including increased sarcomere length and reduced full-length titin in organoids carrying truncating variants. Functional assessment using an organ bath system demonstrated impaired contractile performance, characterized by reduced force generation, increased fatigability following repeated eccentric contractions, and altered length–tension relationships, reflected in decreased resilience in maintaining muscle force following increased lengthening. These findings are consistent with the essential role of titin in preserving sarcomere elasticity and force transmission and establish the relevance of this platform for modeling key structural and functional hallmarks of titinopathies.

Overall, the organoids successfully reproduced key hallmarks of titinopathies, including muscle weakness, increased fatigability, and impaired contractile mechanics, demonstrating their value as a physiologically relevant model to investigate disease mechanisms and evaluate therapeutic strategies.

Building on these results, we are expanding our approach to generate patient-derived cardiac organoids to investigate the mechanisms underlying TTN-associated cardiomyopathy, while comparative transcriptomic profiling of TTN-iPSC-derived MYOrganoids will be performed to identify disease-associated molecular pathways and investigate the mechanisms contributing to phenotypic variability.

Ultimately, this integrated approach will support the development of more precise and personalized strategies for the treatment of patients affected by these disorders.

SESSION POSTERS 1 - 97

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Trajectory of Performance of Upper Limb in patients with Duchenne muscular dystrophy treated with givinostat relative to a modeled natural history cohort

Givinostat, an oral histone deacetylase inhibitor, has been shown to slow disease progression on ambulatory endpoints in boys aged ⩾6 years with Duchenne muscular dystrophy (DMD) in the phase 3 EPIDYS trial and ongoing open-label extension (OLE). The objective of this analysis was to contextualize changes in PUL 2.0 total score in givinostat-treated patients by comparison with disease trajectories projected using a natural history-based predictive model.

The OLE includes patients from prior phase 2 or 3 studies; all received givinostat in the OLE. Index date was defined as the first post-givinostat initiation visit with a PUL 2.0 entry score of 1-5 and an available total score. A PUL 2.0 total score at month 12 or 24 was also required. A prediction model based on the Dutch national DMD registry was applied using average index characteristics (PUL 2.0 score, ambulatory status, age) of eligible patients to predict PUL 2.0 changes over time.

Of 145 patients meeting the index criteria, 115 were evaluable at month 12 and 96 at month 24 (mean [SD] age, 12.6 [2.6] years and 12.5 [2.6] years, respectively). Mean age in the model development sample was 15.1 (5.5) years. Non ambulant patients comprised 20.9% and 21.9% of the months 12 and 24 cohorts, respectively, versus 81.8% of the model development sample. Observed mean (95% CI) PUL 2.0 changes were −0.78 (−1.58, 0.01) at month 12 and −2.26 (−3.11, −1.41) at month 24, compared with predicted counterfactual declines of −4.57 (−5.63, −3.52) and −8.55 (−10.33, −6.77), respectively. Using the current prognostic model, givinostat treatment was associated with a slower average decline in upper limb function than predicted by counterfactual trajectories. Results should be interpreted cautiously, as the predicted decline was derived from a cohort that differed from the givinostat population, potentially overstating the magnitude of the observed-versus-predicted differences.

SESSION POSTERS 1 - 103

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Trial design for the Phase 2 FORGE study evaluating apitegromab in adults with facioscapulohumeral muscular dystrophy

FSHD is a progressively debilitating disease characterized by progressive, facial muscle weakness that spreads to the shoulders and lower limbs. Patients with later adult-onset FSHD often present with progressive muscle weakness, accompanied by a loss of strength and function. The progressive nature of this disease highlights the potential benefit for therapeutic intervention using a muscle-targeted approach to build muscle and potentially improve strength and motor function.

Apitegromab is a muscle-targeted treatment for SMA that selectively inhibits activation of myostatin, a negative regulator of muscle growth. In previous clinical studies for SMA (Phase 2 TOPAZ, NCT03921528; Phase 3 SAPPHIRE, NCT05156320), apitegromab was well-tolerated and reliably improved motor function across a broad range of patients who were also receiving SMN-targeted treatment (nusinersen/risdiplam). Nonclinical studies in a FLExDUX4 murine model of FSHD showed that a murine analog of apitegromab (muSRK-015) significantly increased skeletal muscle mass, muscle force, and endurance.

FORGE is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study that will assess the efficacy, pharmacokinetics, pharmacodynamics, safety, and tolerability of apitegromab in patients with FSHD.

Approximately 60 ambulatory adult patients (aged 18-60 y) with genetically confirmed FSHD (FSHD1/FSHD2), a clinical severity score of 1.5-3 (Ricci score), and baseline 10MWRT time ⩽5s, will be recruited to participate in the FORGE study. Individuals with any medical condition, clinically significant laboratory result, or ECG value that may compromise safety, interfere with study compliance, or confound the interpretation of the results, are ineligible for the study. Patients eligible for enrollment will be randomized to receive apitegromab 10 mg/kg monotherapy or placebo by intravenous infusion Q4W. FORGE will include a screening period of up to 4 weeks, a 52-week treatment period (13 doses), and a 20-week safety follow-up period for patients not entering the open-label extension study. The primary endpoint will be percent change from baseline in total lean muscle volume by MRI at week 52.

Supported by the pivotal outcomes from previous clinical and preclinical work, the FORGE study will investigate apitegromab in the adult FSHD patient population. FORGE is expected to be conducted across 20 sites in North America and Europe.

SESSION POSTERS 1 - 108

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Targeting endoplasmic reticulum and mitochondria to alleviate protein aggregation in oculopharyngeal muscular dystrophy

Oculopharyngeal muscular dystrophy (OPMD) is a rare late-onset genetic myopathy, affecting mainly eyelid and pharyngeal muscles leading to ptosis and dysphagia. OPMD is caused by a mutation in Poly-A Binding Protein Nuclear 1 (PABPN1) gene that codes for a polyadenylation factor. This results in PABPN1 nuclear aggregates in OPMD skeletal muscle sequestrating mRNA and proteins and thus induce subsequent muscle alterations. Moreover, OPMD is characterized by impairment of several protein homeostasis (proteostasis) actors; proteasome, autophagy, chaperones. Such defects are usually associated with global misfolding defects like non-nuclear amyloid deposits (NNAD), but not yet in OPMD.
Besides the classical PABPN1 nuclear aggregates, we identified an accumulation of non-nuclear amyloid deposits (NNAD) in muscle biopsies from OPMD patients compared to healthy donors, thanks to fluorescent probe proteostat®. Furthermore, RNA sequencing analysis of human OPMD muscle biopsies strongly indicated that endoplasmic reticulum (ER) and mitochondria organelles were widely affected in human OPMD biopsies. Indeed, ER and mitochondria are both key players in cell proteostasis as ER lumen is the folding site for the protein of the secretory pathways (1/3 of the proteome) and mitochondria possess their own protein synthesis/folding/import machineries. Interestingly, in culture, human OPMD muscle cells were more susceptible to develop NNAD than healthy cells following an ER stress induction. Consistently, we found that OPMD muscle cells were characterized by a depletion in ER calcium, which is essential for proper ER protein folding. Importantly, restoring the ER calcium content by pharmacological activation of SERCA pump protected the OPMD cells from further NNAD development. Similar improvements were also achieved by improving the mitochondrial function with NAD+ booster nicotinamide riboside, as well as the pharmacological modulation of ER-mitochondria contacts.
Overall, we identified new protein aggregates in human OPMD that are closely linked to ER and mitochondrial function. Targeting these organelles represents promising therapeutic strategies against OPMD.

SESSION POSTERS 1 - 111

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Force-Velocity-Endurance (FoVE) Mapping of the Adductor Pollicis: Independence of Muscle Capacities

Introduction
Clinical evaluation of muscle function traditionally relies on maximal isometric force. However, this single metric reflects only a fraction of functional capacities and fails to predict contraction velocity or fatigability. To overcome this, the Force-Velocity-Endurance (FoVE) model provides a comprehensive 3D mapping characterized by key functional indices: initial maximal force (F0i), critical force (F0c), initial maximal velocity (V0i), critical velocity (V0c), and endurance time constant (T). This study aims to model the FoVE surface of the human adductor pollicis in vivo and evaluate the independence of these contractile parameters.

Methods
The adductor pollicis of 23 healthy subjects was evaluated using InviPo, a dedicated ergometer designed for non-invasive in vivo testing via ulnar nerve electrostimulation. Subjects performed the Sinusoidal Allout by Variation of Intensity (SAVOI) test, imposing continuous sinusoidal isokinetic velocity variations during a 5-minute fatiguing exercise [1]. A 7-parameter FoVE model was fitted to Force-Velocity-Time data, and correlation analyses cross-referenced all extracted mapping indices (F0i), F0c , V0i, V0c, T).
Results
The model demonstrated high fitting accuracy (adjusted r2=0.978±0.016; RMSE=0.108±0.044Nm). Mean (±SD) parameter values were: F0i =4.1±0.8Nm, V0i =653.6±108.7βs, F0c=1.9±0.5Nm , V0c=384.6±81.1βs and T=70.1±17.6 s . Correlation analysis revealed a widespread lack of correlation between indices: V0i vs V0c (r=0.03; p=0.914), F0i vs V0i (r=0.29; p=0.089), and F0c vs V0c (r=0.31; p=0.161). The only significant relation was between F0i and F0c (r=0.56; p=0.007) which disappeared when F0c was expressed relative to F0i , confirming that relative force loss is independent of initial capacity.

Conclusion
By demonstrating that isometric strength, shortening velocity, and fatigue resistance are functionally decoupled, these findings highlight the critical need for full-spectrum FoVE mapping to avoid masking key dynamic deficits. Combined with the SAVOI sinusoidal sweep, the InviPo ergometer provides a comprehensive, non-invasive functional phenotyping essential for longitudinal monitoring in neuromuscular diseases.

[1] Bowen et al 2024 Medecine/Science

SESSION POSTERS 1 - 114*

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Lactylation, Epigenetic Regulation and in skeletal muscle adaptation

Lactate is a key metabolite in skeletal muscle, traditionally considered a waste product of glycolysis. However, recent evidence has established lactate as an important signaling molecule capable of regulating cellular functions beyond energy metabolism. In particular, the identification of histone lysine lactylation has revealed a new mechanism linking cellular metabolism to epigenetic regulation. By modifying histones, lactate may influence chromatin state and gene expression, providing a molecular link between metabolic changes and cellular adaptation. Histone lactylation has mainly been investigated in cancer and immune-related contexts, whereas its role in skeletal muscle remains largely unexplored. This represents an important gap in our understanding of muscle plasticity, as lactate levels can fluctuate substantially in response to muscle activity and metabolic stress.
The aim of this project is to investigate whether changes in intracellular lactate levels regulate histone lactylation in skeletal muscle and whether this metabolic-epigenetic pathway contributes to muscle adaptation.
Using C2C12 muscle cells, we found that transient lactate exposure was associated with increased H3K9 lactylation (H3K9La) after 9 hours of recovery. Importantly, this increase was prevented by βalanine, a molecule reported to inhibit one of the main lactyltransferases identified to date, despite continued lactate exposure. In parallel, we investigated this relationship in vivo using an acute high-intensity interval training protocol on a treadmill in male and female rats, followed by tissue collection 24 hours after exercise. Analysis of plantaris muscle fibers revealed an increase in H3K9La across muscle fibers, independently of fiber type, ass. Interestingly, our data also revealed a sex-specific pattern of histone lactylation. Basal H3K9La levels were less heterogeneous across animals in females than in males, and the exercise-induced increase in H3K9La was less pronounced in females. These findings suggest that the regulation of histone lactylation in response to exercise may differ between sexes.
Together, these findings support the hypothesis that lactate-dependent histone lactylation may represent a mechanism linking muscle metabolism to epigenetic regulation and adaptation. We are now investigating the molecular and functional consequences of this pathway, with a particular focus on muscle adaptation and the recruitment and activation of muscle stem cells.

SESSION POSTERS 1 - 117*

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Innervation of Amyotrophic Lateral Sclerosis muscles: role of PS

Amyotrophic Lateral Sclerosis (ALS) is a fatal adult neuromuscular disease, characterized by degeneration of motoneurons and progressive paralysis. Although ALS was first defined as a neuropathology, it is now approached as multisystemic, with a strong implication of the skeletal muscles in the pathogenesis. For example, ALS skeletal muscles present alterations in RNA and protein metabolism and defects in mitochondrial homeostasis (Loeffler et al., 2016). Paraspeckles (PS), nuclear membrane-less organelles, have been shown to participate in the regulation of these pathways and in the response to stress by acting as molecular sponges. Indeed, they sequester and release target RNAs and proteins upon cellular needs. The formation of PS depends on the scaffolding of NEAT1-2, a long non-coding RNA with several RNA-binding proteins. Interestingly, some of these proteins, like FUS and SFPQ, can be mutated in ALS. Also, PS accumulate in the motoneurons of ALS patients (Shelkovnikova et al., 2018) and lab results indicate that primary myotube cultures from ALS patients present alterations in PS number and size independent of NEAT1-2 expression, suggesting a malformation. Moreover, PS lost their stress-sensing function in ALS myotubes. By depleting PS in control myotubes, we uncovered their involvement in the regulation of major muscular pathways such as muscular contraction, oxidative phosphorylation, and thermogenesis.
These results, taken together with the neurodegeneration, led us to investigate the status and role of PS at the neuromuscular junction (NMJ). In the tibialis muscle from the ALS mouse model (SOD1G93A) at the onset of symptoms, we showed an alteration of PS, particularly at the NMJ. Indeed, while in controls there is a PS enrichment in subsynaptic nuclei, it is lost in ALS muscle. This suggests a PS dysregulation at the ALS NMJ. To explore a possible implication of PS in the denervation/reinnervation process occurring in ALS, we studied NEAT1-2 expression in tibialis muscle of B6SJL control mice after a unilateral nerve crush experiment. From 1 day to 28 days post-crush of the sciatic nerve, with a theoretical full reinnervation of the muscle, we observed dysregulation of the expression of NEAT1-2. These suggest an implication of PS in NMJ formation and maintenance. Continuing the nerve crush experiment, as well as mimicking an NMJ in vitro with our muscle cell culture in different conditions, will allow us to explore the PS role in these processes

SESSION POSTERS 1 - 120

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A translational rat model and composite efficacy score to evaluate CAPN3 gene therapy

Limb-girdle muscular dystrophy R1 (LGMD R1, calpain3-related) is caused by pathogenic variants in CAPN3 and leads to progressive muscle weakness. Existing mouse models only partially reproduce the human disease, limiting their value for preclinical evaluation. We therefore generated a CRISPR-engineered Capn3-null rat carrying a frameshift mutation in exon 3 and characterized its phenotype longitudinally from one to twelve months of age.

Capn3-deficient rats developed an early and progressive dystrophic phenotype, including muscle degeneration and regeneration, increased centronucleation and inflammatory infiltrates. Disease severity was muscle-dependent, with the soleus and psoas more severely affected than the tibialis anterior. Transcriptomic profiling revealed distinct muscle-specific responses to calpain-3 deficiency. In the soleus, the phenotype was associated with downregulation of metabolism genes, together with activation of inflammatory and cytoskeletal-remodelling pathways.

Systemic AAV-mediated CAPN3 gene transfer produced widespread calpain-3 expression in skeletal muscles while sparing the heart and improved molecular, histological, biomarker and functional outcomes. To integrate these heterogeneous readouts, we developed a machine-learning-based pipeline combining complementary variables into a quantitative composite score. This approach distinguished Capn3-null from wild-type rats as early as one month of age and sensitively detected therapeutic improvement following gene transfer in a dose dependent manner.

These results establish the Capn3-null rat as a robust and clinically relevant model of calpainopathy, reveal early metabolic and inflammatory components of disease progression, and provide an integrated framework for evaluating therapeutic efficacy. They also support the continued development of systemic AAV-mediated CAPN3 replacement toward clinical translation.

SESSION POSTERS 1 - 123

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Is skeletal muscle metabolically reprogrammed in asymptomatic ALS gene mutation carriers?

Objectives : New studies suggest that Amyotrophic Lateral Sclerosis (ALS) is accompanied by a prolonged presymptomatic period during which compensatory biological mechanisms help maintain motor function. Understanding the underlying molecular mechanisms is essential as this phase represents a crucial therapeutic window for early intervention.

Material and methods : We investigate the muscle gene expression profiles of 10 asymptomatic carriers of ALS-associated mutations (8 carriers of C9ORF72 gene expansions and 2 carriers of SOD1 gene mutations) by RNA-seq. Then we applied advanced bioinformatics analyses to identify the most significant gene clusters involved in the dysregulation of the muscle transcriptome and to develop a pathophysiological model for classifying asymptomatic carriers of ALS-associated genes based on their muscle gene expression profiles.

Results : Specific gene expression profiles were observed in individuals carrying mutations in genes associated with ALS prior to any change in biomarkers predictive of phenotypic conversion and before disease onset. We identified that genes belonging to the two most influential gene groups were linked to the insulin signaling pathway, the thermogenesis pathway, the AMPK signaling pathway, and the Krebs cycle. These pathways are the primary factors contributing to the dysregulation of the muscle transcriptome.

Our findings as a whole confirm that this metabolic reprogramming gradually takes place in skeletal muscle leading up to phenotypic conversion. This metabolic change is characterized by a gradual increase in the expression of SREBF1, which encodes SREPB1, the key transcriptional regulator of lipid synthesis, alongside the gradual activation of the AMPK and insulin signaling pathways. Furthermore, our results suggest that in the muscle of individuals with ALS mutations, the presymptomatic stage is characterized by a gradual increase in the oxidative capacity of muscle fibers and in fatty acid metabolism, followed by a decline in mitochondrial oxidative phosphorylation as phenoconversion approaches.

Conclusion : The identification of metabolic reprogramming in muscle tissue as early as the presymptomatic stage of ALS suggests its early involvement in disease progression and paves the way for the development of therapeutic strategies targeting muscle metabolism.

SESSION POSTERS 1 - 126

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Nesprin-1 mutations trigger nuclear envelope deformations in muscle cells

Nesprin-1 mutations are described to lead to EDMD-like phenotype in patients. Nesprin-1 is one of the largest protein in cells but a smaller isoform is expressed specifically during myogenesis and we have found it to be required for the relocalization of the centrosomal proteins to the nuclear envelope. Its absence or mutation is associated with impaired nucleo-cytoskeletal connections and nuclear mispositioning. In short, the presence of Nesprin-1 at the nuclear envelope is determinant for the transmission of forces from the microtubules to the nuclear lamina. We have previously shown that disrupting this connection was beneficial in LMNAKO hearts where nuclei are softer. To further understand Nesprin-1 implication in nuclear shape and subsequent related diseases, we performed expansion microscopy on differentiated muscle cells and found that Nesprin-1 pathological mutations lead to an accumulation of nuclear tubular invaginations spanning the whole nucleus in myotubes. These tubules, thought to be nucleoplasmic reticulum-like structures, with a lumen inferior to 200nm, contains cytoplasmic proteins, cytoskeletons and nuclear pores. In patients biopsies, we were able to detect similar tubules in fibers nuclei. Our hypothesis suggests that disruption of the nucleo-cytoskeleton connection, due to Nesprin-1 mutations, and the subsequent imbalance of mechanical forces on the nuclear envelope, can trigger nuclear deformations.

SESSION POSTERS 1 - 129

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Distinct slow-to-fast contractile transcriptional remodelling in the mouse soleus and gastrocnemius muscles after 30 days of hindlimb unloading

Microgravity exposes astronauts to skeletal muscle deconditioning, characterized by loss of mass and strength. Because muscles differ in fiber-type composition, functional role, and motor innervation pattern, they exhibit distinct adaptative responses to unloading. Here, we investigated the expression of genes encoding slow and fast contractile protein isoforms in the slow oxidative soleus muscle and the fast glycolytic gastrocnemius muscle of mice submitted to 30 days of hindlimb unloading (HU), an Earth-based model of simulated microgravity.

Thirty-six male C57BL/6J mice were assigned to a control group (CONT) or to 30 days of HU. Soleus (n=9 CONT, n=10 HU) and gastrocnemius (n=10 CONT, n=7 HU) muscles were collected. mRNA levels of genes encoding slow and fast isoforms of myosin heavy chains (Myh1, myh4, Myh7), troponin (Tnnc1, Tnni2, Tnnt1, Tnnt2, Tnnt3) and tropomyosin (Tpm1, Tpm2) were measured by RT-qPCR. The relative distribution of myosin heavy chain (MHC) proteins isoforms, MHC I, MHC IIA, and MHC IIB, were also determined.

While HU induced a comparable loss of muscle mass in gastrocnemius (-28%) and soleus (-31%) ($P<0.0001$), the contractile transcriptional profiles were radically distinct. In the gastrocnemius muscle, changes were limited to significant decreases in the expression of fast isoforms Myh2, Tnni2 and Tpm2. By contrast, the soleus muscle exhibited coordinated contractile remodelling with decreased expression of slow isoforms (Myh7, Tnnc1, Tnnt1, Tpm2) and increased expression of fast-associated isoforms (Myh1, Myh4, Tnni2, Tnnt3, Tpm1). Consistent with this, MHC IIB protein composition shifted toward faster isoforms in the soleus muscle, whereas MHC isoform proportions remained unchanged in the gastrocnemius muscle.

Therefore, despite comparable decrease in muscle mass of the gastrocnemius and soleus muscles, HU elicits a slow-to-fast profile shift only in the soleus muscle, indicating that the magnitude of atrophy and the regulation of fiber-type identity are at least partly governed by distinct mechanisms. Differences in habitual antigravity recruitment and motor innervation may contribute to these divergent responses, although their respective roles remain to be established.

SESSION POSTERS 1 - 132

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Furan fatty acid supplementation protects against muscle atrophy during cancer cachexia

Background and objectives: Cachexia is a multifactorial syndrome frequently observed in cancer patients, characterized by progressive weight loss, muscle atrophy, and systemic inflammation. We recently demonstrated that FuFA-F2, a naturally occurring lipid found in various foods, increases muscle mass in different metabolic contexts (1-3). Here, we investigated whether FuFA-F2 supplementation could prevent tumor-induced muscle wasting and preserve skeletal muscle integrity during cancer cachexia.

Methods: In vitro, C2C12 myotubes were exposed to TNFα and IFNγ to mimic cachectic conditions, and the effects of FuFA-F2 on myotube morphology were assessed. In vivo, cancer cachexia was induced by subcutaneous injection of C26 adenocarcinoma cells into male CD2F1 mice. Three groups were compared: non-grafted control mice, untreated C26 tumor-bearing mice, and C26 tumor-bearing mice orally supplemented with FuFA-F2 (13 mg/kg/day) for 14 days.

Results: In C2C12 myotubes, TNFα and IFNγ exposure reduced myotube area, whereas FuFA-F2 treatment prevented this atrophy and restored myotube area to control levels. In vivo, FuFA-F2 supplementation prevented muscle wasting in C26 tumor-bearing mice without affecting tumor growth or the loss of white adipose tissue. After 14 days, hindlimb muscle weight was reduced by 22% in C26 mice compared with controls, whereas muscle weight in FuFA-F2-treated mice was not significantly different from controls. Consistently, spontaneous wheel activity was markedly reduced in C26 mice during the final four days, whereas FuFA-F2-treated mice maintained activity levels closer to those of controls. RNA-seq analysis revealed extensive transcriptional reprogramming of skeletal muscle in response to C26 tumor growth, with 5,465 differentially expressed genes (DEGs) between Control and C26 mice. FuFA-F2 substantially attenuated this response, with only 366 DEGs between Control and C26 + FuFA-F2 mice, and PCA showed a transcriptomic profile closer to controls. Tumor-induced alterations involved pathways related to proteostasis, inflammation, and tissue remodeling, which were largely prevented or attenuated by FuFA-F2. Consistent with these findings, FuFA-F2 prevented the induction of Myostatin, Activin A, MAFbx and MuRF1, and attenuated muscle fibrosis and local inflammation.

Conclusions: These findings demonstrate that FuFA-F2 preserves skeletal muscle mass and function in the C26 model of cancer cachexia despite ongoing tumor progression.

SESSION POSTERS 1 - 135*

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STMN2, a novel player in AChR clustering at the neuromuscular junction

The neuromuscular junction is a highly specialized synapse in which the postsynaptic membrane is characterized by dense clusters of acetylcholine receptors (AchR). The formation and maintenance of this postsynaptic structure are largely mediated by the muscle-specific kinase (MuSK).
Targeted deletion of the Wnt-binding cysteine-rich domain of MuSK in a mouse model (MuSKΔCRD) results not only in a phenotype reminiscent of congenital myasthenic syndromes but also in upregulation of genes implicated in axonal growth and nerve-muscle target recognition.
Among these genes, is STMN2 a protein previously described in neurons, where it regulates microtubule dynamics and thereby supports axonal growth and regeneration
Our preliminary findings indicate that STMN2 is enriched at the neuromuscular junction and also contributes to the clustering of synaptic acetylcholine receptors.
Mice Stmn2 muscle specific knock-down show an altered NMJ maintenance by promoting AchR anchoring at the postsynaptic membrane.
Altogether, our data provide insight into mecanisms of NMJ formation and maintenance.

SESSION POSTERS 1 - 138

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Link between primate-specific histone variant deposition and FSHD severity

Facioscapulohumeral muscular dystrophy (FSHD) is caused by the aberrant expression of the transcription factor DUX4, which results in the activation of a cytotoxic transcriptional program deleterious to the cell. However, DUX4 expression in FSHD muscle is transient, raising the question of how ponctual DUX4 activity contributes to the persistent molecular and pathological features of the disease. DUX4 induces the expression of the primate-specific histone variants H3.X and H3.Y genes, which in turn are preferentially deposited at DUX4 target genes loci. Because H3.X/Y incorporation into gene bodies is associated with active transcription and maintenance of a permissive chromatin environment, we hypothesize that transient DUX4 activation may establish an epigenetic memory through H3.X/Y deposition, sustaining the DUX4 transcriptional program after DUX4 expression has ceased.

To investigate this hypothesis, we are using a DUX4-inducible myoblast in vitro model to reproduce transient DUX4 activation and characterize its consequences on cellular and molecular phenotypes. Preliminary experiments validated the model and determined the persistence of DUX4-dependent changes following DUX4 withdrawal. We will then test whether interfering with H3.X/Y deposition during DUX4 activation affects the persistence of DUX4 target gene expression and DUX4-dependent cellular phenotypes.

In parallel, because FSHD muscle pathology is characterized by fibrosis and fatty infiltration, we are investigating whether muscle-resident mesenchymal cells may contribute to disease progression. We are performing a comparative analysis of the transcriptomic profiles of FSHD patient-derived and control fibroblast cell lines to identify disease-associated cellular pathways. Finally, single-nucleus CUT&Tag sequencing of patient-derived muscle biopsies will be used to determine the distribution of H3.X/Y deposition across muscle and mesenchymal cell populations and to investigate its potential association with disease severity.

Together, this project aims to determine whether transient DUX4 activation can leave an epigenetic signature that persists beyond DUX4 expression and contributes to the molecular phenotype of FSHD.

SESSION POSTERS 1 - 141*

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Long-term muscle regeneration impairment by whole-body irradiation

Scenarios involving radio-nuclear threats are among the military's current biomedical priorities. As muscle injuries are common in conflict zones, their co-occurrence with irradiation could be a significant concern. Although skeletal muscle has a high regenerative capacity, this could be impaired in such a context. This study therefore investigates the detrimental effect of total body irradiation on muscle regeneration following injury.
We used a rat model of radiocombined injury, involving a localized muscle injury (notexin into the soleus muscle) and total body irradiation (TBI, 8 Gy of Cobalt-60 gamma rays). An irradiated group (without injury) confirmed the presence of a hematopoietic syndrome (transient pancytopenia) and moderate mortality. Clinical assessments were conducted 63 days after post-injury (DPI). Blood and muscle samples were collected at various time points and subjected to histological and transcriptomic analyses. The results for the radiocombined group were then compared with those for two other groups: one uninjured (the control group) and one injured (but not irradiated).
Following irradiation without injury, Pax7 gene expression decreased by day 4 (-67% compared to the control group) but the number of satellite cells (Pax7+) remained unchanged. Stromal cells were also affected, with PDGFa expression reduced by 59% compared to control animals.
In the radiocombined group, the number of Pax7+ cells did not appear to increase at 4 DPI as was observed in the injured group. At 63 DPI, there was a significant reduction in muscle mass (-24%) and muscle fiber diameter (-34%) compared to injured animals. The number of centronucleated myofibers was also reduced (14% vs 35%), alongside the persistence of embryonic myofibers with aberrant Myf5 and MyoG gene expression. There was a tendency for the quantity of the extracellular matrix to increase with persistent infiltration of macrophages overexpressing CD206 markers at 63 DPI.
This preclinical model demonstrates that TBI impaired muscle regeneration in the long term. This appears to be due to a local effect on muscle stem cells and their microenvironment, which is potentially combined with the systemic alterations induced by the hematological syndrome. Further analyses are ongoing to describe the impairment of the myogenic, stromal and immune compartments in more detail. This will help to adapt the long-term medical management of muscle resulting from exposure to irradiation.

SESSION POSTERS 1 - 144

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Impact cardiovasculaire chez les patients atteints de myasthénie en France : une étude rétrospective à partir de la base de données de l'Assurance Maladie française

Contexte: La myasthénie (MG) est souvent associée à des comorbidités, notamment des maladies cardiovasculaires (CV) et des facteurs de risque CV (FRCV). Certains traitements immunomodulateurs de la myasthénie peuvent augmenter le fardeau cardiovasculaire en exacerbant les FRCV tels que le diabète, l'hypertension ou l'hyperlipidémie. Cette étude rétrospective a évalué le fardeau CV chez les patients myasthéniques en France.

Méthodes: Une recherche dans la base de données de l'Assurance Maladie a identifié des patients âgés de ⩾18 ans avec ⩾1 demande de remboursement liée à la MG entre 2019 et 2020. Les FRCV et les comorbidités CV au sein de cette cohorte ont été évalués pour la même période de 2 ans sur la base des demandes de remboursement avec les codes CIM-10 associés.

Résultats: 5210 patients atteints de MG ont été identifiés (âge moyen 59,6 ans; 55,3% femmes; 62,5% sous corticoïdes). La plupart des patients (53,2%) présentaient ⩾1 FRCV (1–2, 39,5%; ⩾3, 13,6%), le plus souvent l'hypertension, le diabète de type 2, l'obésité, la fibrillation auriculaire et l'hyperlipidémie. Par groupe d'âge, 26,9%, 49,1% et 67,1% des patients âgés respectivement de 18-40 ans, de 40-65 ans et de plus de 65 ans présentaient ⩾1 FRCV. Le nombre de cas d'hypertension, de diabète de type 2, de fibrillation auriculaire et d'hyperlipidémie ont également augmenté avec l'âge. 17,3% des patients présentaient ⩾1 comorbidités CV (1–2, 15,6% ; ⩾3, 1,6%), le plus souvent une cardiopathie ischémique chronique, une insuffisance cardiaque, une athérosclérose/artériopathie périphérique et un infarctus aigu du myocarde. La présence de comorbidités CV a augmenté dans toutes les catégories d'âge (18-40 ans, 1,8%; >40-65 ans, 12,9%; >65 ans, 27,2%).

Conclusion: Une gestion des risques CV est nécessaire chez les patients atteints de MG, notamment une prudence accrue quant à l'utilisation de traitements spécifiques de la MG susceptibles d'exacerber les FRCV.

SESSION POSTERS 1 - 147

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Releasing the Brake on Fast Fibers: Sortilin Inhibition Unlocks Type IIB Muscle Growth

Background: Skeletal muscle fibers respond unequally to mechanical loading. Type I and IIA fibers readily hypertrophy, whereas type IIB glycolytic fibers resist growth despite abundant anabolic receptors. How fiber-specific myokine signaling contributes to this difference remains unknown.

Methods: We analyzed single-nucleus RNA-seq data from mouse plantaris muscles after 7 and 21 days of compensatory overload to observe sortilin surexpression in Myh4 nuclei. Strated from that, overloaded mice were treated with the sortilin inhibitor AF38469 (0.005 g/kg/day, days 3–13), and fiber typing and morphometry were performed using FLASH. A second snRNA-seq dataset was generated from treated overloaded muscles, complemented by SDH staining and myonuclear counts.

Results: Myokine expression was fiber type-specific and remodeled by overload. Progranulin (Grn) was upregulated in all fiber types at 7 days. In contrast, sortilin (Sort1), which mediates progranulin lysosomal clearance, was expressed almost exclusively in type IIB nuclei at 7 and 21 days. AF38469 increased overall hypertrophy, driven by significant growth of type IIB fibers that was absent in controls, and attenuated the fast-to-slow fiber type shift. Under inhibition, Myh4 nuclei upregulated genes for ribosomes, extracellular matrix remodeling and mitochondrial biogenesis. These changes were accompanied by huge IIB fibers, more SDH-positive IIB fibers and increased myonuclear accretion in this fiber type.

Conclusions: Selective sortilin expression in type IIB fibers limits local progranulin availability and restrains their growth. Sortilin inhibition releases a coordinated anabolic, structural and oxidative program in fast glycolytic fibers. The progranulin–sortilin axis is therefore a promising target in conditions of anabolic resistance such as sarcopenia and cachexia.

SESSION POSTERS 1 - 150*

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Orai3 regulates the activation and proliferation of human skeletal muscle stem cells in vitro

Skeletal muscle repair and maintenance rely primarily on the activation of precursor cells, known as muscle stem cells (MuSC). Upon activation, 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 maintain long-term regenerative capacity. Understanding the molecular process that governs the activation and self-renewal of human MuSC is crucial, as any dysfunction can negatively affect muscle regeneration in both aging and muscle-related diseases.

Our work used an in vitro model of human primary muscle cells to study the serum-induced activation of stem cell-like cells (known as reserve cells, RC), and the proliferation of myoblasts. We found that downregulation of the calcium channel Orai3 significantly decreases RC activation and myoblast proliferation. Moreover, Orai3 knockdown alters myogenic progression by increasing the proportion of myoblasts committed to myotube formation. These findings reveal an unexpected role for Orai3 in balancing proliferation and differentiation during human myogenesis. Ongoing investigations are aimed at identifying the mechanisms underlying the reduced proliferative capacity observed upon Orai3 depletion, with particular focus on apoptosis, cellular senescence, and premature differentiation. Altogether, our results suggest that Orai3 acts as a critical regulator of muscle stem cell fate decisions and may represent a key determinant of skeletal muscle regenerative potential.

SESSION POSTERS 1 - 153

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Phase 1 Interim Results Evaluating the Safety, Tolerability, Pharmacokinetics, and Exploratory Efficacy of Salanersen for Spinal Muscular Atrophy (SMA)

Salanersen is a novel, intrathecally administered antisense oligonucleotide in development for SMA. Salanersen corrects splicing of SMN2 pre-mRNA by binding to a region also targeted by nusinersen and is designed to increase SMN protein. Salanersen has a new backbone chemistry that leads to high potency, enabling the potential for high efficacy with once yearly dosing. This Phase 1 study

(NCT05575011/EU CT 2023-505643-39) is evaluating the safety, tolerability, pharmacokinetics (PK), and exploratory efficacy of salanersen.

Part B evaluates open-label (40 mg or 80 mg) salanersen in pediatric participants (aged 0.5–12 years) with SMA previously treated with IV onasemnogene abeparvovec and suboptimal clinical status. Study objectives are to evaluate the safety/tolerability (primary) and PK (secondary) of salanersen. Exploratory objectives include assessment of neurofilament levels, WHO motor milestones, and motor function scales. An interim analysis was performed once all participants had completed at least 1 year of follow-up.

Salanersen was generally well tolerated at the 40 mg and 80 mg dose levels. In participants with elevated baseline (BL) plasma NfL levels, salanersen treatment was associated with a 75% reduction by Day 180, which was sustained over time. Of the 24 participants with 1-year follow-up available, 12 (50%) achieved new WHO motor milestones, many of which were unexpected based on BL functional status and time on previous treatment. Younger participants aged 0.5 to <2 years (n=4 in each dose cohort) showed improvement in HINE-2 total score (mean 6.8 and 7.7-point improvement in the 40 mg and 80 mg dose cohorts, respectively) and CHOP-INTEND total score (mean 4.5 and 10.3-point improvement in the 40 mg and 80 mg dose cohorts, respectively) from BL to Day 360. HFMSE and RULM were assessed in older participants aged 2–12 years (n=8 in each dose cohort); improvement in total scores from BL to Day 360 was observed in 9/16 participants (56%) and 11/15 participants (73%), respectively.

Salanersen 40 mg and 80 mg were generally well tolerated. While the small sample size and heterogeneity in the study population are limiting, the magnitude and consistency of changes observed across all efficacy outcomes measures suggest a clinically relevant impact of salanersen in participants with SMA. The efficacy and safety of salanersen 80 mg is now being evaluated in Phase 3 studies (STELLAR-1, STELLAR-2, SOLAR) across a broad population with SMA.

SESSION POSTERS 2

Mercredi 18 Novembre
19h30 - 20h30

LISTE POSTERS - SESSION 2

Mercredi 18 novembre de 19h30 à 20h30

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LISTE POSTERS - SESSION 2

Mercredi 18 novembre de 19h30 à 20h30

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Efgartigimod chez les patients atteints de myasthénie généralisée et négatifs pour les anticorps anti-récepteurs de l'acétylcholine : Résultats initiaux de l'étude ADAPT SERON

Contexte: Environ 15 à 20% des patients atteints de myasthénie généralisée (MG) sont séronégatifs pour les anticorps anti-RACh, incluant les patients anti-MuSK+, anti-LRP4+ et ceux qui ne présentent pas d'anticorps identifiables contre le RACh, le MuSK et le LRP4 (triple séronégatifs). Il existe un besoin non satisfait de traitements approuvés pour cette population. L'efgartigimod est un fragment Fc d'anticorps IgG1 humain réduisant les taux d'IgG dont les auto-anticorps pathogènes, par blocage du récepteur Fc néonatal. L'étude de phase 3 ADAPT SERON évalue l'efficacité et la tolérance de l'efgartigimod par voie intraveineuse (IV) chez les adultes atteints de MG séronégatifs pour les anti-RACh.

Méthodes: Le diagnostic de MG a été confirmé par un comité d'adjudication. Dans la partie A, en double aveugle contre placebo, les participants adultes ont été randomisés 1:1 pour recevoir 1 perfusion par semaine pendant 4 semaines de 10 mg/kg d'efgartigimod IV ou de placebo, suivies de 5 semaines de suivi. La partie B, une extension en ouvert, est en cours (⩽2 ans).

Résultats: Les résultats incluent 119 participants : 40 anti-MuSK+, 6 anti-LRP4+ et 73 triple séronégatifs; 58 ont reçu l'efgartigimod IV et 61 le placebo. Dans la population globale, la variation du MG-ADL entre l'inclusion et la semaine 4, critère d'évaluation principal, différait significativement (p=0,007) entre l'efgartigimod IV (moyenne ajustée par rapport à la valeur à l'inclusion [IC à 90 %]: −3,35 [−3,98 à −2,72]) et le placebo (1,90 [−2,51 à −1,28]). Des améliorations supplémentaires du MG-ADL ont été observées dans la partie B au cours des cycles de traitement suivants dans les trois sous-groupes. L'efgartigimod IV a été bien toléré sans nouveaux signaux de tolérance. Des analyses complémentaires seront présentées.

Conclusion: Une amélioration statistiquement significative du MG-ADL a été observée par rapport au placebo avec un changement cliniquement significatif. L'efgartigimod IV a été bien toléré.

SESSION POSTERS 2 - 8

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Impact of baseline characteristics on apitegromab efficacy in patients with spinal muscular atrophy

SMA is a neuromuscular disease resulting in a lack of SMN protein, leading to irreversible motor neuron degeneration and progressive skeletal muscle atrophy and weakness. Treatments are available to increase SMN protein levels and stop motor neuron degeneration but have few effects on residual muscle atrophy and weakness. A muscle-targeted treatment may address these unmet needs. Apitegromab is a muscle-targeted treatment for SMA that selectively inhibits activation of myostatin, a negative regulator of muscle growth, leading to increased muscle mass and improved motor function. Here we present clinical evidence supporting the efficacy of apitegromab across broad populations of patients living with SMA.

The Phase 3 SAPPHIRE (NCT05156320) and Phase 2 TOPAZ (NCT03921528) studies assessed the baseline and post-treatment latent myostatin concentrations and clinical efficacy of apitegromab, according to functional status (HFMSE score) and age.

In SAPPHIRE (N=188; nonambulatory, aged 2-21 years), baseline latent myostatin concentrations were similar regardless of disease severity (HFMSE score) or age (2-12 vs 13-21 years). Participants were grouped into tertiles by baseline latent myostatin concentration or HFMSE score to assess apitegromab outcomes across disease severity. Across all baseline latent myostatin and HFMSE tertiles, apitegromab increased total latent myostatin through week 52; HFMSE score changes from baseline to week 52 favored apitegromab vs placebo, with LSM differences (95% CI) based on baseline latent myostatin tertiles of 1.2 (-0.86, 3.20), 2.5 (-0.29, 5.21), and 1.5 (-1.01, 3.96) points and LSM differences (95% CI) based on baseline HFMSE tertiles of 1.5 (-0.06, 3.14), 1.2 (-1.71, 4.18), and 2.8 (0.14, 5.36). Furthermore, in TOPAZ, ambulatory participants (n=12), total latent myostatin concentrations were sustained over the course of 4 years and associated with functional stability (RHS), with a mean (95% CI) change from baseline of -0.2 (-4.3, 3.9) points.

Effective target engagement was observed, regardless of age, in SAPPHIRE. Changes from baseline to week 52 in motor function (HFMSE) favored apitegromab across age groups; LSM differences (95% CI) vs placebo were 1.8 (0.3, 3.32) and 1.8 (-1.06, 4.57) points for the 2-12- and 13-21-year-old age groups, respectively.

These results demonstrate that apitegromab efficacy is broadly applicable across all patients living with SMA, regardless of disease severity or age.

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Efficacité clinique durable et tolérance à long terme de l'efgartigimod intraveineux dans le traitement de la myasthénie généralisée : ADAPT NXT Partie B

Contexte: La tolérance et l'efficacité de l'efgartigimod, fragment Fc d'IgG1 humaine qui bloque le FcRn, étaient bonnes après son administration en cycles fixes ou toutes les deux semaines (Q2W) chez des participants atteints de myasthénie généralisée au cours de la partie A de l'étude de phase 3b ADAPT NXT (NCT04980495). La partie B de l'étude a étudié l'efficacité et la tolérance à long terme de l'efgartigimod chez les participants recevant une posologie Q2W ou toutes les trois semaines (Q3W).

Méthodes: Dans la partie A, les participants randomisés (ratio 3:1) recevaient une posologie Q2W ou en cycles fixes de 10 mg/kg d'efgartigimod pendant 21 semaines. La posologie en cycles fixes impliquait 4 perfusions hebdomadaires suivies d'une période inter-traitement de 4 semaines. Dans la partie B, tous les participants ont reçu une posologie Q2W pendant l'extension de 105 semaines. Les participants pouvaient passer à une posologie Q3W, en fonction de l'évaluation clinique.

Résultats: 65/69 participants de la partie A [94,2%] ont poursuivi le traitement dans la partie B; 57,8% (37/64) sont passés à une posologie Q3W et 59,5% (22/37) sont restés sous la posologie Q3W. La durée moyenne du traitement Q3W était de 382 jours. Les améliorations moyennes du score MG-ADL se sont maintenues jusqu'à la semaine 126. 81,2% (56/69) des participants ont connu une amélioration du score MG-ADL de≥5 points, et 56,5% (39/69) ont atteint une expression minimale des symptômes (MSE; score MG-ADL, 0-1) à un moment au cours de l'étude. Dans la partie B, 51,6% (32/62) ont atteint la MSE. L'efgartigimod a été bien toléré quel que soit le schéma posologique. Les données issues de l'analyse finale de l'étude seront présentées.

Conclusion: L'efgartigimod a montré des bénéfices durables chez les participants atteints de MG sous traitement à long terme, tout en restant bien toléré quel que soit le schéma posologique.

SESSION POSTERS 2 - 20

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Quantitative super-resolution imaging and deep learning reveal early mitochondrial network remodeling and altered mitochondria-lysosome interactions in Pompe disease muscle

Pompe disease (glycogen storage disease type II) is an autosomal recessive lysosomal storage disorder caused by acid α-glucosidase deficiency, leading to lysosomal glycogen accumulation, autophagosome buildup, and defective autophagic flux. Mitochondrial abnormalities, traditionally described by electron microscopy as paracrystalline inclusions, cristae loss, and swollen structures, have long been considered secondary consequences of lysosomal dysfunction. However, the spatial organization, organelle crosstalk, and fiber-type-specific progression of these alterations in skeletal muscle remain poorly understood. We combined super-resolution image scanning microscopy with deep learning-based segmentation to quantitatively assess mitochondrial and lysosomal remodeling, and their direct physical interactions, in Pompe disease ($Gaa^{-/-}$) mice. Organelles were analyzed at pre-symptomatic (1 month) and symptomatic (4 months) stages across different muscle types (Soleus, Gastrocnemius), fiber types, and subcellular regions (subsarcolemmal, intermyofibrillar). Mitochondrial network structure was altered as early as 1 month of age, whereas density changes became widespread at 4 months in a fiber-type- and region-dependent manner. Alongside early lysosomal enlargement and late-stage spatial clustering, we observed a progressive, region-specific increase in mitochondria-lysosome contacts, most pronounced in the intermyofibrillar region. This quantitative framework provides a powerful tool for monitoring pathophysiology and evaluating therapeutic interventions in Pompe disease.

SESSION POSTERS 2 - 26

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Sex-related differences in a mouse model of Dnm2-related autosomal dominant centronuclear myopathy

Dynamin-2 (DNM2)-related centronuclear myopathy (CNM) is a congenital neuromuscular disorder characterized by impaired postnatal muscle growth and muscle weakness. Although disease severity varies among individuals, the contribution of biological sex to disease progression remains unknown. We hypothesized that biological sex modifies disease severity through sex-specific molecular adaptations that influence skeletal muscle homeostasis.

To determine the impact of biological sex on disease progression and to identify the mechanisms underlying sex-dependent differences in DNM2-related CNM, functional, histological, biochemical analysis, and high-throughput proteomic analyses were performed on the tibialis anterior muscles from one- and two-month-old male and female Knockin-dnm2R465W/+ (KI) mice. To investigate the role of estrogen, disease progression was further assessed following ovariectomy in KI females, and estradiol supplementation in KI males.

KI males developed significantly greater muscle growth impairment, force deficit, and histopathological abnormalities than KI females. Proteomic analysis revealed marked sex differences, with males exhibiting extensive mitochondrial remodeling affecting oxidative phosphorylation complexes and mitochondrial architecture, whereas females largely preserved their mitochondrial proteome. Female KI muscles also showed selective enrichment of ribosomal proteins, together with enhanced antioxidant response, including increased glucose-6-phosphate dehydrogenase activity and upregulation of glutathione-related enzymes, and improved glutathione redox homeostasis. Notably, estradiol supplementation increased muscle mass and improved muscle histopathology in KI males.

We demonstrate that biological sex is a critical determinant of disease progression in DNM2-related CNM. More broadly, our findings underscore the importance of considering biological sex to better understand the pathophysiology of neuromuscular diseases and to guide the development of therapeutic strategies.

SESSION POSTERS 2 - 32

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Regenerative Adipose Stromal Cells in Muscle Injury: Cell-Cell Communication and Age-Related Alterations

Skeletal muscle regeneration relies on coordinated interactions between stromal, immune and vascular cells, yet the contribution of adipose stromal cells (ASCs) to this process remains incompletely understood. We recently identified a distinct subpopulation of subcutaneous ASCs that is mobilized following muscle injury, migrates into damaged muscle and contributes to tissue regeneration. Building on this observation, we sought to better characterize the functional properties of these cells and the signaling mechanisms underlying their regenerative potential.

Using single-cell transcriptomic data and complementary cell–cell communication approaches, including CellChat and NicheNet, we investigated the signals received and emitted by this ASC subpopulation upon muscle injury. Particular attention was given to pathways related to immune regulation, inflammatory mediators and cell migration, in order to identify communication programs that could account for the selective mobilization of these cells and their ability to influence muscle repair. These analyses highlighted specific immune- and migration-associated signaling networks potentially contributing to their regenerative phenotype.

We next investigated whether this regenerative ASC state is affected by aging. Analysis of independent public single-cell datasets revealed age-associated alterations in the corresponding ASC populations and their molecular programs, including pathways involved in intercellular communication and regenerative functions. Together, these results provide new insight into the functional specialization of regenerative ASCs and suggest that age-dependent remodeling of their signaling properties may contribute to impaired tissue regeneration during aging.

SESSION POSTERS 2 - 38*

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Integrating patient serum proteomics from the PROMOT study and muscle-derived omics to identify potential biomarkers and therapeutic targets in oculopharyngeal muscular dystrophy (OPMD)

Oculopharyngeal muscular dystrophy (OPMD), is a late-onset autosomal dominant neuromuscular disorder with particularly high prevalence in certain populations, including French Canadians in Quebec (1/1,000) and Israel's Bukharan Jews (1/600). It is caused by an expansion of GCN repeats in its PABPB1 coding region, leading to a longer polyalanine tract in PABPN1 protein that results in PABPN1 intranuclear aggregates. Characterized by progressive eyelid drooping, swallowing difficulties, and proximal limb weakness in advanced stages, OPMD significantly impacts quality of life and longevity. Although cell/ gene/pharmacological-based therapies are reaching the clinic, no curative treatment is currently available and the lack of validated, minimally invasive biomarkers of disease-modifying therapies limits clinical trial design. The PROMOT initiative applies a multi-omics strategy to accelerate therapeutic development, with OPMD as a flagship indication. We performed SomaScan proteomics on serum from 45 OPMD patients enrolled in a natural history study in Canada, collected at two time points (two years apart), and from 11 control individuals. We identified 64 differentially expressed circulating proteins between patients and controls, with a high presence of muscle-derived proteins in the serum of OPMD patients. The serum-signature from OPMD patients is well defined when compared to other muscle diseases and aging. The correlation analysis between the changes in the patient's serum proteomics with the disease severity, dysphagia and other clinical and phenotypes variables, allowed us to identified potential candidates for disease/treatment progress monitoring related to extracellular matrix remodelling, fibrosis and inflammation. In addition, we crossed the serum proteomics results from OPMD patients with the secretome of differentiated myotubes from control (n=4) and OPMD (n=5) human muscle cell lines to distinguish circulating changes of muscle origin from systemic responses. This approach aims to link circulating biomarkers to muscle pathology and to nominate actionable targets for OPMD.

SESSION POSTERS 2 - 44

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Open-Label Extension Analysis Shows Potential Delay in Age at Loss of Ambulation in Patients With Duchenne Muscular Dystrophy Treated With Givinostat

Givinostat is an oral histone deacetylase inhibitor that was investigated in the phase 3, randomized, double-blind, placebo-controlled EPIDYS trial, in patients with DMD aged ⩾6 years (NCT02851797). A 2021 interim analysis of an ongoing, single-arm, open-label extension (OLE; NCT03373968) showed a delay in median age at persistent loss of ambulation (LoA; permanent inability to walk independently) in givinostat-treated patients compared with a matched, natural history corticosteroid-treated external control group. This updated analysis evaluated the effect of longer-term givinostat treatment, in combination with standard-of-care corticosteroids, on LoA in patients with DMD aged ⩾6 years using two additional years of follow-up (data cutoff at 2023).

The ongoing OLE study includes patients who completed a prior phase 2 givinostat study (NCT01761292) or EPIDYS, and those screened but not randomized in EPIDYS. All patients who received ⩾1 month of givinostat in combination with corticosteroids were included. Median age at persistent LoA was calculated using Kaplan–Meier survival analysis.

Among the 225 patients analyzed, 78 experienced persistent LoA. The median (95% CI) age at persistent LoA was 17.3 (15.5-18.1) years.

This updated interim analysis evaluated LoA in patients with DMD with two additional years of data from the OLE. The results suggest that givinostat treatment combined with corticosteroids, consistently delays the onset of LoA in patients with DMD. The median age at persistent LoA was 17.3 years in OLE, compared with published estimates of 11.0-13.4 years from a meta-analysis of patients treated with corticosteroids alone. These findings suggest a delay in LoA with givinostat treatment.

SESSION POSTERS 2 - 50

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FLASH: Innovative Integrated Enzymatic- Fluorescent Labeling for Automated Muscle Fiber Typing, Metabolic and Morphometric Analysis

Background: Skeletal muscle is a dynamic tissue capable of structural and metabolic remodeling in response to physiological and pathological stimuli. These adaptations are central to understanding the mechanisms underlying conditions such as genetic myopathies, cancer, aging, and recovery from injury. Muscle fiber characterization—assessing fiber type, size, and metabolic profile—is essential for such studies. However, conventional histological methods often rely on serial tissue sections and multiple staining protocols, which are time-consuming, require significant biological material, and introduce methodological bias.

Methods: We developed FLASH (Fluorescence-based Labeling for Assessing Skeletal muscle Histology), a novel methodology combining enzymatic (SDH or GPDH) and quadruple fluorescent labeling (Laminin, MYH4, MYH2, MYH7) on a single muscle section. The resulting images were analyzed using a custom macro in Fiji/ImageJ, integrating the Cellpose segmentation algorithm. This automated pipeline detects individual muscle fibers, quantifies their cross-sectional area , identifies fiber types based on myosin isoform expression, and measures enzymatic staining intensity. Batch analysis was implemented to process entire image folders automatically. Validation was performed by comparing automated fiber detection with expert manual segmentation using correlation analysis and Bland-Altman plots.

Results: The FLASH method allowed simultaneous assessment of both contractile and metabolic properties within individual fibers on the same section, removing the need for serial cuts. The automated image analysis achieved high accuracy in fiber detection ($r > 0.95$ compared to manual annotation) and produced consistent CSA and fiber-type quantification, even under suboptimal staining conditions. The macro enabled significant time savings by automating the complete analysis workflow, including ROI generation and Excel data export for each image.

Conclusions: FLASH provides an efficient and robust tool for high-throughput skeletal muscle histology. By combining enzymatic and fluorescent co-labeling with machine learning-based image analysis, this method improves reproductibility, reduces experimental complexity, and minimizes user bias. FLASH is particularly well-suited for large-scale or longitudinal studies investigating muscle adaptation in health andisease.

SESSION POSTERS 2 - 56

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Expanding the Spectrum of DAG1-Related Myopathy: A Dominantly Inherited Missense Variant in a Romanian Family

Biallelic pathogenic variants in DAG1 cause a spectrum of dystroglycanopathies, including limb-girdle muscular dystrophy R16 (LGMD R16). More recently, heterozygous loss-of-function variants have been associated with hyperCKemia and mild muscular manifestations. We report a family with a dominantly inherited mild-moderate muscular phenotype associated with a heterozygous missense DAG1 variant.

Four affected members of a Romanian family, a father and his three sons, underwent clinical and genetic evaluation. Muscle biopsies were available from the father and two sons. Alpha-dystroglycan glycosylation was assessed in muscle (two patients), and atomic force microscopy (AFM) was performed on patient-derived myoblasts (one patient).

The three children presented with exercise-induced fatigability and myalgia, associated with markedly elevated serum creatine kinase levels, reaching >10,000 U/L in the eldest son. Clinical presentation was mild-moderate, with a normal neurologic examination and no significant cardiorespiratory involvement. Their father had longstanding mild lower-limb myalgia with normal CK levels. The intermittent character of the myalgias, along with the eosinophil-rich inflammatory features observed on the muscle biopsy of the eldest son, were suggestive for a myositis diagnosis. Genetic investigations identified the heterozygous DAG1 variant NM_004393.6:c.887G>A, NP_004384.5:p.(Gly296Asp), segregating with the phenotype in all four affected family members. Muscle biopsies (father and two sons) showed mild, nonspecific myopathic abnormalities, including fiber-size variability, internalized nuclei and regenerating fibers. Reduced alpha-dystroglycan glycosylation was demonstrated in muscle from two affected individuals. Furthermore, AFM analysis of patient-derived myoblasts from the father showed markedly reduced cellular stiffness compared with controls.

These findings expand the inheritance and phenotypic spectrum of DAG1-related muscular disease and support the pathogenicity of the p.(Gly296Asp) variant. We show that, in addition to heterozygous loss-of-function variants, missense DAG1 variants may cause a dominantly inherited, relatively mild muscular phenotype.

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Highlights and key learnings from 15 years of the TREAT-NMD Advisory Committee for Therapeutics (TACT): A multi-disciplinary, independent expert approach to improve translational research in NMDs at all stages of the pipeline

The TREAT-NMD Advisory Committee for Therapeutics (TACT) provides academic and industry applicants involved in therapy development in the neuromuscular disease (NMD) space with constructive, multidisciplinary expert advice in order to help derisk NMD drug development and avoid potential therapies entering clinical trials prematurely and to improve trial design. The ultimate goal of TACT is to reduce the risk of type 1 errors (concluding a treatment is effective, while it is not), type 2 errors (concluding a treatment is not effective, while it is), or risks of questions and regulatory rejections later on in development. TACT celebrated its 15th birthday in 2024. From 2009–2024 TACT reviewed 90 applications, 68 from Industry and 22 from Academia. This perspective paper summarizes how TACT has evolved from its initiation. Furthermore, based on our experience, we list recurrent mistakes, such as not collecting sufficient information in pre-clinical studies, omitting wild type references in animal studies and choosing the wrong or too many outcome measures in clinical trials. By sharing common errors in preclinical and clinical trial design and providing lessons learned we aim to further improve therapy development in the NMD space

SESSION POSTERS 2 - 68*

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Myasthénie de l'enfant : expérience du service de neurologie de l'hôpital national Ignace Deen

Introduction : La myasthénie auto-immune est rare chez l'enfant, encore peu documentée en Afrique subsaharienne où l'accès aux explorations immunologiques et radiologiques est limité. Nous rapportons l'expérience du service de neurologie de l'hôpital national Ignace Deen de Conakry dans la prise en charge de la myasthénie de l'enfant, l'objectif de l'etude était de décrire les caractéristiques épidémiologiques, cliniques, paracliniques, thérapeutiques et évolutives de la myasthénie de l'enfant en contexte à ressources limitées.

Méthodes : Étude rétrospective descriptive sur 3 ans, portant sur les enfants de moins de 16 ans suivis pour myasthénie au service de neurologie de l'hôpital national Ignace Deen. Les données sociodémographiques, cliniques, électroneuromyographiques, scannographique , immunologiques, thérapeutiques et évolutives ont été colligées.

Résultats : Douze enfants ont été colligés, soit une incidence moyenne de 4 cas par an. Le sex-ratio était de 1,4 en faveur des garçons. L'âge moyen était de 8,4 ans (extrêmes 2-15 ans). Le ptosis, uni ou bilatéral et fluctuant, constituait le principal motif de consultation (75 %), associé à une diplopie (33 %) et une fatigabilité musculaire généralisée (42 %). Le délai moyen de consultation était de 4,5 mois (extrêmes 15 jours-14 mois), avec un délai diagnostique global de 11,8 mois. L'ENMG, réalisé chez 83 % des patients, objectivait un décrément significatif supérieur à 10 % chez tous les patients testés. Le scanner thoracique, réalisé chez 50 % des patients (accès limité), retrouvait une hyperplasie thymique chez 2 patients (33 %), sans thymome. Les anticorps antirécepteurs de l'acétylcholine, dosés chez 58 % des patients, étaient positifs chez 71 % d'entre eux. Les formes cliniques étaient oculaires pures (50 %), généralisées (42 %) et bulbaires (8 %). Le traitement reposait sur les anticholinestérasiques chez tous les patients, associés à une corticothérapie (33 %) et à l'azathioprine (17 %) ; les immunoglobulines et échanges plasmatiques n'étaient pas disponibles localement. Une crise myasthénique est survenue chez 17 % des patients, avec un décès (8 %).

Conclusion : La myasthénie de l'enfant à Conakry se caractérise par un retard diagnostique important et un accès restreint aux explorations immunologiques et radiologiques, imposant une adaptation du raisonnement clinique aux ressources locales et un renforcement de l'accès aux tests essentiels.
Mots-clés : myasthénie ; enfant ; Afrique subsaharie

SESSION POSTERS 2 - 74*

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Enhancing a 3D Bioprinting System for Skeletal Muscle Tissue Engineering to Generate Advanced and Reproducible Preclinical Models of Neuromuscular Diseases

3D engineered skeletal muscle tissues (eSMT) are promising alternatives to conventional in vitro models, which do not fully reproduce the cellular and structural organization, maturation, and functionality of native skeletal muscle. Moreover, these models represent an ethical and valid approach to reduce animal use while providing a powerful platform for preclinical studies.
3D eSMTs are typically composed of a combination of biomaterials and stem cells, which are assembled into three-dimensional constructs using techniques such as bulk molding and 3D bioprinting. Poly(ethylene glycol)-fibrinogen (PEG-fibrinogen, PF) is a biosynthetic, photopolymerizable hybrid matrix that possesses cell-adhesive motifs and favorable mechanical properties, making it an excellent biomaterial for 3D tissue engineering. As previously demonstrated by our group, PF can be used as a bioink for 3D bioprinting to generate highly organized 3D eSMTs. However, further optimization of the bioink formulation is required to improve the reproducibility of the bioprinting process and enhance the mechanical properties of the printed constructs.
In this work, a formulation combining PF with poly(vinyl alcohol) (PVA) and βcyclodextrin (βCD) was optimized. PVA significantly improved the printability of the bioink, whereas βCD enhanced its mechanical stability. Moreover, the addition of these components exhibited no cytotoxic effects and did not alter cell behaviour.
The new bioink substantially improved the 3D bioprinting process, ensuring high reproducibility and fidelity in replicating skeletal muscle architecture. Within the printed fibers, myoblasts aligned and differentiated into mature, functional, millimeter-long myofibers. Finally, we demonstrated that the incorporation of fibro-adipogenic progenitors (FAPs) into the bioink enhanced extracellular matrix deposition, thereby increasing the mechanical stability and long-term viability of the eSMT.
Overall, we present an advanced tissue engineering strategy for generating preclinical models that recapitulate the three-dimensional architecture and key aspects of the biological niche of human skeletal muscle.

SESSION POSTERS 2 - 80

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Genetic and Pharmacologic Inhibition of Myostatin Restores Muscle Mass in a Dynamin 2-Related Centronuclear Myopathy Mouse Model

Autosomal dominant centronuclear myopathy (ADCNM), most commonly caused by mutations in the dynamin 2 (DNM2) gene, is a rare congenital myopathy characterized by progressive muscle weakness and atrophy. We hypothesized that inhibiting myostatin, a key negative regulator of skeletal muscle mass, could counteract muscle deconditioning in ADCNM. MRI and immunohistochemical analyses showed that knockin-dnm2R465W/+ (KI) mice exhibited impaired postnatal muscle growth between 1 and 2 months of age, resulting in persistent muscle hypotrophy (-15%, $p < 0.05$). This defect was associated with a significant reduction in the number of satellite cells (-53%, $p < 0.001$ at 1 month and -68%, $p < 0.01$ at 2 months), the central accumulation of dense NADH-TR staining in more than 20% of muscle fibres, an upregulation of atrophy-related E3 ligases mRNA (Trim63 + 50%, $p < 0.001$ and +87%, $p < 0.001$; Fbxo32 + 39% $p < 0.05$ and +95%, $p < 0.001$ at 1 and 2 months of age, respectively) and impaired autophagy. Genetic deletion of myostatin in KI mice fully restored muscle mass and normalized muscle function to wild-type conditions. Pharmacological inhibition of myostatin with a soluble activin type IIB receptor fused to IgG1 Fc fragment (sActRIIB-Fc, 5 mg kg-1 twice weekly starting at 4 weeks of age for 4 weeks) also robustly restored muscle mass to wild-type values, primarily via activation of the Akt-mTOR pathway. However, this anabolic effect was transient, as muscle mass returned to baseline 5 weeks after treatment cessation. Importantly, despite increased muscle mass, sActRIIB-Fc treatment did not improve muscle force and key molecular features, including defects in the transcriptional regulation of proteostasis, mitochondrial organization and excitation-contraction coupling. These findings indicate that therapeutic strategies should not be evaluated solely based on their anabolic effects, but also on their ability to sustainably restore muscle performance notably beyond the duration of the treatment.

SESSION POSTERS 2 - 86

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Téloméropathies et atteinte musculaire : description d'une série de quatre cas

Les téloméropathies sont des maladies génétiques rares associées à un raccourcissement pathologique des télomères, responsables d'atteintes multiviscérales. Il n'y a pas d'atteinte neurologique périphérique notamment musculaire clairement documentée à ce jour. Nous rapportons quatre observations suggérant l'existence chez certains patients d'un phénotype myopathique particulier.
Étude descriptive rétrospective de quatre patients évalués au CRMNM du CHU de Bordeaux, présentant une téloméropathie confirmée ou fortement suspectée et des anomalies musculaires cliniques et paracliniques.

Résultats
Quatre patients (deux femmes, deux hommes), âgés de 17 à 47 ans, présentaient une involution graisseuse des muscles paravertébraux, prédominante au niveau lombaire ou dorsal. Trois patients présentaient également des anomalies scapulaires et/ou faciales, évoquant un phénotype facio-scapulo-huméral atypique. Une camptocormie était observée chez un patient. Les CPK étaient normales ou peu élevées. La recherche de FSHD1 était négative chez les trois patients explorés. Deux patients présentaient une variation de TERT, une patiente une variation de TERC ; le quatrième présentait un raccourcissement télomérique franc sans variant identifié en NGS à ce jour.

Discussion et conclusion
Ces observations suggèrent une possible expression musculaire des téloméropathies, caractérisée par une atteinte axiale prédominante, parfois associée à un phénotype pseudo-FSHD. Une altération de la capacité régénérative musculaire liée au raccourcissement télomérique pourrait être envisagée. Des investigations histologiques, génétiques et épigénétiques complémentaires, ainsi qu'une étude prospective multicentrique seront nécessaires pour préciser la nature, la fréquence et les mécanismes de cette association.

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Preclinical development of allele-specific silencing therapy for centronuclear myopathies

Centronuclear myopathies (CNMs) are congenital disorders characterized by muscle weakness, hypotonia, myofiber atrophy, and abnormal nuclei position. Autosomal dominant CNM (AD-CNM) is caused by pathogenic variants in DNM2, with more than 35 different mutations identified. X-linked CNM is caused by mutations in MTM1. In this form, DNM2 is abnormally upregulated, and previous studies have shown that reducing DNM2 can improve disease-related phenotypes.
We previously developed a therapy by allele-specific RNA interference (AS-RNAi) to silence the mutated DNM2 mRNA while preserving expression of the normal allele. Proof of concept was achieved in a mouse model and patient-derived fibroblasts, carrying the most frequent DNM2 mutation in CNM. To develop a more versatile strategy applicable regardless of the causative mutation, we designed allele-specific small interfering RNAs (siRNAs) targeting two frequently heterozygous non-pathogenic DNM2 single-nucleotide polymorphisms (SNPs). This approach enables controlled and allele-selective reduction of DNM2 expression.
Here, we aimed to evaluate the therapeutic potential of allele-specific DNM2 silencing in patient-derived muscle cells from both DNM2- and MTM1-related CNM. In DNM2-CNM muscle cells, we validated the efficacy and specificity of siRNAs and demonstrated improvement of disease-associated cellular defects after treatment. In MTM1 patient-derived myotubes carrying heterozygous DNM2 SNPs, we validated the efficacy and specificity of SNP-targeting siRNAs to achieve approximately 50% reduction in DNM2 mRNA and protein. Notably, siRNA also improved disease-associated cellular defects in MTM1-mutant cells, including impaired myogenic differentiation and cellular adhesion.
Overall, these results reinforce the proof of concept of the DNM2 silencing therapy by demonstrating functional benefit in a relevant patient-derived cell model and support that controlled DNM2 silencing may help alleviate key pathological features in both DNM2- and MTM1-mutant muscle cells.

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Can furan fatty acid supplementation counteract musculoskeletal disorders and improve healthy ageing?

Background and objectives
Sarcopenia and osteoarthritis are major factors in functional decline, risk of falls, disability and mortality in the elderly. In a global context of ageing populations, particularly in France, the prevalence of these diseases, which affect quality of life, is becoming a major public health issue. We recently demonstrated that FuFA-F2, a naturally occurring lipid found in various foods, increases muscle mass in different metabolic contexts, partly mimicking the effects of exercise. This study explores the potential benefits of FuFA-F2 supplementation in slowing age-related musculoskeletal disorders, and improving mobility, well-being and longevity in mice.
Methods
40 male and 40 female C57BL/6J mice aged 16 months were fed their respective diets (standard diet or standard diet enriched with 0.05% FuFA-F2/kg diet) for 6 to 10 months. Their physical performance, behavior and physiological status (lean and fat mass, well-being, behavioral test) were evaluated throughout the study. At the end, mice were euthanized and the tissues (muscles and leg joints) were collected for analysis.
Results
Our preliminary findings indicate that FuFA-F2 attenuated the decline in total body weight and fat mass in mice in both sexes. Furthermore, FuFA-F2 supplementation mitigated age-related sarcopenia, as evidenced by the preservation of muscle mass and strength in aged mice. RNA-seq analysis of skeletal muscle revealed extensive transcriptional differences between aged control mice and mice receiving FuFA-F2 supplementation, with approximately 6,000 differentially expressed genes (DEGs) in both sexes. These changes were associated with preservation of pathways involved in muscle homeostasis, including proteostasis, oxidative and lipid metabolism, and neuromuscular function. FuFA-F2 supplementation also maintained transcriptional programs associated with mitochondrial oxidative capacity and muscle integrity, consistent with its protective effects against age-related muscle wasting and functional decline. Overall, FuFA-treated mice maintained better physical condition and quality of life.
Conclusions
These results show that chronic supplementation with FuFA-F2 could help to limit age-related decline in musculoskeletal function. FuFAs could be used as a food supplement to promote healthy ageing, contributing to a solution for sarcopenia.

SESSION POSTERS 2 - 104*

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Muscle development without motoneurons: body-wide characterization of skeletal muscles in Olig2Cre/Cre mice

Innervation is required for proper growth and specialization of muscle fibers, yet the mechanisms underlying this dependence remain poorly understood. Motoneuron–myofiber dialogue is established during embryogenesis and persists throughout life through reciprocal signaling. Motoneurons release acetylcholine and agrin to promote muscle activity and postsynaptic differentiation, whereas myofibers secrete myokines, such as BDNF and neurturin, that act retrogradely on motoneurons and can reprogram their identity in the adult. However, how these neurokines and myokines shape muscle development and the pairing of motoneuron and fiber subtypes remains unclear. To define the development processes that depend on motoneurons, we used Olig2Cre/Cre mice, in which motoneuron specification fails at the progenitor stage, resulting in skeletal muscles that develop in the complete absence of somatic motor axon innervation. Olig2Cre/Cre embryos and control littermates were analyzed at E18.5 and E13.5 using. Transcriptomic analysis, immunofluorescence of limb sections and whole-mount diaphragms, analysis of isolated back muscle fibers, and bulk RNA sequencing were used to characterize transcriptional changes associated with the absence of motoneurons. These complementary approaches were used to assess myotube formation and growth, fiber-type specification, and acetylcholine receptor (AChR) prepatterning.

Bulk RNA-seq revealed a global downregulation of the myogenic program. Fiber number was strongly reduced while the satellite cell-to-fiber ratio was preserved. Some distal hindlimb muscles, such as the gastrocnemius, were greatly and significantly affected. Inflammatory genes were strongly upregulated, consistent with massive macrophage infiltration in muscle sections. Innervation-related genes were downregulated, and α-bungarotoxin staining showed that AchRs were still present but failed to be clustered. In the diaphragm, fiber number was similarly reduced, and central AChR clustering was largely lost, as in isolated back muscle fibers. Our findings help to distinguish motoneuron-dependent from intrinsic programs muscles of distinct embryonic origins. snRNA-seq and spatial transcriptomics analyses are ongoing to resolve these changes at the cellular level and identify candidate motoneuron–myofiber signals.

SESSION POSTERS 2 - 109*

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Calcium dysregulation in Duchenne Muscular Dystrophy: A predominant role for mechanosensitive channels?

Duchenne muscular dystrophy (DMD) is a severe neuromuscular disorder caused by mutations in the dystrophin gene. Loss of dystrophin compromises membrane stability and promotes chronic intracellular calcium overload, a key driver of muscle fiber degeneration. This study investigated the calcium dysregulation in human DMD myotubes, focusing on store-operated calcium entry (SOCE) and mechanosensitive calcium influx.
Experiments were performed using immortalized DMD and control muscle cell lines (MyoLine, Paris) and primary human myotubes following dystrophin knockdown, .
First, we assessed SOCE in control and DMD myotubes after 3 days of differentiation. Basal intracellular calcium levels, SOCE amplitude and slope were similar in control and DMD myotubes. Consistently, expression of the major SOCE components STIM1 and ORAI1 was unchanged. Mechanosensitive calcium entry was then examined using hypotonic shock (HS), which increases membrane tension. HS induced a sustained intracellular calcium rise in DMD myotubes that was inhibited by EGTA and Gd^{3+}, indicating extracellular calcium influx. The response was almost completely suppressed by the mechanosensitive channel inhibitor GsMTx4 and by the recently described PIEZO1 inhibitor SC-560. Although PIEZO1 mRNA expression was unchanged, dose-response experiments with the selective PIEZO1 agonist Yoda2 revealed a reduced EC50 in DMD cells, suggesting enhanced PIEZO1 sensitivity in the dystrophic context.
Together, these findings indicate that altered mechanosensitive calcium signaling, rather than increased SOCE activity, may contribute to calcium dysregulation in human DMD myotubes. Further experiments using pharmacological or gene-silencing approaches are required to gain more insight into the molecular mechanisms underlying this abnormal calcium influx.

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Syndrome d'Ehlers Danlos cyphoscoliotique lié à FKBP14 : un diagnostic à évoquer avec une implication majeure pour le suivi vasculaire

Les variants biallélliques pathogènes de FKBP14, codant la protéine FKBP22 (FK506-binding protein 22), sont responsables d'une forme rare de syndrome d'Ehlers-Danlos cyphoscoliotique dit de type 2 (SEDk type 2, OMIM #614557, ou SED-FKBP14), décrit pour la première fois en 2012. FKBP22 est une peptidyl-prolyl cis-trans isomérase du réticulum endoplasmique, impliquée dans le repliement et la maturation de plusieurs protéines de la matrice extracellulaire, notamment des collagènes III, VI et X, intervenant ainsi dans l'organisation du tissu conjonctif.

Le SEDk-FKBP14 associe classiquement hypotonie congénitale, une cyphoscoliose précoce, une hypermobilité articulaire, une hyperextensibilité cutanée et une surdité neurosensorielle. L'atteinte musculaire, parfois au premier plan, avec décalage des acquisitions motrices et progrès moteurs secondaires peut orienter vers une myopathie congénitale. Certaines anomalies histopathologiques peuvent entretenir l'incertitude (variation de taille de fibre, infiltration adipeuse, centralisation nucléaire, aspect de central-core ou multi-mini core, disproportion de fibres de type I). Une atteinte musculaire proximale pendant la petite enfance associée à l'hypermobilité et la cyphoscoliose peut aussi orienter vers une collagénopathie VI, qui présente d'autre spécificités (rétractions, moindre prévalence de l'atteinte cardiaque), mais un large spectre phénotypique.

Parmi les autres diagnostics différentiels, on peut citer le SEDk lié à PLOD1, le SED lié à CHST14 (SED musculocontractural), et le syndrome de Larsen notamment.

La proximité phénotypique de ces entités rend difficile le diagnostic qui est fréquemment fait suite à des analyses génétiques élargies.

Le phénotype des mutations FKBP14 se situe donc à la frontière entre myopathie et maladie du tissu conjonctif. Or, l'atteinte du tissu conjonctif peut s'accompagner de complications vasculaires potentiellement léthales. Le diagnostic revêt donc une importance particulière pour adapter le suivi de des patients (surveillance et prévention cardiovasculaire).

Nous rapportons plusieurs observations de patients présentant des variants biallélliques de FKBP14, aux présentations cliniques variables incluant une complication vasculaire grave, afin d'illustrer la diversité et l'importance de l'atteinte musculaire dans cette affection rare, et de discuter ses implications diagnostiques ainsi que les modalités de suivi, notamment vasculaire.

SESSION POSTERS 2 - 115

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Chronic Electrical Conditioning Drives Distinct Functional Phenotypes in Engineered Human Skeletal Muscle Tissues

Three-dimensional engineered muscle tissues (EMTs) provide promising human models to investigate skeletal muscle physiology and disease. However, their limited maturation remains a major challenge, particularly when disease-related functional phenotypes need to be detected. We previously developed MyoStretch, a custom platform designed to improve EMT maturation through controlled mechanical loading and chronic electrical conditioning (CEC).

We have now investigated whether different patterns of electrical activity can further promote EMT functional maturation and orient their contractile properties. Human myogenic cells were embedded in fibrin-based hydrogels and subjected to controlled mechanical stretch before chronic electrical conditioning using two stimulation paradigms designed to mimic distinct patterns of motor neuron activity. CEC20 consists of repeated 20-Hz trains and was designed to promote a slow-like phenotype, whereas CEC70 uses short 70-Hz trains to promote a fast-like phenotype.

Both CEC paradigms improved EMT contractile force compared with non-conditioned tissues. Functional characterization also revealed differences in contractile kinetics between CEC20- and CEC70-conditioned EMTs, particularly in relaxation, consistent with the emergence of distinct slow- and fast-like functional properties.

We are currently investigating whether these functional differences are associated with distinct molecular signatures. Molecular characterization will focus on markers of slow/fast contractile identity and calcium handling, in order to determine whether the different stimulation patterns induce coordinated functional and molecular adaptations.

Finally, we are evaluating whether CEC20 and CEC70 differentially reveal disease-associated functional alterations in Duchenne muscular dystrophy EMTs. Comparing slow- and fast-oriented conditioning may help uncover disease phenotypes that remain poorly detectable in immature or unconditioned tissues.

Together, these results show that combining controlled mechanical loading with specific patterns of chronic electrical stimulation improves EMT maturation and provides a means to tune their functional properties. This approach may contribute to the development of more physiologically relevant human skeletal muscle models for studying muscle diseases and evaluating therapeutic strategies.

SESSION POSTERS 2 - 118*

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Ultrafast micrometric laser structuring of polymer surfaces for highly organized skeletal muscle tissue modeling

INTRODUCTION: Skeletal muscle differentiation requires coordinated myoblast elongation, alignment, fusion, and maturation into organized multinucleated myofibers. Conventional 2D culture poorly recapitulates muscle architecture, limiting the study of muscle development and disease phenotypes in vitro.

OBJECTIVE: We investigated whether femtosecond-laser-induced micrometric topographies on standard culture plates could provide physical cues to promote skeletal muscle cell organization and differentiation, and evaluated their potential for neuromuscular disease modeling.

METHODS: Laser-structuring process was optimized to obtain anisotropic topographies suitable for skeletal muscle modeling. The physics proprieties of the laser-structured (LS) surfaces were investigated, considering surface hydrophobicity and their potential to provide mechanical cues for cell guidance. C2C12-derived myotubes morphology and organization were evaluated by immunofluorescence and comprehensive image-based analysis, while myogenic differentiation and maturation were assessed by RT-qPCR and western blotting. Optimized LS surfaces were subsequently used to characterize myotube phenotypes derived from healthy, Duchenne muscular dystrophy (DMD), and facioscapulohumeral muscular dystrophy (FSHD) human immortalized myoblasts.

RESULTS: LS surfaces were biocompatible and promoted the formation of highly aligned and elongated myotubes, together with increased late-stage expression of MyoD, Desmin, MHC, Myomaker, and C-met, consistent with enhanced myogenic maturation and fusion. Moreover, the superior organization of LS culture enabled single-fiber-level phenotyping and revealed distinct abnormalities in DMD and FSHD myotubes, including reduced diameter, impaired maturation, and abnormal branching.

CONCLUSION: LS surfaces provide an innovative and promising approach to obtain advanced 2D cell cultures able to better recapitulate skeletal muscle architecture, with potential applications in neuromuscular disease modeling and therapeutic screening.

SESSION POSTERS 2 - 121*

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Jellyfish: an entry point to understand the origin of muscle systems

Sarcomeres are the contractile units of striated muscles. Their highly ordered macromolecular architecture has been elucidated using cutting-edge techniques in both insects and vertebrates (i.e., bilaterian animals), revealing a set of conserved sarcomere proteins across these groups. Cnidarians, as the sister group to bilaterians, hold a key position for understanding muscle evolution, in particular medusae, which bear sarcomeres on the underside of their bell. However, genes encoding Titin and Troponin were not found in cnidarians genome, and homologs of Z-disc proteins were not found to be associated with medusa striated muscles. Therefore, despite strong similarities in their ultrastructure, medusa sarcomeres are thought to have originated independently from those of bilaterians. Here, we introduce the scyphozoan Pelagia noctiluca as a new model for studying sarcomere structure and myofibrillogenesis. We generated a toolbox of 16 custom-made antibodies targeting homologs of sarcomere proteins from the predicted proteome of Pelagia noctiluca. Coupling these antibodies with actin staining and STED super-resolution imaging, we established the first molecular map of cnidarian sarcomeres. Remarkably, we found that 14 of these proteins occupy positions highly similar to those of their bilaterian counterparts, including actin crosslinkers at the Z-disc and a Titin homolog at both the M-line and the Z-disc. Moreover, taking advantage of the direct development of Pelagia noctiluca, we uncovered similarities between myofibrillogenesis in cnidarians and vertebrates. By Morpholino-based knockdown strategy, we clarified the function of two homologs of Z-disc proteins in bilaterians. We demonstrated that the actin cross-linker Filamin, plays a fundamental role in Z-disc cohesion and myofibril integrity, contrary to alpha-actinin which was localized along the entire actin thin filaments. Finally, we found that most of sarcomere proteins examined also localized in actomyosin filaments of smooth muscles and non-muscular epithelial cells, supporting the hypothesis that sarcomeres evolved through the specialization of a deeply conserved actomyosin-based contractile system. Altogether, our findings support a common and ancient evolutionary origin of the molecular machinery composing sarcomeres, while highlighting a fundamental difference in Z-disc organization between cnidarians and bilaterians.

SESSION POSTERS 2 - 124*

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Muscular bioenergetic metabolism shows condition-specific signatures in murin models of Limb Girdle Muscular Dystrophy R1: a key status for biomarker identification and therapy individualization?

Limb-Girdle Muscular Dystrophy R1 (LGMDR1) is an autosomal recessive genetic disease caused by mutations in the CAPN3 gene, encoding the calcium-dependent cysteine protease calpain-3. Loss of functional CAPN3 leads to sarcomere disorganization, calcium dysregulation and mitochondrial alterations, resulting in altered muscle function and metabolic defects. Improving metabolic function therefore represents a key therapeutical target that may be addressed through tailored pharmaceutical and non-pharmaceutical approaches, including exercise. Determining the nature and origin of the metabolic status across the heterogeneous manifestations of the disease could ensure proper therapeutic design and biomarker identification. We investigated these by analyzing how metabolic alterations could vary according to muscle-type, sex, or disease severity.

We performed comprehensive metabolomic profiling using UHPLC–HRMS, complemented by the absolute quantification of tricarboxylic acid (TCA) cycle intermediates and short-chain fatty acids (SCFAs) by UPLC–MRM–MS/MS. Analyses were conducted in the fast-twitch glycolytic tibialis anterior (TA) and slow-twitch oxidative soleus (SOL) muscles from female and male wild-type (WT) and CAPN3-KO C57 mice, as well as from male Sprague–Dawley rats. Untargeted and targeted metabolomic datasets were processed and analyzed using R packages and MetaboAnalyst 6.0.

Our analyses showed a decrease in relative quantity of long-chain and medium-chain acylcarnitine (LCACs, MCACs) in muscles from male CAPN3-KO animals compared with WT, with a trend to increase in female. These patterns were independent of species (mouse and rat) or muscle typology. We also observed species-independent, muscle-specific change in the relative content of glycolysis intermediates with an increase in fast-twitch TA and a decrease in the slow-twitch SOL. This suggests sex-dependent differences in βoxidation signatures together with muscle-specific glycolytic adaptations. Finally, we identified a hallmark CAPN3-KO signature with an increase in resting amino acids (AA) metabolism, particularly isoleucine, valine and leucine with sex, species and muscle-specificities.

Our study highlights condition-specific metabolic signatures in CAPN3-KO animals that may support the identification of biomarkers and the development of individualized strategies to improve muscle function.

SESSION POSTERS 2 - 127*

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How to decipher Golgi apparatus-dependent protein transport in skeletal muscle cells ?

Skeletal striated muscle represents around 40% of the total body weight and are involved in voluntary contraction. During the myogenic development, somite-derived muscle progenitors went through a differentiation process leading to a multinucleated cell called myofiber. This process involves a drastic reorganization of the cell architecture and activity. The Golgi apparatus transitions from a perinuclear localization in myogenic progenitors to dispersed elements in myofibers. The Golgi apparatus is a dynamic and an essential organelle where proteins are modified, and sorted to specific places. This organelle produces and receives continuously some vesicles from endocytic pathway or from the endoplasmic reticulum. Vesicle's production from the plasma membrane (endocytic route) and from the Golgi apparatus (anterograde route) is permitted thanks to Dynamin-2, a small GTPase, that leads to membrane scission during budding. While protein homeostasis is critical to maintain cellular integrity, the molecular mechanisms underlying protein traffic in skeletal muscle cells remain poorly understood. My work is to functionally characterize the Golgi apparatus and protein transport regulation within skeletal muscle. I established human induced pluripotent stem cells (hiPSC)-derived myogenic progenitors which fuse to form a multinucleated cell, called myotube. The first aim of my work is to determine the protein composition of this organelle during the differentiation of the myogenic cells. For this I differentiated hiPSC expressing a Golgi-TurboID construct that permits the biotinylation of proteins associated to the Golgi apparatus. My work also includes to the quantitative analysis of the spatial distribution of Golgi elements along myogenic differentiation. I will use hiPSC that express a fluorescent membrane marker and perform a 3D-segmentation to determine the position, the number of Golgi elements and the volume they occupy in the cell. Then, I will study the transport of proteins using the tool Retention Using Selective Hooks (RUSH) to synchronize the transport of proteins. Altogether, our work will help us to understand specific transport mechanisms at play within skeletal muscle. Investigating these processes in physiological and Dynamin-2-centronuclear myopathy contexts will uncover deregulated mechanisms that may serve as molecular levers for therapeutic strategies.

SESSION POSTERS 2 - 130*

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Muscle-specific developmental alterations in response to early sensorimotor restriction and effects of whole-body vibration or environmental enrichment

Childhood is a critical period of growth and maturation during which regular physical activity contributes to the development of the motor system. Conversely, reduced physical activity may impair skeletal muscle growth and maturation. We hypothesized that sensorimotor restriction (SMR) during the first four postnatal weeks would alter the postnatal growth (mass and cross sectional area, CSA), and maturation (MyHC isoform expression) of the soleus (SOL) and extensor digitorum longus (EDL) muscles. We also evaluated two independent countermeasure paradigms: whole-body vibration (WBV) as a preventive intervention during SMR, and environmental enrichment as a remediation strategy after SMR.

Rats pups underwent hindlimb immobilisation for 16 h/day from birth (P0) to postnatal day 28 (P28) and were compared with age-matched controls. Muscle weight, fibre CSA and myosin heavy chain (MyHC) composition were assessed on SOL and EDL at P15, P28, and P60. Two interventions were tested independently: preventive 30-Hz whole-body vibration (WBV) from P5 to P15 or environmental enrichment after completion of SMR, from P28 to P60.

SMR induced distinct developmental trajectories in SOL and EDL. SOL fibre CSA was lower in SMR rats than in controls at P15, P28, and P60, together with a slow-to-fast MyHC shift at P15 and P28. In EDL fibre CSA was higher at P15 and returned to control values at P28 and P60, whereas a fast-to-slow MyHC shift emerged at P28 and persisted at P60.
Preventive WBV did not preserve a control-like phenotype: at P15, it further reduced SOL fibre CSA, and altered EDL fibre-type composition, suggesting delayed or altered fibre maturation. At P28, no effect of WBV on CSA. Post-restriction environmental enrichment did not significantly reverse the main SMR-induced abnormalities at P60 in both muscles.

Overall, early SMR induces long-lasting, partly persistent and muscle-specific alterations in postnatal muscle growth and phenotype. Neither preventive WBV nor post-restriction environmental enrichment produced an overall beneficial effect, emphasizing the importance of muscle type, developmental timing and intervention strategy.

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Fascial mesenchymal stromal cells: emerging players in skeletal muscle regeneration

Skeletal muscle regeneration relies on the coordinated interplay of multiple cell types around muscle satellite cells. Beyond resident intramuscular populations, our previous work in mice revealed that adipose stromal cells (ASCs) from subcutaneous adipose tissue (ScAT) rapidly infiltrate injured muscle and contribute to regeneration. Preliminary findings suggest that connective tissue structures, particularly fasciae, may provide an unconventional route for this migration. We therefore investigated the fascia lata as a potential reservoir and migration hub for stromal progenitor cells following adjacent skeletal muscle injury.

Using complementary non-destructive imaging and tissue-dissociation approaches, we characterized the cellular composition, dynamics, morphology, and three-dimensional organization of the murine fascia lata following glycerol-induced quadriceps injury.

We identified a substantial population of fascial cells sharing the immunophenotypic profile of ASCs, suggesting that the fascia lata represents a previously underappreciated reservoir of mesenchymal stromal progenitor cells. Following muscle injury, the number of these cells decreased in the fascia lata as early as 3 hours post-injury, concomitant with their accumulation in the injured muscle. By 14 hours, their numbers also began to decline in ScAT, while fascial cell numbers returned to baseline and continued to increase in the muscle. These distinct temporal dynamics suggest a potential sequential mobilization of stromal cells from the fascia and ScAT toward the injured muscle.

Muscle injury also induced marked structural remodeling of the fascia lata, characterized by altered fascial stromal cell morphology, including changes in cell size and pseudopodial architecture, alongside profound disorganization of the collagen network. These changes were associated with increased podoplanin expression in fascial stromal cells, suggesting injury-induced phenotypic remodeling.

Together, our findings identify the fascia lata as a potential reservoir of stromal progenitor cells and suggest that it may provide a connective tissue route for ScAT-derived ASCs to reach injured muscle. These findings uncover a potential role for fascia in coordinating extramuscular cell recruitment during skeletal muscle regeneration, broadening our understanding of the cellular and structural mechanisms that support tissue repair.

SESSION POSTERS 2 - 136*

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Effect of Adiponectin knockout in the context of skeletal muscle deconditioning and reconditioning in mice

Introduction: Muscle deconditioning leads to Disuse Muscle Atrophy (DMA) and persistent muscle weakness, impairing rehabilitation. To develop pharmacologic therapeutic approaches, the mechanisms underlying exercise training (ET) benefits must be clarified. Increased evidence suggests Adiponectin (ApN) as a therapeutic option for muscle disorders, but its contribution to muscle adaptation upon disuse and to the subsequent response to reloading and rehabilitation remains to be established.
Methods: Male ApN-KO (6; 129-Adipoqtm1Chan/J) and matching WT mice were subjected (or not) to hindlimb unloading and immobilization (HLUI). Following HLUI (or control conditions), animals were reloaded and then submitted to 8 weeks of endurance ET. Myofiber cross-sectional area (CSA) and fiber-type composition were assessed by immunofluorescence (laminin/myosin heavy chain subtypes) and morphometric analyses in the slow-twitch Soleus and the fast-twitch Tibialis Anterior (TA) muscles.
Results:
The Soleus muscle of ApN-KO HLUI mice exhibited a more pronounced DMA severity and an increased proportion of type IIa myofibers as compared to WT. Following ET, Soleus muscle recovered, even in absence of ApN but its CSA in ApN-KO mice exceeded that of WT mice. HLUI has a “pre-conditioning-like effect” increasing the ET-mediated type IIa/I myofiber transition. This effect is prevented in the absence of ApN, suggesting impaired muscle plasticity during ET.
In the TA muscle, preliminary results suggest a greater CSA reduction upon HLUI in ApN-KO mice as compared to WT. In HLUI mice, following ET, fibre-type distribution seems not significantly altered by the lack of ApN. However, recovery of myofiber CSA seems incomplete in ApN-KO HLUI mice. In particular, type IIx myofiber CSA remained reduced after ET in both genotypes, with a greater reduction in ApN-KO mice.
Conclusion: Our study highlights that the loss of ApN protective properties aggravates atrophy and impairs compensatory mechanisms initiated upon muscle deconditioning, particularly fiber-type switches. This has persistent consequences in muscle plasticity during rehabilitation. The history of mechanical loading influences the subsequent adaptive response to ET and ApN signaling is involved in this process.

SESSION POSTERS 2 - 139*

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The heart: a model of resistance to metastases

Cancer is one of the leading causes of death worldwide, with at least 60% of cancer-related deaths attributable to metastases. The metastatic process is a complex cascade with a low success rate, which may be explained by the "Seed and Soil" hypothesis, stating that some organs provide a more favorable microenvironment for metastatic development. Interestingly, the heart is an extremely rare site of metastasis, although their occurrence is suspected to be increased with myocardial pathologies. This study aimed to assess the impact of physiological heart contraction on the final steps of the metastatic cascade (extravasation, colonization). Conditioned media from non-contracting (NCH) and contracting hearts (CH) were collected using an ex vivo Langendorff perfusion system. A549 lung cancer cells were exposed to conditioned media for 24 hours. Proliferation, cell cycle, death, motility, and migration were assessed using EdU labeling, flow cytometry, live imaging, microscopy, and scratch assays. A549 spheroids were also exposed to conditioned media for 7 days. Finally, conditioned medium from hearts subjected to ischemia (45 minutes (min)) - reperfusion (20 min) (I/R) was tested to assess the impact of I/R-induced metabolic stress. CH-conditioned medium reduced A549 cell proliferation, with a 22% decrease in EdU-positive cells after 24 hours ($p<0.01$) and a 36% reduction in spheroid area after 7 days ($p<0.05$) as compared with NCH medium. A549 cells exposed to CH medium tended to accumulate in G1 (+11%, $p=0.0548$), while the proportion of cells in G2/M decreased by 43% ($p<0.05$). No effect on motility was observed, whereas migration capacity was reduced by 48.5% ($p=0.0494$). Interestingly, I/R-conditioned medium did not reduce A549 cell proliferation, suggesting that I/R counteracts the beneficial effect of contraction. These results suggest that physiological heart contraction creates an inhospitable microenvironment for metastatic lung cancer cells by reducing their colonization and migration. I/R-induced metabolic alterations may counteract this protective effect. Metabolomic and proteomic analyses will be performed to identify contraction-related key molecules involved in the heart's resistance to metastases.

SESSION POSTERS 2 - 142

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Final results from the JEWELFISH study: 5-year risdiplam treatment in non-treatment-naïve individuals with SMA

Background: Risdiplam (EVRYSDI®) is a centrally and peripherally distributed, oral survival of motor neuron 2 (SMN2) pre-mRNA splicing modifier that has been widely approved for the treatment of spinal muscular atrophy (SMA).
JEWELFISH (NCT03032172) was a multicenter, open-label study that assessed the safety, tolerability and pharmacokinetic (PK)–pharmacodynamic (PD) relationship of daily risdiplam in non-treatment-naïve patients with SMA (aged 6 months–60 years at enrolment) who previously received nusinersen (SPINRAZA®), onasemnogene abeparvovec (ZOLGENSMA®), olesoxime or were previously enrolled in Study BP29420 (MOONFISH) with RG7800 (RO6885247).

Results: The enrolled population (N=174) included a broad range of ages (1–60 years), SMA types (1–3), SMN2 copy numbers (2–4) and motor functions (non-sitters, sitters and walkers).
We have previously presented data after 2 years of treatment with risdiplam. The last patient enrolled in JEWELFISH completed their final study assessment after 5 years of risdiplam treatment in February 2025. Here we present the final safety, exploratory efficacy and PK-PD data from the JEWELFISH study.

Conclusions: Final data from the JEWELFISH study will provide important insights on the long-term safety, PD and exploratory efficacy of risdiplam in a broad population of non-naïve patients with SMA.
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Genomic stress drives activation of interferon signaling and innate immune pathways during SMA Type II myoblast differentiation

Spinal muscular atrophy (SMA) is a neuromuscular disorder caused by loss of the SMN1 gene. The SMN protein is ubiquitously expressed and has several roles in the cell, including the regulation of RNA metabolism and genome stability. Although SMA is primarily considered a motor neuron disease, because of its ubiquitous expression, loss of SMN leads to systemic pathological consequences, including in skeletal muscle. To better understand the cell-intrinsic effects of SMN loss on myoblast differentiation, we characterized three human SMA Type II myoblast cell lines and controls in vitro. We observed impaired myogenic differentiation, including reduced fusion index and nuclei alignment. RNA sequencing analysis and OLINK -proteomics on the SMA myoblasts revealed activation of DNA damage pathways and innate immune activation, confirmed by the presence of 53BP1 foci and increased phosphorylation of the H2AX histones, as well as accumulation of R-loop structures and an increase of single-stranded DNA in the cytoplasm. Resolution of R-loops and DNA damage is known to cause the presence of immunogenic DNA: RNA species in the cytoplasm, activating sterile inflammation pathways. Treating control myoblasts with double-stranded DNA or a cGAS agonist phenocopied the differentiation defects in SMA myotubes. Conversely, treating SMA myoblasts with a STING inhibitor improved fusion. In summary, our results demonstrate that SMN loss exerts a cell-intrinsic impairment in muscle precursor cells, suggesting that the observed muscle dysfunction in Type II patients is not only a consequence of impaired innervation but also of the sterile inflammation caused by the genomic instability after SMN loss.

SESSION POSTERS 2 - 148

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Perceptions et attentes des patients vis-à-vis des traitements de la myasthénie généralisée auto-immune (MG) : résultats d'une enquête patients

INTRODUCTION : La myasthénie auto-immune (MG) est une maladie neuromusculaire qui impacte la qualité de vie. Récemment, de nouveaux traitements ont été développés. Ils se distinguent notamment par leurs voies et leurs fréquences d'administration. La compréhension des perceptions et attentes des patients sont essentielles pour optimiser l'adhésion aux traitements.

METHODE : Une enquête a été menée auprès de 109 patients adultes atteints de MG (70 recrutés via les associations de patients et 39 via des professionnels de santé). Les données recueillies incluaient les caractéristiques démographiques, le score MG-ADL, les modalités de traitement, l'implication dans les décisions thérapeutiques et les critères cliniques et modalités pratiques dans le choix d'un traitement.

RESULTATS : L'âge moyen des patients était de 53,7 ans, 71 % étaient des femmes, et le score MG-ADL moyen était de 5,5. La majorité (84 %) avait déjà reçu un traitement intraveineux. Seuls 38 % se sentaient suffisamment informés sur le choix de leur traitement, le médecin restant leur principale source d'information. Bien que 30 % se sentaient impliqués dans le choix thérapeutique, 95 % souhaitaient y participer activement ou de manière consultative. Les patients privilégient les critères cliniques : maintien de l'efficacité/contrôle des symptômes (top 3 : 83 %), l'absence d'effets indésirables (62 %) et la rapidité d'action (61 %). Les critères pratiques sont moins influents, avec la fréquence d'administration (45 %) et la voie d'administration (29 %) comme principaux facteurs. Parmi les modalités pratiques, la fréquence (70 %) et le lieu de traitement (69 %) sont les plus déterminants.

CONCLUSION : Ces résultats mettent en évidence la nécessité de l'implication du patient et d'une prise en compte des priorités cliniques et modalités pratiques pour la prise en charge thérapeutique et l'adhérence au traitement.

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Amélioration clinique rapide et réduction de l'utilisation des corticoïdes sous efgartigimod dans la myasthénie généralisée : résultats préliminaires de l'étude PREMIER

CONTEXTE: Le traitement de la myasthénie généralisée (MG) comprend des corticoïdes, lesquels, à long terme induisent des effets secondaires importants. L'étude prospective PREMIER décrira les patients américains atteints de MG traités par efgartigimod.

MÉTHODES: Les participants: des adultes du programme d'accompagnement des patients sous efgartigimod n'ayant pas reçu d'efgartigimod ou exposés pendant ⩽2 jours et non inclus dans un essai clinique. Ils ont rempli des questionnaires avant le début du traitement, puis toutes les 4 semaines jusqu'à la semaine 56. L'efficacité était évaluée par MG-ADL. Les patients rapportaient leur consommation de corticoïdes avant chaque questionnaire. Les résultats jusqu'à la semaine 32 sont présentés.

RÉSULTATS: 143 patients inclus ont commencé le traitement par efgartigimod; 52 ont rempli le questionnaire de la semaine 32 et 75% sont restés sous efgartigimod. L'âge moyen à l'inclusion était de 64,8 ans; 48,9% étaient des femmes. La plupart avaient déjà utilisé des corticoïdes (83,9%); 14,0% avaient déjà utilisé des anti-C5, des anti-FcRn, et du rituximab. Le score moyen MG-ADL à l'inclusion était de 8,6. À la semaine 4, le score MG-ADL s'était amélioré de 4,1 points ($p<0,001$). Les améliorations se sont poursuivies jusqu'à semaine 32. La proportion de patients sans corticoïdes est au départ de 38,5% et 54,0% à la semaine 4 ($p<0,05$), 59,6% à la semaine 32 ($p<0,05$). Parmi les participants utilisant des corticoïdes au départ (56,6%, n=81/143), 35,7% (n=10/28) avaient arrêté les corticoïdes à la semaine 32, la proportion recevant des corticoïdes à forte dose (>10 mg/jour) a diminué de 69,1% (n=56/81) à 28,6% (n=8/28) ($p<0,05$).

CONCLUSION : Les patients myasthéniques traités par efgartigimod ont eu une amélioration des symptômes et une réduction de l'utilisation de corticoïdes à partir de la semaine 4 et jusqu'à la semaine 32. Les données permettront de mieux décrire le traitement à long terme par efgartigimod en vie réelle.

SESSION POSTERS 2 - 154

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Complications cliniques et survie sans événement dans la DMD, en France à partir de la BNDMR

La dystrophie musculaire de Duchenne (DMD) est une maladie génétique liée à l'X caractérisée par une perte progressive de la force musculaire conduisant à des complications motrices, respiratoires, cardiaques et orthopédiques sévères. L'étude EpiDuch avait pour objectif d'évaluer en vie réelle en France la prévalence globale des complications de la DMD, ainsi que la séquence temporelle de leur survenue et la survie sans événement au moyen d'une étude longitudinale rétrospective.
Une cohorte de patients, avec un code de DMD entre 2014 et 2023, a été sélectionnée dans la BNDMR chainée au SNDS. Elle comporte 669 patients masculins disposant d'une date de diagnostic validée (466 patients prévalents diagnostiqués avant 2017 et 203 patients incidents diagnostiqués entre 2017 et 2023). Les taux d'incidence cumulés des complications ont été décrits chez les patients prévalents et chez les patients incidents alors que le délai d'apparition des complications a été estimé par la méthode de Kaplan-Meier dans la cohorte incidente.
95,3% des patients diagnostiqués avant 2017 (âge moyen : 4.5 ans) et 70,0% des diagnostiqués entre 2017 et 2023 (4.9 ans) ont présenté au moins une complication liée à la DMD. Dans la cohorte prévalente, la perte de la marche avec utilisation d'un fauteuil roulant concernait 89,5% des patients, les atteintes respiratoires 81,5%, la scoliose 53,0%, la dénutrition 43,6%, les complications cardiaques 47.4-49.4%, l'ostéoporose ou fractures 26,0% et l'obésité 15.2%-17.2%. Dans la cohorte incidente, le taux cumulé de survenue d'au moins une complication atteignait 57,9% [IC95% : 50,9-65,1] à 3 ans post-diagnostic. Les complications présentant les délais d'apparition les plus courts étaient la perte de la marche avec un délai médian au fauteuil roulant de 50,0 mois (IC95% : 45,5-58,7) et l'atteinte respiratoire avec un délai médian de 75,7 mois (IC95% : 52,4-NA). Les autres atteintes survenaient plus tardivement à 4 ans post-diagnostic : dénutrition (16,8%), scoliose (9,3%), ostéoporose/fractures (4,5%), troubles cardiaques (3,3%) et obésité (2,3%). Aucune mortalité n'a été enregistrée sur la période de suivi de la cohorte incidente.
L'étude EpiDuch démontre le fardeau clinique considérable de la DMD en France. Elle précise la chronologie des troubles fonctionnels, dominée initialement par la perte de la marche et le déclin respiratoire, soulignant la nécessité absolue d'un suivi pluridisciplinaire standardisé et très précocement instauré.

SESSION POSTERS 3

Jeudi 19 Novembre
10h30 - 11h00

LISTE POSTERS - SESSION 3

Jeudi 19 novembre de 10h30 à 11h00

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9		SEFERIAN	Andreea	Clinical pharmacology of apitegromab in spinal muscular atrophy
15		GRAMPA	Valentina	The comparative efficacy and safety of risdiplam versus high-dose nusinersen in children with Type 1 SMA
21		GUERENNE	Laura	Effet du ravulizumab sur la réduction de la corticothérapie chez les adultes atteints de myasthénie grave généralisée : analyse post hoc de l'essai de phase III CHAMPION MG
27		GUILHEM	Solé	Characterisation of patients with generalised myasthenia gravis on rozanolixizumab treatment in European Managed Access Programmes
33		GUILLEMAUD	Jules	Characterization of resident macrophages in resting and regenerating skeletal muscle
39	*	GUTKOWSKI	Lisa	Study of the pathophysiology of muscular abnormalities associated with Noonan Syndrome
45		GYENGE	Melinda	Do clinical manifestations of DM1 differ between countries? A registry-based comparison of French and Canadian cohorts
51	*	HAYAT	Hassan	All for JUN, and JUN for all: a shared regulatory hub across inherited muscle disorders
57	*	HOH	Pazé	From Cytoskeleton to Nucleus: Novel Functions of ACTG2 in gastrointestinal smooth muscle cell and in Chronic Intestinal Pseudo-Obstruction
63		IBRAHIM	Christelle	PROFIL IRM DES CANALOPATHIES MUSCULAIRES : cohorte rétrospective Montpelliéraine
69	*	IDOUX	Romane	Expanding the Phenotypic Spectrum of ATP2A2-Related Disorders to Neuromuscular and Neurodevelopmental Diseases
75	*	IDRIS	Tahir	The novel roles of STIM1L in skeletal muscle architecture
81	*	ISSA	Fayez	HIRA-mediated H3.3 deposition inhibits WNT pathway to restrain the fibrotic fate of fibro-adipogenic progenitors
87		JAULIAC	Edgar	C-MAF Transduces Fast Motor Neuron Firing to Sustain Fast-Glycolytic Myofibers and Neuromuscular Junctions
93	*	JULIEN	Geoffroy	Évaluation de la fonction motrice à l'ère des thérapies innovantes dans la myopathie de Duchenne : une revue narrative.
99	*	KOENIG	Camille	Characterisation of resident macrophages in the Skeletal Muscle during exercise
105		LEJEUNE	Julie	Fonctions cognitives et parcours scolaire dans la dystrophie musculaire de Duchenne : données du registre français DYS

SESSION POSTERS 3 - 3

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Hematological effects of vamorolone in boys with Duchenne Muscular Dystrophy (DMD) - comparison with prednisone

Background: Prednisone (PRED) increases hematocrit, causes neutrophilia, and reduces blood eosinophils. Vamorolone (VAM) is a dissociative corticosteroid with a unique mode of action,

Objectives: Compare the effect of VAM and PRED on peripheral blood cell counts (BCC).

Methods: VISION-DMD (VBP15-004) was a randomized double-blind study assessing PRED 0.75mg/kg/d or VAM 6mg/kg/d in boys with DMD. Longitudinal changes from baseline (CBL) of peripheral BCC were assessed at weeks 2, 6, 12, 18 and 24. GUARDIAN (SNT-IV-VAM-011) is assessing the long-term safety and effectiveness of VAM in boys with DMD who have completed prior studies.

Results: In VISION-DMD, haematocrit (CBL mean±SEM: +0.04±0.01 vs +0.03±0.1 L/L) and lymphocytes (CBL +1.05±0.16 vs +1.13±0.17 109/L) increased similarly after 24 weeks of PRED or VAM, respectively. PRED had more effect on total leucocytes, mainly due to an impact on neutrophils (CBL mean±SEM: +0.88±0.30 109/L) that was not observed in VAM-treated patients (CBL mean±SEM: -0.03±0.32 109/L). Monocyte counts increased more with PRED than VAM (CBL mean±SEM: +0.24±0.04 vs +0.10±0.03 109/L, respectively). Platelets increased more with PRED than with VAM, with a peak at week 2 (CBL mean±SEM: + 55±11 109/L and +30±15 109/L, respectively). Eosinophil counts were suppressed with PRED but not VAM. In GUARDIAN, 66% of patients had haematocrit levels and 45% had lymphocyte counts above the normal range for age at baseline (mean duration of treatment 5.2 y; mean daily dose 4.7 mg/kg/d). Only 16%, 5%, and 3% had elevated leucocyte, neutrophil, or monocyte counts, respectively; low eosinophils were observed in 8%; 1 patient had a low platelet count (192 109/L).

Conclusion: VAM does not share all the effects of PRED on blood cell counts. It increases red blood cells but does not induce neutrophilia and does not suppress eosinophils. These differences must be considered when interpreting neutrophil counts in the context of infections.

SESSION POSTERS 3 - 9

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Clinical pharmacology of apitegromab in spinal muscular atrophy

Apitegromab is a muscle-targeted treatment for SMA that selectively inhibits activation of myostatin, a negative regulator of muscle growth. Here we characterize the clinical pharmacology of apitegromab using PK/PD data from healthy individuals (Phase 1 SRK-015-001; aged 18-55y) and patients living with SMA (Phase 2 TOPAZ and Phase 3 SAPPHIRE; aged 2-21y) receiving IV apitegromab.

Results from the Phase 1 study showed apitegromab PK was linear and dose-proportional across the 1-30 mg/kg dose range. Dose-dependent increases in total latent myostatin, a reliable PD marker, were observed at week 4 between 1 and 10 mg/kg, with no meaningful differences for doses of 10, 20, and 30 mg/kg. At higher apitegromab doses (20 and 30 mg/kg), target engagement was similar to that at 10 mg/kg, with target engagement sustained for a longer period.

TOPAZ study (apitegromab 2 and 20 mg/kg) results showed a 10-fold increase in dose was associated with a 10-fold increase in PK, a ~2.3-fold increase in total latent myostatin concentration, and a notable difference in efficacy (mean change from baseline in HFMSE score of 7.1 [20 mg/kg] vs 5.3 [2 mg/kg]) at month 12. Integrated PK/PD and exposure-response (ER) modeling performed with TOPAZ data showed no meaningful differences in predicted PD and efficacy between the 10 and 20 mg/kg doses, suggesting target saturation at 10 mg/kg. Results from SAPPHIRE confirmed the model predictions. At month 12, SAPPHIRE results showed dose proportional PK; however, PD profiles were superimposable for 10 and 20 mg/kg, with similar efficacy and safety, confirming target saturation at 10 mg/kg. Moreover, there were no clinically distinct differences in efficacy or safety. In separate analyses, the ER model-predicted placebo-corrected change from baseline in HFMSE at week 52 for the SAPPHIRE population aged 2-12y, was 1.66 vs 1.67 points for the apitegromab 10 vs 20 mg/kg groups, respectively.

Taken together, these results demonstrate that target saturation is achieved at 10 mg/kg and that the benefit–risk profile of apitegromab is optimized at this dose.

SESSION POSTERS 3 - 15

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The comparative efficacy and safety of risdiplam versus high-dose nusinersen in children with Type 1 SMA

Risdiplam and nusinersen are approved therapies for spinal muscular atrophy (SMA). Untreated infants with Type 1 SMA fail to achieve major motor milestones and typically do not survive past 2 years. As head-to-head trials are lacking, indirect treatment comparisons adjusted for cross-trial differences can inform treatment decisions.

This study compared the efficacy and safety of the approved risdiplam dose (0.2 mg/kg daily in children aged 2 months to <2 years; 0.25 mg/kg daily in children ⩾2 years and <20 kg) versus the investigational higher-dose (HD) nusinersen regimen (50/28 mg) in children with Type 1 SMA treated in clinical trials.

Patient-level risdiplam data were obtained from 58 children receiving the pivotal dose in FIREFISH (Part 1 n=17, Part 2 n=41; NCT02913482) and aggregate nusinersen data from 50 children in DEVOTE (Part B, infantile onset; NCT04089566).

Unanchored matching-adjusted indirect comparisons evaluated outcomes, adjusting for age at first dose, disease duration, and baseline CHOP-INTEND score. Cox proportional-hazards models compared overall and event-free survival.

After matching, baseline characteristics were similar across groups. The effective sample size for risdiplam was 33.2 (a 43% reduction). Compared with HD nusinersen (n=50) at 15 months, risdiplam showed a 75% reduction in death risk (95% CI 11–93%) and a 76% reduction in death or permanent ventilation risk (95% CI 34–92%). Despite adjustments for known prognostic factors, unobserved baseline differences may confound non-randomised comparisons.

Risdiplam was associated with a lower risk of death or permanent ventilation versus HD nusinersen in children with Type 1 SMA over 15 months. Additional data sources should be consulted to expand on these findings.

SESSION POSTERS 3 - 21

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Effet du ravulizumab sur la réduction de la corticothérapie chez les adultes atteints de myasthénie grave généralisée : analyse post hoc de l'essai de phase III CHAMPION MG

Introduction : Chez les patients atteints de myasthénie grave généralisée (MG), l'utilisation à long terme de corticoïdes est associée à des effets indésirables graves. Le ravulizumab a démontré une efficacité et un profil de sécurité cliniquement significatifs au cours de la période contrôlée randomisée (PCR) et de la période d'extension en ouvert (PEO) de l'essai de phase III CHAMPION MG (NCT03920293) mené chez des adultes atteints de MG. L'épargne cortisonique induite par le ravulizumab a été évalué chez les patients ayant reçu des corticoïdes en concomitance pendant la période OLE. Méthodes : Les patients, randomisés selon un rapport 1:1, ont reçu du ravulizumab ou un placebo pendant 26 semaines (RCP), puis du ravulizumab en ouvert pendant ⩽ 4 ans (OLE). L'ajustement des doses de corticoïdes était autorisé pendant la période OLE, à la discrétion des investigateurs. Les variations des scores « Myasthenia Gravis-Activities of Daily Living » (MG-ADL) et les modifications des doses de corticoïdes ont été évaluées et comparées entre le début de la période OLE (OLEbaseline) et la dernière évaluation de la période OLE (OLElast). Résultats : Au total, 113 des 161 patients ayant intégré la phase OLE ont reçu des corticoïdes par voie orale pendant cette phase (placebo-ravulizumab, n = 64; ravulizumab-ravulizumab, n = 49) et 60 patients (53,1 %) ont réduit ou arrêté leur traitement quotidien par corticoïdes entre OLElast et OLEbaseline (diminution moyenne de la dose : 5,8 mg/jour). Parmi ces patients, les scores MG-ADL moyens ont diminué au cours de l'étude RCP de 2,0 points dans le groupe placebo et de 3,3 points dans le groupe ravulizumab. Au cours de l'étude OLE, les scores moyens MG-ADL ont encore diminué de 2,5 points dans le groupe placebo-ravulizumab (P = 0,0002) et de 1,4 point dans le groupe ravulizumab-ravulizumab (P = 0,0087). Dans l'ensemble, les doses moyennes de corticoïdes ont diminué de 12,7 mg/jour (62,0 %) entre OLEbaseline et OLElast (placebo-ravulizumab, −12,3 mg/jour [61,7 %] ; ravulizumab-ravulizumab, −13,3 mg/jour [62,4 %]). Lors de la dernière évaluation de l'étude OLE, 51,7 % des patients ayant réduit leur consommation de corticoïdes recevaient ⩽ 5 mg/jour, dont 23,3 % avaient complètement arrêté les corticoïdes. Conclusions : Les patients ayant reçu du ravulizumab pendant la période OLE de CHAMPION MG ont pu réduire ou arrêter leur consommation quotidienne de corticoïdes tout en continuant à présenter une amélioration des scores MG-ADL.

SESSION POSTERS 3 - 27

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Characterisation of patients with generalised myasthenia gravis on rozanolixizumab treatment in European Managed Access Programmes

Introduction: Generalised myasthenia gravis (gMG) is a chronic autoimmune disease. MycarinG (Phase 3/ NCT03971422) and its open-label extension studies (MG0004/NCT04124965 and MG0007/NCT04650854) showed that the efficacy of rozanolixizumab, a neonatal Fc receptor blocker, was maintained over repeated treatment cycles across multiple myasthenia gravis (MG)-specific outcomes in patients with gMG. Managed Access Programmes (MAPs) enable pre-authorisation treatment for patients with severe/debilitating/life-threatening conditions, where available treatments are deemed inadequate.

Objective: To describe rozanolixizumab utilisation and patient characteristics in MAPs initiated under compassionate use in France, Italy and Spain.

Methods: This was an observational, retrospective, longitudinal cohort study of adults with gMG initiating rozanolixizumab treatment in MAPs in France, Italy and Spain between November 2022 and May 2025. The primary objective was to describe baseline demographics and disease characteristics of patients at treatment initiation. Change from baseline in MG Activities of Daily Living (MG-ADL) and Garches scores were also assessed when available.

Results: Overall, 21 patients from France, 44 from Italy and <5 from Spain were included. Mean (standard deviation [SD]) age was 64.8 (18.2), 54.0 (16.6) and 61.5 (16.5) years, respectively. Most patients were female (71.4%, 75.0% and 50.0%, respectively). Baseline (mean [SD]) MG-ADL score was 9.0 (6.7) in France and 7.4 (2.6) in Italy. Additional data were available for Italy: mean (SD) number of years since initial MG diagnosis was 11.9 (12.1) and 36.4% of patients had an MG diagnosis <5 years. In the 2 years prior to enrolment, MG crises occurred in 7.1% of patients and MG-related hospitalisations occurred in 55.0%. Prior to enrolment, 93.2% of patients received immunosuppressants, 70.5% received cholinesterase inhibitors and all patients received corticosteroids. Treatment outcomes data will be presented in the poster.

Conclusion:
Baseline characteristics of the patients who entered the rozanolixizumab MAPs were indicative of a population with moderate-to-severe gMG. Funding: UCB.

SESSION POSTERS 3 - 33

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Characterization of resident macrophages in resting and regenerating skeletal muscle

In skeletal muscle, resident macrophages are localized within the connective tissues including the epimysium, perimysium, and endomysium. While macrophages are known to regulate homeostasis in various organs, their role in skeletal muscle remains poorly defined. This is due to the lack of markers for distinguishing recruited from resident macrophages. We aimed to identify reliable markers of muscle-resident macrophages at steady state and during skeletal muscle regeneration.
We used several mouse models including the CX3CR1-GFP mouse to track blood monocyte recruitment and the CX3CR1-CreERT2-tdT mouse to label recently recruited resident macrophages. We evaluated, by immunofluorescence, the expression of canonical residency markers (CD169, MHCII, Lyve1, and Tim4) in muscle macrophages. Post-lesional muscle regeneration was studied using a physiological injury model, combined with clodronate-mediated monocyte depletion to isolate the contribution of resident macrophages.
Using histology, we found that, at steady state, the gastrocnemius muscle contained about 133,000 CD64pos resident macrophages, predominantly located in the epimysium surrounding the muscle. Only 10-15% of resident macrophages expressed CX3CR1-GFP while, 40% were positive in the CX3CR1-CreERT2-tdT model, suggesting their partial hematopoietic origin. CD169 was expressed by all resident macrophages, while Lyve-1 and Tim4 were expressed by 75 and 50 %, respectively. Following injury, recruited macrophages rapidly expressed CD169 and MHCII, representing, respectively, 43% and 76% of muscle macrophages, indicating rapid residency marker acquisition. Under monocyte depletion, resident macrophages expanded, with 60% more macrophages in severely versus mildly injured muscle, suggesting local proliferation.
We showed that blood monocytes contribute to the resident macrophage population in skeletal muscle both at steady state and during regeneration. Current work investigates their inflammatory profile and function to define their contributions to homeostasis and repair.

SESSION POSTERS 3 - 39*

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Study of the pathophysiology of muscular abnormalities associated with Noonan Syndrome

Life expectancy continues to increase, but healthy life expectancy (healthspan) has plateaued. With the accumulation of chronic diseases and the development of frailty, the poor health of older adults leads to increased dependency and has a major economic impact on our society. Understanding the mechanisms underlying aging therefore represents a major research challenge in order to identify therapeutic targets, but this is made difficult by the entanglement of multiple processes -the so-called hallmarks of aging- manifesting over time. The study of certain genetic diseases that share; early in life, symptoms commonly observed during aging is of great interest, both for patients affected by these diseases and for improving our understanding of natural aging. Indeed, since the genetic mutation drives aging-associated symptoms independently of chronological age, the dysregulations it causes may also occur during aging, representing promising therapeutic targets for the treatment of age-related diseases. Noonan syndrome is a rare genetic disorder caused by a mutation in the PTPN11gene, which encodes the protein tyrosine phosphatase SHP2, leading to its hyperactivation. This disease is characterized by a phenotypic triad consisting of short stature, facial dysmorphism, and congenital heart defects. However, recent studies from my group and others have highlighted symptoms that are similar to those specifically observed in older individuals, such as impaired bone health, insulin resistance (type 2 diabetes), and chronic inflammation.

By studying a mouse model of this disease, we have demonstrated a reduced lifespan together with a frailty phenotype associated with severe impairment of locomotor function. We have characterized a sarcopenic phenotype (loss of muscle mass and strength) associated with chronic tissue and systemic inflammation, as well as the presence of senescence-associated gene expression markers in several tissues.

Our project now aims to (1) understand the mechanisms underlying this complex phenotype and try to reverse it and (2) determine whether SHP2 dysregulation contributes to the development of age-related sarcopenia in the context of physiological aging. This will at once improve our knowledge of Noonan syndrome pathophysiology and pave the way for new therapeutic approaches to alleviate sarcopenia.

SESSION POSTERS 3 - 45

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Do clinical manifestations of DM1 differ between countries? A registry-based comparison of French and Canadian cohorts

Myotonic dystrophy type 1 (DM1) is one of the most prevalent inherited neuromuscular disorders worldwide. It is characterized by marked clinical heterogeneity, reflecting both its multisystem involvement and wide range of ages at onset, from the prenatal period to late adulthood. This difference in disease expression and severity is in part explained by the size of the CTG repeat expansion. Whether the clinical phenotype of DM1 differs across countries remains unclear. Cross-country comparative studies may reveal population-specific differences and help inform international research efforts and clinical care strategies. To our knowledge, no such international comparative study has been previously reported.

We used data from the international DM-Scope registry to compare French and Canadian DM1 cohorts. To ensure comparability, Canadian participants (n = 275) were matched 1:2 with French individuals (n = 550) based on age, sex, age at onset, and disease duration. Key variables analyzed included age at diagnosis, disease duration, sex, clinical phenotype, cardiac device implantation (pacemaker or implantable cardioverter-defibrillator), diabetes, use of ventilatory support, muscular impairment assessed by the Muscular Impairment Rating Scale (MIRS), CTG repeat length, and presence of cataracts. Additional analyses were performed in the overall French DM1 registry population (n = 3,347).

Mean age at diagnosis was 26.1 years in the French cohort and 26.7 years in the Canadian cohort. Mean disease duration was 21.0 versus 20.6 years, and mean age at last follow-up was 47.1 versus 47.3 years, respectively. A detailed comparison of muscular and multisystem involvement in the two cohorts will be presented at the meeting. Overall, French and Canadian DM1 populations share many clinical characteristics while also exhibiting distinct clinical variations. This cross-country comparative study provides insight into common clinical patterns and geographic variability, and may inform international research initiatives, clinical trial design, and patient care strategies.

SESSION POSTERS 3 - 51*

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All for JUN, and JUN for all: a shared regulatory hub across inherited muscle disorders

Inherited musclar disorders (MDs) arise from diverse genetic defects affecting distinct cellular processes, including those involving the sarcolemma, nuclear envelope, and lysosomes. Despite this heterogeneity, they share pathological features such as inflammation, extracellular matrix remodeling, and altered cellular homeostasis. These shared pathological features suggest that genetically distinct MDs may engage common molecular response. However, whether these features are driven by common transcriptional programs and shared upstream regulatory mechanisms remains poorly understood.

To investigate shared molecular mechanisms across inherited muscle diseases, we performed an integrative transcriptomic analysis combining publicly available bulk RNA-sequencing datasets with transcriptomic data generated from patient-derived hiPSC models. We included genetically distinct MDs, comprising Duchenne muscular dystrophy (DMD), Pompe disease, Danon disease, Emery-Dreifuss muscular dystrophy, and DNM2-related centronuclear myopathy. Differential gene expression and pathway analyses were complemented with transcription factor activity inference using decoupleR to identify regulatory mechanisms recurrently altered across diseases.

Cross-disease integration revealed shared transcriptional alterations involving inflammatory signaling, extracellular matrix remodeling, and cellular homeostasis. Importantly, transcription factor activity inference consistently highlighted the AP-1 transcriptional complex as a recurrent regulatory signature across several disease datasets. In particular, JUN emerged as a candidate upstream regulator of shared dysregulated transcriptional programs.

SESSION POSTERS 3 - 57*

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From Cytoskeleton to Nucleus: Novel Functions of ACTG2 in gastrointestinal smooth muscle cell and in Chronic Intestinal Pseudo-Obstruction

Chronic intestinal pseudo-obstruction (CIPO) is a rare and severe visceral myopathy characterized by impaired gastrointestinal motility in the absence of mechanical obstruction. Approximately 40% of pediatric cases are associated with heterozygous variants in ACTG2, which encodes γ-smooth muscle actin (γSMA), a major component of the contractile apparatus of gastrointestinal smooth muscle cells (SMCs). Although γSMA is primarily considered a cytoplasmic protein involved in cytoskeletal organization and contraction, other actin isoforms have been shown to exert nuclear functions, including interactions with transcriptional and chromatin-remodeling complexes.

We therefore investigated whether γSMA may also have a nuclear function in gastrointestinal SMCs and whether this function is altered by the pathogenic ACTG2 R257C variant. Using nuclear/cytoplasmic fractionation of human and chick gastrointestinal SMCs, we detected endogenous γSMA within the nuclear compartment. To identify potential nuclear pathways involving γSMA, we performed protein-interaction screening and identified several candidate nuclear partners. We next compared the interaction profiles of wild-type ACTG2 and the R257C variant. While several partners were shared between the two forms, the R257C variant displayed additional and variant-specific interactions. Notably, one R257C-specific partner is involved in transcriptional/chromatin regulation and shows a spatial and regionalized expression pattern within the developing gastrointestinal tract. Its expression is also inversely associated with the contractile marker CNN1 during gastrointestinal development.

These findings support a previously unrecognized nuclear role for γSMA and suggest that pathogenic ACTG2 variants may alter nuclear protein networks in addition to disrupting cytoskeletal organization. Ongoing chromatin-based analyses are aimed at identifying ACTG2- associated genomic targets and determining how these interactions are modified by the R257C variant. These mechanisms will subsequently be investigated in chick animal model and in human intestinal organoid models carrying pathogenic ACTG2 variants.

Our work therefore opens a new mechanistic perspective on ACTG2-related visceral myopathy, linking alterations in the contractile cytoskeleton to nuclear and transcriptional regulation in intestinal SMCs.

SESSION POSTERS 3 - 63

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Profil IRM des canalopathies musculaires : cohorte rétrospective Montpelliéraine

Introduction : Les canalopathies musculaires, sous-groupe rare des maladies neuromusculaires, sont causées par des mutations des canaux ioniques. L'IRM musculaire est cruciale pour le diagnostic mais les données dans la littérature sont limitées. L'objectif de cette étude est de décrire les anomalies IRM et d'identifier un éventuel pattern spécifique associé à chaque mutation génétique.

Méthode : Étude rétrospective monocentrique au CHU de Montpellier incluant les patients majeurs avec une canalopathie musculaire confirmée génétiquement et ayant eu une IRM musculaire corps entier 3T. Les données démographiques, génétiques, cliniques et radiologiques sont analysées.

Résultat : 16 patients ont été inclus. L'IRM musculaire montre des anomalies variées chez 9 patients et prédominantes au niveau des fessiers, des cuisses et des mollets, avec une atteinte plus marquée dans les paralysies périodiques.

Discussion : 82% des patients avec anomalie significative à l'IRM avaient une paralysie périodique, avec atteinte prédominante des adducteurs et, chez les porteurs de la mutation CACNA1S, et dans la loge antérieure de la cuisse. Sur 3 patients, un seul a montré une stabilité musculaire à 5 ans, tandis que les 2 autres ont présenté une progression de l'involution graisseuse. Les hypersignaux STIR dans les muscles suggèrent un processus inflammatoire ou fonctionnel. Les patients avec déficit moteur ont une atteinte radiologique marquée ; une infiltration graisseuse discrète seule n'est pas corrélée à un déficit. Une atteinte linguale significative, sans symptômes bulbaires, était présente chez 2 patients, non décrite à ce jour. L'IRM musculaire est souvent normale dans les myotonies non dystrophiques. L'infiltration graisseuse est plus marquée chez les patients SCN4A avec phénotype PP.
L'étude est limitée par sa petite taille de patients (n=16), l'absence de patients atteints du syndrome d'Andersen-Tawil, et le manque de suivi longitudinal et de groupe contrôle. Des études prospectives multicentriques sont nécessaires.

Conclusion : Les paralysies périodiques sont les plus associées à des anomalies IRM, touchant les fessiers, cuisses postérieures et adducteurs. Les mutations CACNA1S affectent la cuisse antérieure.
L'évolution des atteintes musculaires semble progressive et asymétrique, avec une préservation relative de certains muscles.

SESSION POSTERS 3 - 69*

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Expanding the Phenotypic Spectrum of ATP2A2-Related Disorders to Neuromuscular and Neurodevelopmental Diseases

Pathogenic variants in ATP2A2, encoding the sarco/endoplasmic Ca2+-ATPase SERCA2, are classically associated with autosomal dominant skin disorders such as Darier disease, in which impaired calcium homeostasis disrupts keratinocyte adhesion. Increasing evidence, however, supports a broader role for ATP2A2 across multiple tissues.

During my previous postdoctoral work, we identified a rare heterozygous ATP2A2 variant, c.1583G>A (p.R528Q), in five unrelated families with recurrent rhabdomyolysis, characterised by repeated episodes of severe muscle breakdown often triggered by viral infections, fever or intense exercise.

SERCA2 is essential for intracellular Ca^{2+} homeostasis and exists as two isoforms: SERCA2a, predominantly expressed in slow-twitch skeletal muscle and heart, and SERCA2b, ubiquitously expressed. In skeletal muscle, SERCA2a mediates cytosolic Ca^{2+} reuptake into the sarcoplasmic reticulum during muscle relaxation. We hypothesised that the p.R528Q variant impairs SERCA2a function, leading to defective Ca^{2+} handling and rhabdomyolysis.

To investigate this mechanism, we combined studies in patient-derived myotubes with a CRISPR/Cas9 knock-in zebrafish model carrying the orthologous p.R527Q variant. Mutant zebrafish showed reduced swimming performance without overt morphological abnormalities. Muscle analyses revealed reduced slow-fibre cross-sectional area, mitochondrial abnormalities, fibrosis, and a shift from slow- to fast-fibre identity. Calcium imaging showed delayed SERCA-mediated Ca^{2+} reuptake in patient myotubes and reduced Ca^{2+} transient amplitudes in slow muscle fibres of mutant larvae, supporting impaired calcium homeostasis.

More recently, we identified four additional ATP2A2 variants associated with neurodevelopmental disorders (ND), suggesting a broader but poorly understood role of SERCA2 in the brain. My current postdoctoral project aims to investigate the role of SERCA2b in neurodevelopment and neuromuscular physiology and to functionally validate the most pathogenic ND-associated variants using iPSC-derived neurons and CRISPR-edited zebrafish models. Brain and muscle morphology will be assessed by High-Resolution Episcopic Microscopy, together with behavioural tests in zebrafish and patch-clamp combined with calcium imaging in iPSC-derived neurons.

These findings will establish, for the first time, a link between ATP2A2 variants and ND, and expand the phenotypic spectrum of ATP2A2-related diseases.

SESSION POSTERS 3 - 75*

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The novel roles of STIM1L in skeletal muscle architecture

Ca2+ homeostasis is highly essential for normal cell function and is regulated by several key proteins, including the Stromal Interaction Molecule 1 (STIM1) in the sarco/endoplasmic reticulum (SR/ER). Along with the plasma membrane channel Orai1, STIM1 triggers store-operated calcium entry (SOCE) upon Ca2+ depletion in the SR/ER, thereby replenishing intracellular stores. A longer isoform of STIM1, STIM1 Long (STIM1L), was previously shown to be expressed specifically in skeletal muscle and brain. STIM1L contains an additional 106 amino acids with characteristics of an actin binding domain (ABD). While previous research shows that STIM1L is involved in SOCE, its other potential physiological roles remain unclear. Given the presence of the ABD, we hypothesized that STIM1L also contributes to cytoskeletal organization and architectural functions in skeletal muscles. Using AlphaFold and co-immunoprecipitation experiments, we demonstrated that STIM1L interacts with α-actinin, a key protein located in the Z-discs of skeletal muscle sarcomeres, in primary human myotubes. To further explore the role of STIM1L on muscle architecture, we employed a lentivirus-based doxycycline-inducible system to downregulate either all STIM1 isoforms (the long and canonical) or only STIM1L during myotube differentiation. Disrupting STIM1L expression led to a reversible disorganization of α-actinin, and an increase in its protein expression, independently of STIM1L-induced SOCE. Further experiments with cycloheximide suggested that the protein stability of α-actinin is also enhanced upon downregulation of either STIM1L or both isoforms of STIM1. Treatments with MG132, a proteasome inhibitor, indicated that α-actinin is degraded through the proteasome in primary human skeletal myotubes. Interestingly, inhibiting the proteasome led to a stark and reversible disorganization of α-actinin, similar to that observed after downregulating STIM1L.
These findings reveal a novel role for STIM1L in regulating proteasome-mediated α-actinin degradation and hence its stability and organization. This structural, Ca2+-independent function of STIM1L opens new area of research for understanding the establishment and maintenance of skeletal muscle architecture.

SESSION POSTERS 3 - 81*

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HIRA-mediated H3.3 deposition inhibits WNT pathway to restrain the fibrotic fate of fibro-adipogenic progenitors

Chromatin architecture is fundamental to the regulation of gene expression and cell lineage determination. However, the specific contribution of the histone variant H3.3 and its chaperone HIRA to transcriptional regulation during somatic cell lineage progression, remains largely unexplored. Using tissue-specific and inducible mouse models, we assessed the consequences of HIRA deletion in Fibro-Adipogenic Progenitors (FAPs), a key muscle-resident stem cell population, in homeostasis and injured skeletal muscled.

HIRA deficient FAPs show an intrinsic defect in proliferation and increased apoptosis highlighted by an altered cell trajectory during muscle regeneration. HIRA cKO FAPs are also primed towards a fibrotic fate both in vivo and in vitro, as seen by higher intramuscular fibrosis throughout regeneration and strong fibrotic differentiation in culture. Single cell RNA-sequencing in homeostasis and at different regeneration timepoints validated these phenotypes and revealed a metabolic defect in the cKO. Seahorse stress testing confirmed global impairment of both oxidative phosphorylation and glycolysis energy production.
Mechanistically, we identified WNT signaling pathway as the mediator of the increased fibrotic potential, and its inhibition completely restores FAP fibrotic differentiation in HIRA cKO. ATAC sequencing confirmed WNT-mediated fibrosis and revealed a global shift in chromatin accessibility at key fibrotic loci. HIRA cKO FAPs further adopt a pro-inflammatory phenotype, altering their crosstalk with satellite and immune cells as confirmed by co-culture experiments. Ongoing CUT&Tag for H3.3, HIRA and key PTMs will establish the mechanistic link between HIRA-mediated H3.3 deposition and these defects.

Collectively, these results identify HIRA-mediated H3.3 deposition as a critical epigenetic safeguard of FAP identity and function, with implications for understanding fibrosis in skeletal muscle.

SESSION POSTERS 3 - 87

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C-MAF Transduces Fast Motor Neuron Firing to Sustain Fast-Glycolytic Myofibers and Neuromuscular Junctions

The transcriptional decoder of slow motoneuron firing, calcineurin and NFAT, has been mapped in detail, yet no equivalent has been described for the fast firing that maintains type IIb glycolytic identity. We identify c-MAF as this decoder and characterise its operation.

Single-nucleus multiome of innervated and 7-day denervated mouse tibialis anterior shows that only IIb and IIx myonuclei form distinct denervated clusters, IIa remaining indistinguishable from controls. Accessibility at region A1 of the fMyh super-enhancer collapses entirely, Myh4 losing close to 90% of promoter accessibility and transcript while the Myh1 promoter is retained; c-MAF and SIX motifs are depleted from IIb myonuclei and RUNX1 and AP-1 motifs gained. Genome-wide analysis of half-MARE spacing identifies three nucleosome-compatible geometries encoding distinct programmes: same-gyre near 40 bp at developmental loci, cross-gyre near 75 bp at contractile and calcium genes, full-nucleosome near 147 bp at secretory machinery. Denervation opens the same-gyre class and exposes HOX and AP-1 motifs, so that loss of the nerve does not only close the fast programme but reopens a developmental regulatory space.

c-MAF nuclear accumulation is circadian and restricted to fast fibers. Patterned stimulation establishes that translocation requires 100 Hz and not 20 Hz firing, and depends on postsynaptic acetylcholine receptor activation rather than mechanical loading, since tenotomy preserves it and βbungarotoxin abolishes it. Luciferase assays at A1 reveal a two-component lock: c-MAF alone reverses HDAC5 repression, and KAT2B amplifies c-MAF-dependent activation without acting alone, its occupancy being c-MAF-dependent and restricted to the half-MARE.

Conditional c-Maf deletion produces region-specific MYH4 to MYH1 transitions, NMJ fragmentation with AChR turnover reaching denervation levels, and FOXO3-driven atrophy through direct binding to an intronic Foxo3 enhancer. The same regional transition, c-Maf downregulation and atrophy programme appear in SOD1 G93A mice at 90 days, and nuclear exclusion of c-MAF is already detectable in a substantial fraction of myonuclei at 50 to 60 days, before anatomical denervation.

c-MAF thus couples 100 Hz acetylcholine-driven calcium transients to pioneer-like chromatin maintenance of fast-fiber identity, defining a frequency-to-chromatin axis whose disruption recapitulates the regional vulnerability of ALS.

SESSION POSTERS 3 - 93*

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Évaluation de la fonction motrice à l'ère des thérapies innovantes dans la myopathie de Duchenne : une revue narrative

La myopathie de Duchenne est la dystrophie musculaire la plus fréquente chez l'enfant.
La perte de la dystrophine, protéine du cytosquelette membranaire, entraine une faiblesse proximale évidente vers 3-5 ans (marche dandinante, signe de Gowers, hypertrophie des mollets) qui progresse vers une perte de la marche (11-14 ans sous corticothérapie). A cela s'ajoutent des troubles neuro-orthopédiques secondaires (scoliose, rétractions musculo-tendino-articulaires), une atteinte des muscles cardiaques et respiratoires et fréquemment des troubles cognitifs.

La corticothérapie et la prise en soin pluridisciplinaire (respiratoire, cardiaque, nutritionnelle, orthopédique) ont modifié l'histoire naturelle. Le développement et l'usage de certains outils d'évaluation (6MWT, NSAA, MFM) l'ont précisé (pronostic fonctionnel, corrélation avec l'atteinte cardiaque et respiratoire). Cependant, aucun d'entre eux n'est suffisant pour évaluer toutes les composantes de la fonction motrice, à tous les stades. Leurs limites psychométriques (sensibilité, effet plancher et plafond) ont conduit à s'intéresser aux méthodes de mesure instrumentales (myométrie, imagerie musculaire quantitative, AQM) qui mettent à jour les connaissances sur l'histoire naturelle. La recherche sur les thérapies innovantes nécessite des critères de jugement sensible au changement, cliniquement pertinents et utilisables aux différents stades évolutifs.
La variabilité phénotypique, les progrès en génétique et la recherche en thérapie génique conduisent à compléter l'évaluation du clinicien (ClinRO, PerfO, mesures instrumentales) par observations des patients et/ou de leurs aidants (PRO/ObsRO). Le caractère multidimensionnel de la fonction motrice et l'usage de ces approches d'évaluation complémentaire imposent d'aborder la fonction motrice suivant le cadre conceptuel de la classification internationale du fonctionnement (CIF).

Cette revue propose une synthèse des méthodes d'évaluation clinique de la fonction motrice (membres supérieurs, membres inférieurs, tronc) suivant le cadre de la CIF, le stade de la maladie, en distinguant ClinRO, PerfO, PRO/ObsRO. Dans un second temps, elle discute les autres composantes (fonctions cognitivo-motrices, équilibre et contrôle postural, intégration sensorielle, schéma corporel, proprioception) et dimensions (qualité de vie) qui pourraient être prises en compte dans cette évaluation. Elle explore les méthodes d'évaluation instrumentale.

SESSION POSTERS 3 - 99*

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Characterisation of resident macrophages in the Skeletal Muscle during exercise

Resident macrophages are key players in tissue homeostasis, with a broad range of functions including immune surveillance, tissue remodelling and metabolic regulation. While their role has been extensively described in organs such as the liver and the heart, their features in striated skeletal muscle remain poorly understood. The resident macrophages have been primarily studied in the context of injury, where they are known to be essential for the recruitment of circulating monocytes. However, nothing is known about their behaviour during physiological stress such as exercise. Addressing this gap requires a steady state baseline of the resident macrophage characteristics, and suitable in vivo models to explore differences during training.

We therefore investigated their spatial distribution within hindlimb muscles. We show their preferential localisation in the epimysium and their anatomical relationship with the blood vasculature. We were able to establish their molecular phenotype through classical resident macrophage surface markers such as TIM4 and LYVE1 but also less-common ones. Notably, we highlight a shared common surface marker, CD169, expressed by all resident macrophages in the tissue. After exercise, we depict an increase of the resident macrophage population and track changes in the previous evocated markers. Finally, with a CD169 depletion targeted model we confirmed selective depletion of resident macrophages while preserving monocyte populations. This tool provides a crucial experimental framework to understand specific contribution of resident macrophages to muscle adaptation during exercise.

Together, our results give a first comprehension of resident macrophage skeletal muscle characteristics, and allow the design of an in vivo model to study their physiological response to physical activity, with potential applications for muscle diseases.

SESSION POSTERS 3 - 105

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Fonctions cognitives et parcours scolaire dans la dystrophie musculaire de Duchenne : données du registre français DYS

La dystrophie musculaire de Duchenne (DMD) est une maladie neuromusculaire liée au gène DMD, responsable d'une faiblesse musculaire progressive mais également d'atteintes neurodéveloppementales susceptibles d'altérer les fonctions cognitives, les apprentissages et la scolarité. Le registre français des dystrophinopathies DYS, soutenu par l'AFM-Téléthon et le réseau FILNEMUS, recueille depuis 2019 des données cliniques, génétiques et fonctionnelles en vie réelle.
L'objectif de cette étude est de décrire les caractéristiques cognitives et le parcours scolaire des patients atteints de DMD inclus dans le registre DYS.
Une analyse descriptive du registre DYS a été réalisée à partir de l'extraction du 23 septembre 2026. Les patients vivants atteints de DMD avec un diagnostic génétique confirmé ont été inclus.
Parmi les788 patients inclus, un retard cognitif, isolé ou associé à un retard moteur, était rapporté chez 16.1% des patients et des troubles autistiques chez 1.1.
Des données de scolarité étaient disponibles chez 739 patients. L'âge médian à la dernière scolarisation était de 14,9 ans [10,6-17,9]. Le type d'établissement scolaire était renseigné pour 728 patients : 13,7% étaient scolarisés en milieu ordinaire sans accompagnement spécifique, 43,8% en milieu ordinaire avec un accompagnant d'élève en situation de handicap (AESH), 8,2% en ULIS/CLIS (dispositifs d'inclusion scolaire) et 22,5% en IME/IEM (structures médico-éducatives spécialisées).
Les derniers niveaux scolaires les plus fréquemment rapportés étaient le primaire (26,1%), le collège (23,5%) et le lycée (21,6%). Quarante-quatre patients (7,0%) avaient accédé à l'enseignement supérieur.
Une évaluation du quotient intellectuel était disponible pour 200 patients. L'âge médian lors de la dernière évaluation était de 7,9 ans [6,5-10,4]. Les tests les plus utilisés étaient le WISC (66,3 %) et le WPPSI (18,1%). 48,1% des patients avaient un fonctionnement intellectuel normal et 27,0% un fonctionnement intellectuel limite ou une déficience intellectuelle.
Les données du registre DYS soulignent l'importance des atteintes cognitives dans la dystrophie musculaire de Duchenne et leur impact sur la scolarité. La fréquence des troubles cognitifs et des aménagements scolaires observée dans cette cohorte souligne l'importance d'une évaluation neuropsychologique précoce et d'un accompagnement adapté.

SESSION POSTERS 4

Jeudi 19 Novembre
13h30 - 14h00

LISTE POSTERS - SESSION 4

Jeudi 19 novembre de 13h30 à 14h00

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16	*	LABELLA	Beatrice	Clozapine-Induced Toxic Myopathy and Rhabdomyolysis: Evidence from Proteomic Profiling
22	*	LAGARRIGUE	Charlotte	Role of DEC1 and its target genes in macrophage properties during muscle regeneration
28	*	LALLEMAND	Aurélie	Skeletal Muscle Adaptations To Individualized Home Based Exercise Training Versus Standardized Exercise Training in People with Recently Diagnosed Multiple Sclerosis.
34	*	LE GARFF	Mathilde	Heterogeneity of skeletal muscle damage and muscle stem cell fate in response to sepsis
40		LEJEUNE	Julie	Le Registre Français des Calpainopathies (CALPA) : mise en place et premiers résultats
46	*	LESSARD	Lola	Urinary glucose tetrasaccharide (Glc4) in late-onset Pompe disease: a biomarker of disease progression and treatment response?
52		LESSARD	Lola	First Canadian Data from the DM-Scope Registry: Clinical and epidemiological profile of Myotonic dystrophy type 1 (DM1)
58	*	LIMPENS	Maëlle	Selection of peptides for a muscle-targeted delivery of ASOs directed against DUX4 mRNAs through complementary approaches in silico, in vitro and in vivo
64	*	LITTRE	Marie-Céline	Study of Satellite Cells in COPD-associated sarcopenia (SCOOP project
70		MACAUX	Gaspard	Cell-Hub: a complete graphical platform for single-nucleus RNA sequencing analysis applied to healthy and pathological skeletal muscle
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SESSION POSTERS 4 - 4

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Fertility in Risdiplam-Treated Adult Males with Spinal Muscular Atrophy (SMA): the MARLIN study

Background
SMA is a genetic, progressive neuromuscular disease. Risdiplam (EVRYSDI®) is an orally-administered survival of motor neuron 2 pre-mRNA splicing modifier approved by the U.S. Food and Drug Administration for the treatment of pediatric and adult individuals with SMA. Based on animal studies, male fertility may be compromised with risdiplam treatment. Therefore, understanding the effects of risdiplam on the fertility journey of males with SMA is important for clinical decision-making given increasing family planning ambitions afforded by disease-modifying therapies (DMTs). The ongoing MARLIN study collects and describes fertility-related outcomes in adult males with SMA who have received risdiplam.

Objective
To characterize the fertility journey and outcomes in adult males with SMA who are taking or have taken risdiplam and are actively attempting to conceive or who have conceived.

Results
Baseline data (cut-off: 9/22/2025) in four men with SMA (Type 2, n=2; Type 3, n=2) and their female partners are presented. The mean (SD) age of the men was 36.0 years (3.2). All men were taking risdiplam, with one having stopped treatment for >1 month in the past. Two of the four couples conceived (one spontaneously and one via fertility treatment) while the men were on risdiplam treatment; both resulted in pregnancies that led to full-term live births, with no additional pregnancies reported in this cohort to date.

Conclusions
Initial results from the MARLIN study provide evidence directly addressing patient and clinician concerns about fertility while on risdiplam. This evidence is vital for future family planning discussions among patients and clinicians in the era of effective DMTs.

SESSION POSTERS 4 - 10

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Motor innervation as a developmental gatekeeper of skeletal muscle identity: a single-nucleus multiome of the never-innervated muscle

Motor innervation is classically framed as a trophic modulator of an otherwise cell-autonomous muscle program, a reading anchored in postnatal denervation paradigms that necessarily test maintenance of an already-instructed muscle rather than its establishment. We exploit the peroneal muscular atrophy (PMA) mouse, in which a Limk1 mutation prevents the peroneal nerve from ever forming, to interrogate the developmental role of innervation in a tibialis anterior (TA) that has never received motor input.

Single-nucleus multiome of PMA TA at P25 captures the muscle where poly-innervation would have resolved, fast myosin heavy chain (MYH) isoforms segregated, and embryonic progenitor states been extinguished. None of these events proceeds normally. An ectopic adipocyte population carrying a Pax7+/Prdm16+/Nr2f2+/Gata6+ signature, distinct from FAP-derived adipocytes, is read as a retained bipotent trunk mesoderm progenitor that fails to be cleared on schedule; MuSCs connect trajectorially to that pool, enter early differentiation with high MYOG, and fail to complete it. At the chromatin level the fMyh super-enhancer is not engaged: half-MARE and SIX motifs are depleted, NR4A1 motif enrichment is lost, and CTCF-dependent architecture collapses. Immunofluorescence from P0 to P21 shows embryonic MYH specification proceeding without nerve input, whereas the SE-dependent Myh8 to Myh4 transition fails at P7, with MYH3 persistence and paradoxical MYH2 enrichment; MYH7, classically innervation-dependent, is maintained. In hyperactive compensating muscles (FHL, TP, FDL), MYH4 appears earlier than in controls,suggesting dose-dependent coupling between contractile activity and super-enhancer engagement. The paracrine landscape is dominated by NCAM1, semaphorins and TGFβ3, with mature EGFR, cAMP and Notch axes absent.

The motor nerve acts as a developmental gatekeeper of lineage commitment rather than as a trophic accessory,and the function it gates is establishment,distinct from the maintenance that adult denervation probes with the same machinery. The fMyh super-enhancer is read as a coordinator of exclusive promoter selection across the paralogous cluster, myonuclear uniformity being its consequence at fiber scale.

SESSION POSTERS 4 - 16*

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Clozapine-Induced Toxic Myopathy and Rhabdomyolysis: Evidence from Proteomic Profiling

Clozapine is an antipsychotic drug for treatment-resistant schizophrenia and is rarely associated with muscle toxicity. We investigated the molecular mechanisms of clozapine-induced muscle toxicity using proteomic profiling of primary human skeletal muscle cells exposed to clozapine and validated findings in a muscle biopsy from a patient with clozapine-associated rhabdomyolysis.
A 44-year-old woman presented with coma, severe rhabdomyolysis, and acute kidney injury in the context of elevated clozapine levels and recent dengue infection. Muscle biopsy revealed angulated atrophic fibers as well as hypertrophic fibers containing large vacuoles, highlighted with βspectrin and βdystroglycan labelling. Electron microscopy showed autophagic structures, sarcoplasmic reticulum dilation, large lipid droplets and loss of thick filaments. Unbiased proteomic analysis demonstrated marked metabolic remodeling, with upregulation of lipid metabolism and cholesterol biosynthesis pathways, alongside downregulation of sphingolipid metabolism and proteins involved in extracellular interaction, providing first molecular insights into this toxic myopathy.
While concomitant infection and a new-onset critical illness may have contributed, the associated lipid metabolic signature suggests a drug-related mechanism. This reprogramming of lipid-handling proteins parallels the established metabolic systemic effects of clozapine and could impact organellar integrity. In particular, sarcoplasmic reticulum dilation may reflect membrane remodeling associated with altered lipid homeostasis, although additional mechanisms such as calcium dysregulation can also contribute.
Together, these findings provide mechanistic insight into clozapine-associated toxic myopathy and identify disrupted lipid homeostasis as a potential driver of muscle injury. Moreover, they highlight the need for increased vigilance in patients with muscle symptoms or elevated creatine kinase during clozapine treatment.

SESSION POSTERS 4 - 22*

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Role of DEC1 and its target genes in macrophage properties during muscle regeneration

Macrophages play an essential role in muscle regeneration. After an injury, monocytes infiltrate the tissue and differentiate into pro-inflammatory macrophages, which promote the proliferation of muscle stem cells, induce fibroblast death and phagocytose debris. Phagocytosis of debris induces the switch from pro-inflammatory to anti-inflammatory macrophages, which stimulate muscle cell differentiation and collagen secretion by fibroblasts.
Our laboratory identified the transcription factor DEC1 as an essential regulator of the switch of macrophages. The aim is to investigate how DEC1 and its target genes regulate macrophage properties in muscle regeneration. We found that DEC1 is expressed by pro-inflammatory Ly6Cpos macrophages and then its expression is switched off by phagocytosis of debris, known as efferocytosis. This enables macrophages to acquire anti-inflammatory properties. The knockout (KO) of Dec1 in pro-inflammatory Ly6Cpos macrophages sorted from muscle reduced the proliferation of muscle stem cells and promoted their fusion, demonstrating the importance of DEC1 in macrophage properties.
Next, we identified Pianp as a potential DEC1 target gene. Indeed, Pianp expression was upregulated in Dec1 KO sorted macrophages during regeneration. In vitro, the loss of function of Pianp in Dec1 KO macrophages reduced muscle stem cell fusion. These results suggest that PIANP acts downstream of DEC1 to regulate the anti-inflammatory properties of macrophages and that DEC1 represses the expression of Pianp.
Altogether these results show the essential role of DEC1 in the switch of macrophages. Its expression is required to activate the pro-inflammatory program and inhibit the anti-inflammatory program. Then its expression must be repressed via efferocytosis in order to activate the anti-inflammatory program.

SESSION POSTERS 4 - 28*

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Skeletal Muscle Adaptations To Individualized Home Based Exercise Training Versus Standardized Exercise Training in People with Recently Diagnosed Multiple Sclerosis

Background : Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system. People with MS (PwMS) commonly experience fatigue, reduced physical capacity and skeletal muscle alterations. Our preliminary findings suggest that individualized home-based exercise training (IND) provides additional benefits in reducing fatigue and improving cardiorespiratory capacity in recently diagnosed fatigued PwMS compared with a home-based standard training program (STAND) (unpublished data).
This study aimed to investigate skeletal muscle adaptations following these two training programs in PwMS.

Methods : Thirty-one adults with recently diagnosed relapsing-remitting MS, low disability (Expanded Disability Status Scale <4) and significant fatigue (Fatigue Severity Scale >4) were included. Participants were randomly assigned to an IND group (n = 16), with exercise sessions adapted according to physical capacity and fatigue, or to a STAND group (n = 15) following fixed parameters based on international recommendations. Paired pre- and post-training muscle samples were available for 22 participants (nIND = 11 ; nSTAND = 11). Maximal oxygen consumption (VO2max) was measured before and after training. Muscle fiber type distribution and cross-sectional area (CSA) were assessed by immunofluorescence while metabolic characteristics were investigated by enzymatic analyses (myokinase, creatine kinase, enolase, citrate synthase), histoenzymatic analyses of cytochrome c oxidase and lipid droplet quantification, with the latter two analyses ongoing.

Results : VO2max increased over time ($p < 0.001$), with a significant time x group interaction ($p = 0.027$), driven by a significant increase in the IND group ($p = 0.001$). No significant changes was observed in muscle fiber type distribution or CSA in either groups. Citrate synthase activity increased following training ($p=0.020$), with no significant time x group interaction ($p=0.268$). No significant changes were observed for the other metabolic markers ($p > 0.05$). No significant correlation was observed between changes in citrate synthase activity and VO_2max ($p = 0.328$).

Conclusion : Cardiorespiratory capacity improved more in IND than STAND. Both programs were associated with increased citrate synthase activity, without detectable changes in muscle fiber composition or CSA. Individualized and standard training programs do not differ in their short-term impact on muscle characteristics.

SESSION POSTERS 4 - 34*

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Heterogeneity of skeletal muscle damage and muscle stem cell fate in response to sepsis

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. It is a leading cause of intensive care unit (ICU) mortality (30-50% with complications). Survivors often develop chronic disabilities, including rapid muscle atrophy and weakness within 10 days of ICU admission (Mankowski et al., 2021). The pathogenesis of sepsis-induced myopathy is multifactorial, including persistent inflammation, enhanced proteolysis, and impaired muscle stem cell repair (Yoshihara et al., 2023; Schmitt et al., 2023). In human, phasic muscles, which are enriched in glycolytic fibers appear more susceptible to damage than oxidative postural muscles, suggesting a fiber-type specific heterogeneity in sepsis-related muscle injury (De Jonghe et al., 2002). Yet, the molecular basis of this heterogeneity remains unclear.

To investigate this phenomenon, we used a mouse model of abdominal sepsis induced by caecal ligation and puncture (CLP) surgery and analyzed the differential responses of the tibialis anterior (TA, fiber type II-rich phasic) and the soleus (SOL, fiber type I-rich postural) muscles at 4 and 7 days post-surgery (dps). Sham-operated mice served as controls.

CLP-induced sepsis induced 40% mortality in mice within 4 dpi, accompanied by systemic inflammation¬—evidenced by elevated blood macrophage and neutrophil counts— and a reduction in muscle grip strength up to 7 dps, confirming systemic infection and muscle weakness. In septic mice, SOL muscle mass remained unchanged, whereas TA weight decreased significantly at both timepoints. Histological analysis revealed a 30% decrease in myofiber size in septic TAs, while SOL myofibers remained unaffected. Molecular analysis further confirmed this heterogeneity, as only septic TA muscles exhibited increased expression of proteolysis-related genes (Atrogin-1 and Murf1) at both 4 and 7 dps. Importantly, sepsis did alter the relative proportion of myofiber types in either muscle but selectively reduced the size of type IIb myofibers, with type I, type IIa and type IIx remaining unaffected. Additionally, muscle stem cell density was diminished only in septic TA muscles at 7 dps but preserved in SOL muscles.

Collectively, our results demonstrate that sepsis selectively targets glycolytic type IIb myofibers and decreases muscle stem cell pool in phasic muscles, potentially explaining muscle damage heterogeneity. Future studies will explore the underlying molecular mechanisms.

SESSION POSTERS 4 - 40

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Le Registre Français des Calpainopathies (CALPA) : mise en place et premiers résultats

Les calpainopathies sont des maladies neuromusculaires rares liées à des variants pathogènes du gène CAPN3, responsables principalement de la dystrophie musculaire des ceintures de type LGMDR1. Elles se caractérisent par une faiblesse musculaire proximale progressive débutant généralement dans l'enfance ou l'adolescence. Afin d'améliorer les connaissances sur l'histoire naturelle de ces maladies et de préparer les futurs essais thérapeutiques, l'AFM-Téléthon a développé le registre national des calpainopathies (CALPA), en cours de déploiement au sein des centres experts du réseau FILNEMUS.
Lancé en décembre 2025, ce registre vise à centraliser les données cliniques, biologiques, génétiques et sociodémographiques des patients atteints de calpainopathies suivis en France. Plus de 350 variables standardisées sont recueillies, couvrant les domaines diagnostiques, cliniques et génétiques, ainsi que les évaluations motrices, respiratoires et cardiaques et les traitements reçus. Le registre est conforme aux exigences réglementaires françaises et européennes en matière de protection des données personnelles (RGPD, CNIL) et bénéficie d'un dispositif dédié de contrôle qualité.
Au 21 septembre 2026, 60 patients sont identifiés comme potentiellement éligibles. Dix-sept patients sont déjà enregistrés dans la base de données et parmi eux, les données phénotypiques complètes sont disponibles pour 4 patients atteints de LGMDR1. Ces premières inclusions illustrent la faisabilité du recueil prospectif et standardisé des données au sein du registre.
Le registre CALPA permet d'identifier les patients susceptibles de participer aux futurs essais cliniques tout en fournissant une description standardisée de l'évolution de la maladie en vie réelle. Grâce à la structuration des données recueillies, il contribue aux études cliniques et épidémiologiques et soutient le développement de nouvelles approches thérapeutiques. Il constitue ainsi une ressource nationale essentielle pour améliorer les connaissances et la prise en charge des patients atteints de calpainopathies.

SESSION POSTERS 4 - 46*

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Urinary glucose tetrasaccharide (Glc4) in late-onset Pompe disease: a biomarker of disease progression and treatment response?

Background. Glycogen storage disease type 2, also known as Pompe Disease, is a rare lysosomal disorder defined by biallelic GAA gene mutations causing acid βglucosidase deficiency. Late-onset Pompe disease (LOPD) is characterized by progressive limb-girdle and axial muscle weakness, with early respiratory involvement. Enzyme replacement therapy (ERT) can slow disease progression and reduce mortality, highlighting the need for reliable longitudinal biomarkers. Urinary glucose tetrasaccharide (Glc4), a glycogen-derived biomarker widely used in Pompe disease, may reflect disease burden; however, its long-term prognostic value and utility for monitoring treatment response in LOPD remain incompletely defined.

Objective. To evaluate Urine Glc4 as a predictive biomarker of disease severity, progression, and ERT response in LOPD.
Methods. Data from the French Pompe Registry were retrospectively analyzed, including demographic, biochemical, genetic, and clinical outcome measures. Urine samples were collected between 2014 and 2024. Glc4 levels were measured by tandem mass spectrometry, expressed relative to urinary creatinine, using age-adjusted reference ranges.

Results. Eighty five LOPD patients were included, with ~1,000 urine samples analyzed (1–20 per patient) over 10 years. Glc4 kinetics were assessed at baseline and multiple intervals up to 24+ months. Changes and rates of change were correlated with clinical outcomes including walking tests and spirometry. Analyses accounted for age, sex, disease severity, progression, duration, genetic subgroup, and ERT type/duration.

Conclusion. This work clarifies the role of urine Glc4 in patient stratification and personalized medicine in LOPD offering guidance to clinicians and biologists in their practice in monitoring disease evolution and optimizing care.

SESSION POSTERS 4 - 52

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First Canadian Data from the DM-Scope Registry: Clinical and epidemiological profile of Myotonic dystrophy type 1 (DM1)

Background: The DM-Scope registry, initiated in France in 2005, expanded to Canada to form the International DM-Scope (iDM-Scope), a multicenter database collecting standardized real-world data on individuals with type 1 myotonic dystrophy (DM1).

Methods: Sociodemographic, clinical, and genetic data from Canadians with DM1 with ⩾1 visit between 2019 and 2025 were retrospectively and prospectively collected. Analyses were cross-sectional and based on the most recent visit.

Results: A total of 722 individuals with DM1 from seven Canadian centers were included (53% female). Age at inclusion was 46 [35-59] years. Clinical phenotypes included congenital (7%), infantile (14%), juvenile (23%), adult (27%), late-onset (14%), asymptomatic (1%), and no phenotype available (15%). CTG repeat length was 592 [169-919] repeats.
Loss of unassisted ambulation occurred in 12% at a median age of 51 [44-60] years. Death was reported in 11% at a median age of 59 [52-68] years, most commonly due to cardiac causes and aspiration pneumonia. Sixty percent reported somnolence. Median BMI was 25 [21-30] kg/m); 15% were underweight and 26% obese. Abnormal EKG was observed in 48% and diabetes mellitus in 13%. Digestive involvement was reported by 44%.
Cardiac device implantation occurred in 26% (pacemaker) and 3% (defibrillator), and cataract surgery occurred in 33% of patients. Non-invasive ventilation was used by 33%.
Reported medication were most frequently painkillers (74%), psychostimulants (33%), and anti-myotonia agents (9%).

Conclusion: This first Canadian iDM-Scope analysis demonstrates marked heterogeneity in DM1 expression, with multisystem complications contributing variably to individual disease burden beyond genetics alone. IDM-Scope provides a robust platform for personalized risk stratification and longitudinal outcome assessment, while international harmonization enables the generation of comparative data to better inform clinicians, researchers, and other stakeholders.

SESSION POSTERS 4 - 58*

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Selection of peptides for a muscle-targeted delivery of ASOs directed against DUX4 mRNAs through complementary approaches in silico, in vitro and in vivo

In a therapeutic goal for FSHD, antisense oligonucleotides (ASOs) directed against DUX4 mRNAs have been developed at UMONS. However, ASO use is limited by its restricted tissue delivery, lack of tissue selectivity, and rapid clearance. By screening a phage- display library of linear peptides against #1 myotubes or #2 a muscle-membrane protein (MMP), we selected peptides (MSPep) that specifically bind to muscle surface proteins. The 4 most promising MSPeps were synthesized with rhodamine conjugation and added to cell culture media to study their internalization into myotubes, hepatocytes, or renal cells. At all tested doses (10,40 µM), MSPepIC (from screening #1) and MSPep1-3 (from screening #2) were internalized into myotubes after 2h of incubation. As expected, MSPepIC and MSPep1-3 were not internalized by renal cells that do not express endogenous MMP. MSPep 1-3 were only internalized by renal cells when they were transfected with an MMP expression plasmid. MSPepIC was internalized by hepatocytes but to a lesser extent as compared to myotubes. MSPep1 is internalized by hepatocytes at a bigger extent than MSPepIC and MSPep 2-3, likely due to its helical tertiary structure. We designed MSPep-ASO complexes in silico based on literature data and
collaborators' expertise. Ongoing experiments aim to evaluate the ability of MSPep-ASOs to target skeletal muscle and deliver ASO efficiently into muscle cells.

SESSION POSTERS 4 - 64*

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Study of Satellite Cells in COPD-associated sarcopenia (SCOOP project

In a therapeutic goal for FSHD, antisense oligonucleotides (ASOs) directed against DUX4 mRNAs have been developed at UMONS. However, ASO use is limited by its restricted tissue delivery, lack of tissue selectivity, and rapid clearance. By screening a phage- display library of linear peptides against #1 myotubes or #2 a muscle-membrane protein (MMP), we selected peptides (MSPep) that specifically bind to muscle surface proteins. The 4 most promising MSPeps were synthesized with rhodamine conjugation and added to cell culture media to study their internalization into myotubes, hepatocytes, or renal cells. At all tested doses (10,40 µM), MSPepIC (from screening #1) and MSPep1-3 (from screening #2) were internalized into myotubes after 2h of incubation. As expected, MSPepIC and MSPep1-3 were not internalized by renal cells that do not express endogenous MMP. MSPep 1-3 were only internalized by renal cells when they were transfected with an MMP expression plasmid. MSPepIC was internalized by hepatocytes but to a lesser extent as compared to myotubes. MSPep1 is internalized by hepatocytes at a bigger extent than MSPepIC and MSPep 2-3, likely due to its helical tertiary structure. We designed MSPep-ASO complexes in silico based on literature data and
collaborators' expertise. Ongoing experiments aim to evaluate the ability of MSPep-ASOs to target skeletal muscle and deliver ASO efficiently into muscle cells.

SESSION POSTERS 4 - 70

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Cell-Hub: a complete graphical platform for single-nucleus RNA sequencing analysis applied to healthy and pathological skeletal muscle

Single-cell and single-nucleus RNA sequencing have become essential for dissecting tissue heterogeneity and intercellular interactions in complex organs. Skeletal muscle is a prime example: its function relies on the coordinated interplay between myofiber subtypes, muscle stem cells, motoneurons, fibro-adipogenic progenitors, endothelial cells, and immune populations, whose communication networks are reshaped in pathological conditions. However, the bioinformatics expertise required to perform these analyses remains a barrier for many laboratories, and existing graphical tools typically cover only individual steps without integrating the full analytical pipeline.

Here we present a complete end-to-end analysis of healthy and diseased mouse skeletal muscle using Cell-Hub, an open-source R/Shiny platform requiring no programming. Developed iteratively alongside experimental researchers. Cell-Hub integrates Seurat v5, CellChat 2, and Monocle 3 within a unified Docker-containerized interface. It covers the full pipeline from data loading and quality control through normalization, clustering, doublet detection, multi-dataset integration with batch correction, differential expression, co-expression analysis, exclusive biomarker detection, ligand-receptor communication inference, and trajectory analysis with pseudotime ordering.

We integrated snRNA-seq datasets from control and pathological hindlimb muscles to characterize shifts in cell-type composition, identify condition-specific markers, and compare intercellular communication networks between states. The exclusive biomarker detection module, based on a specificity score combining detection-rate differential and expression magnitude, identified genes highly specific to each population. Ligand-receptor analysis revealed rewiring of signaling networks.

All analyses, from raw count matrices to publication-ready figures, were performed entirely through the graphical interface without writing a single line of code, demonstrating that comprehensive single-cell analysis of skeletal muscle is accessible to laboratories without dedicated bioinformatics support.

SESSION POSTERS 4 - 76*

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Remote Longitudinal Motor Monitoring in children under 4 years of age with Duchenne Muscular Dystrophy (DMD): Preliminary Results

Children with Duchenne muscular dystrophy (DMD) are frequently symptomatic before the age of 4 years, yet there is still limited information available on this age group. Characterizing motor performance in this age group is increasingly important as diagnosis and therapeutic intervention occur earlier.
Objective: To longitudinally monitor motor development in children with DMD under 4 years of age using wearable sensors in their everyday environment.
Methods: Active NBS-DMD is an academic, multicenter, fully remote observational study launched in December 2025 at the Liège Neuromuscular Reference Centre (Belgium). Children with DMD under 4 years of age are monitored using Syde® wearable sensors, worn on both ankles, during a 4-week recording period at baseline, and for 3 weeks every three months thereafter, for up to 2.5 years. Outcomes include the SV95C, representing the speed of the fastest 5% of recorded strides. SV95C is a validated digital endpoint in ambulant patients with DMD aged 4 years and older; it's use in younger children is exploratory.
Results: Since December 2025, 18 children with DMD have been enrolled. Diagnosis followed blood testing performed for unrelated medical conditions (e.g., allergies or renal disorders) in 11 children, family screening in three, and investing of motor delay in four. Mean age at diagnosis was 13 months (SD 8.7). 15 participants (83.3%) had a deletion, and three (16.7%) a point mutation.
At diagnosis, 11 (61%) children were reported as asymptomatic. By study inclusion, parents reported symptoms in 16 (89%) including hypotonia, muscle weakness, and motor delay. Median age at independent walking was 15 months (P25: 14; P75: 23).
The first 15 children who completed a one-month Syde® monitoring period all recorded ⩾50 h of data, allowing derivation of the digital measures. Median SV95C was 1.17 m/s (P25: 1.05; P75: 1.27), compared with 2.14 m/s (P25: 1.80; P75: 2.40) in control children aged 1 to 8 years. The mean median stance percentage (MSP) was 65.4% (SD 1.7). At baseline, intraclass correlation coefficients for SV95C and MSP were 0.92 and 0.95, respectively (n = 13).
Conclusion: These preliminary results support the feasibility of remote wearable-based motor monitoring in children with DMD under 4 years, with good compliance. This approach provides objective measures of early walking performance in an age group for which quantitative natural history data remain limited.

SESSION POSTERS 4 - 82

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DEVOTE Part C and ONWARD Integrated Results: Exploring High Dose Nusinersen in Nusinersen-Experienced Participants with Spinal Muscular Atrophy (SMA)

DEVOTE (NCT04089566), a 3-part (A, B, C), Phase 2/3 trial, and ONWARD (NCT04729907), an ongoing Phase 3 open-label long-term extension study of DEVOTE, were designed to evaluate safety, tolerability, and PK of an investigational high dose (50/28 mg) nusinersen regimen in participants with SMA.

In Part B, participants receiving the high dose regimen showed statistically significant improvement over a matched sham comparator on the primary endpoint of change in CHOP-INTEND from baseline (BL) to Month (M) 10. The high dose safety profile was similar to the 12 mg regimen.

DEVOTE Part C (supportive; open-label) enrolled 40 children and adults (aged 4–65 years; 1–4 SMN2 copies) with infantile- or later-onset SMA who transitioned to the high dose regimen, following ⩾1 year of 12 mg nusinersen treatment. Participants received one 50 mg loading dose 4 months ±14 days after their last 12 mg dose, followed by two 28 mg maintenance doses on Days 121 and 241. ONWARD enrolled 39 participants who had completed M10 in DEVOTE Part C. The primary objective of DEVOTE Part C and ONWARD was to assess the safety and tolerability of the high dose regimen.

At interim data cut (May 30, 2024; up to 2.7 years of follow-up) in ONWARD, high dose nusinersen was generally well tolerated, with an adverse event (AE) profile broadly consistent with the 12 mg regimen. AEs were reported in 39/40 (98%) participants overall; 29 (72.5%) experienced AEs that were mild or moderate in severity; 10 (25.0%) experienced ⩾ 1 severe AE. Serious AEs were reported in 13 (33%) participants. The majority of participants showed consistent trends of improvement and maintenance in HFMSE and RULM from BL to M20. Ambulatory participants who completed the 6MWT at M20 maintained their total distance walked and fatigability. BL Plasma NfL levels in participants aged <18 years were within the range of healthy controls of similar ages and remained low after transitioning to high dose nusinersen.

DEVOTE Part C and ONWARD evaluated the safety and tolerability of high dose nusinersen (50/28 mg) in a broad study population previously treated with 12 mg nusinersen for a median of 3.9 years. The high dose regimen was generally well tolerated, with a safety profile consistent with the 12 mg regimen up to 2.7 years. Motor function improvements were observed across phenotypes and functional status. Collectively, these data support the transition of individuals from the 12 mg to the high dose regimen.

SESSION POSTERS 4 - 88

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Impact des modifications post-traductionnelles sur la localisation des lamines A/C

Les lamines A/C, codées par le gène LMNA, sont des filaments intermédiaires que l'on retrouve principalement sous la membrane interne du noyau. Elles assurent une fonction structurelle et de régulation transcriptionnelle. De nombreuses modifications post-traductionnelles ont été identifiées au niveau des lamines A/C. Parmi ces modifications, la phosphorylation de 3 sérines a été impliquée dans la dépolymérisation totale des lamines A/C juste avant la caryocinèse lors de la mitose. De façon intéressante, ces 3 sites sont également phosphorylés en interphase, à un niveau beaucoup plus faible, les lamines A/C phosphorylées s'accumulant au nucléoplasme.
Les mutations du gène LMNA sont responsables de nombreuses pathologies appelées laminopathies. Parmi ces laminopathies, le groupe le plus représenté correspond aux laminopathies des muscles striés, dont la forme la plus sévère, la dystrophie musculaire congénitale liée au gène LMNA (L-CMD), est caractérisée par une augmentation du pool de lamines A/C au nucléoplasme. Dans ce cadre, notre objectif est d'identifier les modifications post-traductionnelles impliquées dans cette accumulation nucléoplasmique des lamines A/C mutées L-CMD afin de pouvoir contrer ces modifications post-traductionnelles et ainsi relocaliser les lamines A/C à l'enveloppe nucléaire.
L'analyse des données de la littérature ainsi que des expériences de spectrométrie de masse nous ont conduit à sélectionner 9 sites de phosphorylation et 6 sites d'acétylation. Par mutagenèse dirigée, suivi de transfection transitoire en myoblastes C2C12, nous avons ainsi déterminé le taux de délocalisation des lamines A/C porteurs de mutants mimant ou empêchant la phosphorylation ou l'acétylation. Nous avons ainsi déterminé l'implication forte de 4 sites de phosphorylation dont 2 nouveaux, et d'un site d'acétylation dans la délocalisation de la lamine A au nucléoplasme. L'abrogation de la modification post-traductionnelle de ces sites en présence d'une mutation L-CMD est en cours d'analyse mais ne semble pas permettre de ré-adresser les lamines L-CMD à l'enveloppe nucléaire.

SESSION POSTERS 4 - 94*

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Targeting YAP/TAZ Signaling Restores Muscle Phenotype in Centronuclear Myopathy

Centronuclear myopathy (CNM) is a muscle disorder characterized by progressive muscle atrophy and, in severe cases, respiratory impairment. The autosomal dominant form (AD-CNM) is associated with mutations in the DNM2 gene, which encodes dynamin 2, a protein involved in endocytosis, a mechanosensitive process. It has been shown that mouse models expressing constitutively nuclear YAP in adult muscle fibers exhibit a phenotype similar to that observed in CNM.
In this context, we investigated the role of the transcriptional coactivators YAP and TAZ, key regulators of mechanotransduction, as potential therapeutic targets. In AD-CNM, YAP and TAZ are predominantly localized in the nucleus, whereas in healthy muscle cells they are mainly cytoplasmic. This nuclear localization is associated with their activation and the expression of genes involved in cell proliferation. This study aims to better understand the regulatory mechanisms underlying YAP/TAZ dysregulation in CNM and to assess the effects of their inhibition. To this end, we used verteporfin, a compound that disrupts the interaction between YAP/TAZ and their coactivator TEAD.
Our results show that verteporfin treatment restores normal YAP and TAZ levels and significantly improves the fusion index, suggesting a partial rescue of the muscle phenotype.

SESSION POSTERS 4 - 100

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Long-term impact of vamorolone on bone health compared to standard of care glucocorticoids (SoC-GC) in boys with Duchenne Muscular Dystrophy (DMD)

Background: Boys with DMD on standard of care glucocorticoids (SoC-GC) have high vertebral fracture (VF) risk and bone age delay.

Objectives: Indirect comparison of VF and bone age delay in DMD boys after long-term treatment with vamorolone vs SoC-GC.

Methods: Baseline data from 37 patients enrolled in GUARDIAN were used for propensity score matching with a SoC-GC cohort (N=60), previously published (Phung K & Ward LM. Osteoporosis Int. 2023 Jan; mostly on daily deflazacort). VF were evaluated on lateral spine X-rays according to the Genant semi-quantitative methodology, the Spinal Deformity Index (SDI) was calculated (sum of the Genant grades), and bone age was evaluated by BoneXpert™ on hand X-rays.

Results: At the time of the X-rays, mean ±SD ages in vamorolone (N=37) and matched GC (N=31) cohorts were 10.9±1.25 and 11.7±1.53 years. Mean drug exposure was 5.2±0.95 years for vamorolone (190.6 patient-years) vs 5.4±2.06 years on SoC-GC (167.5 patient-years). Mean doses at the time of X-ray were 4.89±1.28 mg/kg/day and 0.65±0.21 mg/kg/day for vamorolone and deflazacort, respectively. 3/37 (8.1%) patients had 9 VF on vamorolone vs 13/31 (41.9%) with 30 VF on SoC-GC (Odds Ratio (95%CI) 0.1296 (0.02903, 0.5789), p=0.0082). The mean SDI for subjects with and without VF was lower on vamorolone vs SoC-GC (0.32 vs 1.06). In the vamorolone cohort, the 3 patients with VF had SDI scores of 1, 3 and 8. In SoC-GC cohort, among the 13 patients with VF, 7 had SDI of 1, while the remaining patients had SDIs of 3, 4 (n=3), 5 and 6. Mean bone age delay was 0.8±1.5 years on vamorolone vs 1.6±1.6 years on SoC-GC.

Conclusions: The prevalence of VF was significantly lower with vamorolone compared to SoC-GC after ~5 years of exposure. Patients on vamorolone should continue to be monitored for VF.

SESSION POSTERS 5

Jeudi 19 Novembre
16h45 - 17h45

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LISTE POSTERS - SESSION 5

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SESSION POSTERS 5 - 5

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Correlation of individual survival of motor neuron (SMN) protein with observed efficacy in the risdiplam clinical trials

Background: Risdiplam (EVRYSDI®) is an oral survival of motor neuron 2 (SMN2) pre-mRNA splicing modifier approved for the treatment of spinal muscular atrophy (SMA).
Safety and efficacy of risdiplam were assessed in clinical studies of patients with SMA, from infants to adults, with a body weight ⩽109 kg and aged ⩽61 years old. Pharmacokinetic and pharmacodynamic data were used to select dosing regimens of 0.2 mg/kg for infants aged between 2 months and 2 years, 0.25 mg/kg for children ⩾2 years old with a body weight <20 kg, and 5 mg for patients with a body weight ⩾20 kg.
Pharmacodynamic markers SMN2 mRNA and SMN protein were assessed in blood samples obtained from all patients over the duration of the study for up to 2 years.

Objectives: Assess the correlation between individual patient SMN protein level and observed efficacy.

Results: Risdiplam's mode of action was confirmed by the shift from SMN2Δ7 mRNA to full-length mRNA. Risdiplam treatment led to a ⩾2-fold median increase in SMN protein levels within 4 weeks of the start of treatment, which was maintained throughout treatment.
Exposure–response analyses assessed the correlation between individual participant SMN protein level and observed efficacy in pivotal studies in patients with Type 1 (FIREFISH Part 2; NCT02913482) and Types 2/3 SMA (SUNFISH Part 2; NCT02908685). Correlation-efficacy analyses were conducted using absolute SMN protein values during the study treatment period and with the change from baseline in SMN protein level obtained for each patient pre- and post-risdiplam treatment.

Conclusions: Clinical studies confirmed the risdiplam mode of action and efficacy in patients. The results of the correlation of SMN protein in blood versus the assessed efficacy endpoints (FIREFISH: sitting, head control, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SUNFISH: 32-item Motor Function Measure, Revised Upper Limb Module) will be presented.

SESSION POSTERS 5 - 11*

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FLNC-related myopathy: a description of 27 unrelated patients from 21 families

Myofibrillar myopathies (MFM) are inherited neuromuscular disorders characterized by protein aggregation and myofibrillar disorganization. FLNC-related myopathy, a subtype of MFM, encompasses a broad clinical spectrum ranging from limb-girdle and distal myopathies to isolated cardiomyopathy. We retrospectively collected a cohort of 27 patients with genetically confirmed FLNC myopathy. Mean age of first symptoms and diagnosis was at 40±14 and 54±17 years of age, respectively. Proximal muscle weakness was identified in 13 patients (48%), distal muscle weakness in 3 patients (11%), proximal and distal weakness in 9 patients (33%) and 2 patients had no limb weakness (8%). Axial weakness was identified in 16 patients (59%), facial weakness in 4 patients (15%), cardiac involvement such as cardiomyopathies (hypertrophic or dilated) in 13 patients (48%), conduction and rhythm disorders requiring an implantable cardioverter defibrillator for 2 patients. Mean value of forced vital capacity was 85±28% and 3 patients had sleep apnea syndrome requiring nocturnal non-invasive ventilation. Muscle magnetic resonance imaging showed fatty replacement mainly in thigh muscles affecting the posterior compartment, pelvic girdle muscles and paravertebral muscles. Mean creatine kinase value was 502±436 U/L. Muscle biopsy showed muscle fiber size variability, intracytoplasmic aggregates, internalized nuclei, rimmed vacuoles and type I muscle fiber predominance. Identified FLNC mutation spectrum included heterozygous missense variants in 22 patients (81%), nonsense variants in 3 patients (11%) and a complex deletion insertion variant in 2 patients (7%). This study reports one of the largest multicenter cohorts of FLNC-related myopathy and confirms that the disease most frequently presents as an adult-onset proximal myopathy with frequent cardiac involvement. We also identify a relatively consistent MRI pattern involving the posterior thigh and paravertebral muscles and demonstrate substantial clinical and pathological heterogeneity despite predominantly missense FLNC variants. No clear genotype-phenotype correlation was identified, despite predominantly missense FLNC variants.

SESSION POSTERS 5 - 17

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Le registre national français des sarcoglycanopathies (SARCO) : mise en place et premiers résultats

Les sarcoglycanopathies sont des dystrophies musculaires des ceintures autosomiques récessives liées à des anomalies des gènes codant les α-, β-, γ- ou δ-sarcoglycanes. Ces maladies ultra-rares se caractérisent par une faiblesse musculaire proximale symétrique associée à une atteinte cardiaque et respiratoire d'expression variable. Malgré le développement récent d'approches thérapeutiques innovantes, notamment en thérapie génique, leur histoire naturelle reste encore insuffisamment documentée.
Afin d'améliorer les connaissances sur ces maladies et de faciliter le développement des futurs essais thérapeutiques, l'AFM-Téléthon a développé le registre national des sarcoglycanopathies (SARCO), lancé en mai 2025 et en cours de déploiement au sein des centres experts du réseau FILNEMUS. Ce registre vise à centraliser les données cliniques, biologiques, génétiques et sociodémographiques des patients suivis en France à travers un recueil harmonisé et sécurisé des données.
Plus de 500 variables standardisées sont collectées, couvrant les domaines clinique, génétique et sociodémographique, ainsi que les évaluations motrices, respiratoires et cardiaques, les traitements reçus et les données de biobanque. Le registre est conforme aux exigences réglementaires françaises et européennes en matière de protection des données personnelles (RGPD, CNIL) et bénéficie d'un dispositif dédié de contrôle qualité.
Au 21 septembre 2026, 33 patients sont identifiés comme potentiellement éligibles. Parmi eux, 23 patients sont enregistrés dans la base de données avec un phénotype confirmé : 6 sont atteints d'α-sarcoglycanopathie (LGMDR3) et 17 de γ-sarcoglycanopathie (LGMDR5). Ces premières inclusions illustrent la faisabilité du recueil prospectif et standardisé des données au sein du registre.
Le registre SARCO permet d'identifier les patients susceptibles de participer aux futurs essais cliniques tout en offrant une description structurée de l'évolution des sarcoglycanopathies en vie réelle. Grâce à l'harmonisation du recueil des données, il contribue aux études cliniques et épidémiologiques, améliore l'accessibilité des données pour les équipes de recherche et constitue une ressource nationale essentielle pour améliorer les connaissances et la prise en charge des patients atteints de sarcoglycanopathie.

SESSION POSTERS 5 - 23

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STELLAR Phase 3 Studies to Evaluate the Efficacy and Safety of Salanersen in Infants with Spinal Muscular Atrophy

Salanersen is a novel, intrathecally administered antisense oligonucleotide in development for spinal muscular atrophy (SMA). Salanersen corrects splicing of survival motor neuron 2 pre-mRNA by binding to a region also targeted by nusinersen and is designed to increase survival motor neuron protein. Salanersen has a new backbone chemistry that leads to high potency, enabling the potential for high efficacy with once yearly dosing. Two linked Phase 3 studies will assess the efficacy and safety of salanersen in infants with SMA who initiate treatment while presymptomatic.

STELLAR-1 is an open-label, single-arm study evaluating salanersen in treatment-naive, presymptomatic infants (aged ⩽ 6 weeks) with SMA and 2 or 3 survival motor neuron 2 (SMN2) copies. Participants will receive 80 mg salanersen annually during the 5-year study. Primary endpoints are attainment of World Health Organization motor milestones that are unexpected without treatment: sitting unsupported at 12-month follow-up and walking independently at 18-month follow-up for participants with 2 and 3 SMN2 copies, respectively.

STELLAR-2 is a randomized, double-blind, sham-controlled study evaluating salanersen in infants with SMA and 2 SMN2 copies who received treatment with onasemnogene abeparvovec (OA) at ⩽ 6 weeks of age. Participants are randomized at approximately 6 months post-OA to active treatment (80 mg salanersen annually) or sham control. After the 12-month controlled period, participants in the sham arm will transition to active treatment. Key efficacy endpoints include plasma neurofilament light chain levels, motor function scales, and electrophysiology between groups at 12-month and 5-year follow-up.

Data generated across STELLAR-1 and STELLAR-2 will provide insights on outcomes among infants who receive presymptomatic treatment with salanersen monotherapy, OA monotherapy, and OA followed by salanersen.

SESSION POSTERS 5 - 29

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Comparative Evaluation of Full-Length and Split-Cas9 for AAV-Mediated RYR1 Editing in Skeletal Muscle

RYR1-related myopathies are inherited neuromuscular disorders for which gene therapy remains challenging due to the large size of the RYR1 coding sequence, which prevents its replacement using conventional AAV vectors. Genome editing offers an alternative strategy to target RYR1 directly, but efficient delivery of CRISPR-Cas9 to skeletal muscle remains a major challenge. Muscle-targeting AAVs (MyoAAVs) provide a promising delivery platform, although their limited packaging capacity constrains the design of Cas9 expression cassettes and the incorporation of regulatory elements. Here, we compared full-length and split-Cas9 strategies for RYR1 knockout following intramuscular administration. Despite lower Cas9 expression, full-length Cas9 achieved editing efficiencies comparable to split-Cas9, with both approaches reducing RYR1 expression. Full-length Cas9 was subsequently selected for systemic administration, resulting in RYR1 editing and protein reduction, accompanied by body weight loss and decreased strength. These findings support the feasibility of MyoAAV-mediated RYR1 genome editing.

SESSION POSTERS 5 - 35*

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Allele-Specific Genome Editing for RYR1-Related Myopathies : Efficacy and Safety

RYR1-related myopathies (RYR1-RM), including central core disease (CCD), multiminicore disease (MmD) and malignant hyperthermia (MH), are caused by pathogenic variants in the RYR1 gene, which encodes the ryanodine receptor 1, a calcium release channel essential for excitation–contraction coupling and skeletal muscle contraction. In dominant RYR1-RM, selective inactivation of the mutant allele represents a promising therapeutic strategy, as a single functional RYR1 allele is sufficient to maintain normal protein levels.

We aimed to develop an allele-specific CRISPR/Cas9 genome-editing strategy capable of selectively targeting and silencing the mutant RYR1 allele, while investigating approaches to improve the safety of Cas9-based therapy by limiting its long-term expression.

An efficient allele-specific gRNA targeting the mutant RYR1 allele was identified, providing a basis for further development of a CRISPR/Cas9 therapeutic approach for dominant RYR1-related myopathies. In addition, the newly designed killer gRNA was successfully validated in vitro and represents a potential strategy to limit prolonged Cas9 expression. The next step will be to combine the allele-specific and killer gRNAs in a single MyoAAV vector, with the aim of reducing the number of vectors required for in vivo delivery and improving the safety and translational potential of this genome-editing approach.

SESSION POSTERS 5 - 41*

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Gene and pharmacological therapies for STAC3 congenital myopathy

STAC3 disorder is a rare and severe congenital myopathy caused by biallelic mutations in the STAC3 gene, which encodes an essential component of the skeletal muscle excitation–contraction coupling (ECC) machinery. Patients typically present congenital muscle weakness, facial and skeletal abnormalities and susceptibility to malignant hyperthermia, while feeding and respiratory difficulties are also commonly reported. The most frequent disease-causing variant is the missense mutation c.851G>C; p.Trp284Ser (W284S). Despite the severity of the disease and its broader relevance to calcium-release disorders, STAC3 disorder has been little studied, resulting in a complete absence of therapeutic options.
Here, we have generated a novel knock-in mouse model carrying the W280S mutation, corresponding to the recurrent human W284S variant. Heterozygous mice are viable and are currently being crossed to generate homozygous animals, that will undergo phenotyping characterization. Growth, locomotor activity and muscle strength will be assessed. Skeletal muscles will be collected for histological and molecular analyses to characterize the myopathic phenotype and underlying disease mechanisms. Furthermore, two complementary therapeutic strategies will be investigated, gene replacement to target the primary molecular defect and pharmacological enhancement of muscle contraction to mitigate its functional consequences. The therapeutic efficacy of each approach will be evaluated based on improvement in the myopathic phenotypes.
Overall, this work aims to establish a clinically relevant experimental model to advance our understanding of the poorly studied STAC3 disorder and provide a unique preclinical platform for therapeutic development. By investigating two complementary therapeutic proof-of-concept approaches, this study may also lay the groundwork for future translational strategies for STAC3 myopathy.

SESSION POSTERS 5 - 47

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L'atteinte des fléchisseurs du cou est fréquente, dès la première évaluation, dans les dystrophies myotoniques de type 2 (DM2)

Introduction : Au cours de la DM2, l'atteinte axiale est décrite. Nous avons étudié la fréquence de l'atteinte des fléchisseurs du cou (FC+) dès la première évaluation dans notre centre de référence neuromusculaire et au cours du suivi.

Méthodes : Étude observationnelle rétrospective incluant les patients ayant une DM2 génétiquement confirmée et évalués dans notre centre. Ont été exclus les dossiers avec données cliniques insuffisantes ou pathologie susceptible de compromettre l'évaluation. Ont été recueillis : âge, sexe, début des symptômes, motif du premier examen, contexte familial, FC+ au premier examen et au dernier suivi. Les analyses ont porté sur l'ensemble de la cohorte et sur un sous-groupe excluant les patients adressés après dépistage (D) génétique familial (« sans-D »).

Résultats : Parmi 73 patients identifiés, 12 ont été exclus (11 pour données insuffisantes, 1 pour atteinte cérébrale associée), donc 61 patients inclus. L'âge moyen à la première évaluation était de 50,5 ± 14,0 ans dans la cohorte entière et 53,3 ± 12,2 ans dans le groupe « sans-D ». Il n'existait pas de prédominance selon le sexe dans la cohorte. Les motifs d'adressage étaient : déficit des ceintures (57,4 %), dépistage familial (18 %), myotonie clinique (16,4 %) et myotonie électrique (8,2 %). Le groupe « sans-D » comprenait 50 patients. La durée médiane de suivi était de 5 ans [0–33]. Au premier bilan, un FC+ était présent chez 28/55 patients (50,9 %) dans la cohorte entière et 26/46 (56,5 %) dans le groupe « sans-D ». Au dernier suivi, ces proportions étaient respectivement de 37/57 (64,9 %) et 36/45 (80 %). Les patients FC+ étaient plus âgés au premier examen : 58,5 vs 44 ans dans la cohorte entière (p=0,0047) et 58,5 vs 51 ans dans le groupe « sans-D » (p=0,0429). Dans ce groupe, un adressage pour déficit des ceintures était plus fréquent chez les FC+ que chez les FC− (84,6 % vs 45 %).

Discussion : L'atteinte des fléchisseurs du cou est fréquente dans la DM2, présente chez environ la moitié des patients dès la première évaluation et chez 80 % des patients non adressés après dépistage familial au dernier suivi. Elle semble associée à un âge plus avancé et à un déficit des ceintures. Ces résultats sont limités par le caractère rétrospectif de l'étude et l'absence de standardisation de l'examen clinique.

SESSION POSTERS 5 - 53

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Characterisation of patients with generalised myasthenia gravis on zilucoplan treatment in European Managed Access Programmes

Introduction: Myasthenia gravis (MG) is a chronic autoimmune disease. In the Phase 3 RAISE study (NCT04115293) and its open-label extension (RAISE-XT/NCT04225871), zilucoplan demonstrated clinically meaningful improvements in MG-specific outcomes in patients with generalised MG (gMG). Managed Access Programmes (MAPs) enable pre-authorisation treatment for patients with a severe/debilitating/life-threatening condition, where available treatments are deemed inadequate and no clinical trials are available.

Objective: Describe zilucoplan utilisation patterns and patient characteristics in MAPs initiated under compassionate use/early access authorisation in France, and compassionate use in Italy and Spain.

Methods: This observational, retrospective, longitudinal cohort study included adults with gMG initiating zilucoplan in MAPs in France, Italy and Spain (December 2021–November 2024). Patient demographics and disease characteristics were described.

Results: Overall, 57 patients from France, 38 from Italy and <5 from Spain were included. Mean (standard deviation [SD]) age was 56.5 (19.8), 56.6 (14.4) and 48.8 (13.6) years, respectively. Most patients were female (50.9%, 65.8% and 75.0%, respectively). Additional data were available for France and Italy. Mean (SD) number of years since initial MG diagnosis was 8.7 (9.2) and 10.6 (9.6); 42.1% and 28.9% of patients, respectively, had an MG diagnosis <5 years. Baseline (mean [SD]) MG-ADL scores were 7.3 (4.7) and 8.7 (3.7), respectively. Garches score improved over time for patients in France. In the 2 years prior to enrolment, MG crises occurred in 61.1% and 10.8% of patients and MG-related hospitalisations occurred in 85.2% and 50.0%, respectively. Prior to enrolment, pyridostigmine use was reported in 73.7% and 97.4% of patients, and corticosteroid use was reported in 75.4% and 100%, respectively. Treatment outcomes data will be presented in the poster.

Conclusion: Patients with gMG who received zilucoplan as part of the MAP had a long disease duration and high rates of prior hospitalisation and crisis, reflecting their unmet clinical need. Funding: UCB.

SESSION POSTERS 5 - 59*

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DUX4 modulates an AMPK response in proliferating and differentiated muscle cells

DUX4 expression has been implicated in several pathophysiological processes contributing to the altered muscle phenotype observed in FSHD, including metabolic stress and mitochondrial dysfunction. In this context, reduced expression of PPARGC1A, encoding the transcriptional coactivator PGC-1β has been reported in immortalized FSHD patient-derived muscle cells. As a central regulator of mitochondrial metabolism and muscle homeostasis, PGC-1βis tightly regulated by post-translational modifications, including phosphorylation by AMP-activated protein kinase (AMPK), a major cellular energy sensor. Building on our expertise in AMPK signaling and its role in muscle metabolism, we investigated the impact of DUX4 expression on the AMPK–PGC-1βsignaling axis using the LHCN-M2-iDUX4 model. We first characterized the early response to DUX4 induction in proliferating myoblasts following doxycycline treatment (62.5 ng/mL; 6,18 and 24 h). We then extended our investigation to differentiated myotubes, in which DUX4 expression was induced for 48 h with doxycycline (62.5 ng/mL) following differentiation.Interestingly, PPARGC1A expression was increased under our experimental conditions along with upregulation of AMPKβ2 and regulatory subunits β3 and β2 in induced myoblasts but not in myotubes. This could be a result of a compensatory response to cope to mitochondrial alterations. Further analysis must be performed to determine the exact role of these key factors.

SESSION POSTERS 5 - 65

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Leveraging patient-derived myoblasts and FAPs to study neuromuscular diseases

The development of innovative therapies for neuromuscular diseases relies on robust, accessible, and physiologically relevant cellular models. Patient-derived myoblasts are particularly valuable as they retain each patient's genetic background. However, the limited proliferative capacity of primary cells restricts their long-term use and large-scale application.
To overcome this limitation, we have established a robust strategy for the immortalization of myoblasts obtained from muscle biopsies of patients with neuromuscular disorders. These immortalized cells preserve the key phenotypic and functional properties of primary myoblasts, including their ability to differentiate and fuse into multinucleated myotubes. To date, our collection includes more than 200 immortalized myoblast lines representing 36 neuromuscular diseases, including DMD, DM1, LGMDR2, OPMD, SMA, FSHD, and healthy controls.
When muscle biopsies are unavailable, patient-derived skin fibroblasts provide an alternative source. After immortalization, these cells are converted into myogenic cells through conditional expression of MyoD, enabling efficient differentiation into multinucleated myotubes. Several immortalized MyoD-converted fibroblast lines have been established from both healthy donors and patients with neuromuscular diseases.
In parallel, Fibro-Adipogenic Progenitors (FAPs), key regulators of muscle regeneration, fibrosis, and tissue remodeling, have emerged as important contributors to neuromuscular disease pathophysiology. To support research in this field, we have generated 19 immortalized FAP lines derived from healthy controls and patients affected by various neuromuscular disorders. Their phenotypic and functional characterization is currently underway.
Together, these cellular models constitute a unique resource for neuromuscular research and the rapid assessment of therapeutic strategies. Through the MyoLine platform, they are made available to the international academic community through collaborative projects and to industrial partners under dedicated material transfer agreements. In addition, MyoLine offers the development of customized cellular models tailored to specific research and preclinical needs.

SESSION POSTERS 5 - 71*

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Adapting to Hypoxia: Skeletal Muscle Plasticity and Regeneration under Sustained Intermittent Hypoxaemia

Episodic hypoxaemia is associated with muscle dysfunction in respiratory insufficiencies, but its effects depend on the hypoxia/reoxygenation pattern. Sustained Intermittent Hypoxemia (SIH) characterizes a large subgroup of COPD patients, yet muscle adaptations to SIH remain poorly known. Impaired muscle regeneration was also suggested in COPD, but the contribution of SIH and underlying mechanisms still need to be clarified.

To decipher the specific effect of episodic hypoxaemia on skeletal muscle regeneration, we used a reductionist mouse model of Sustained Intermittent Hypoxaemia (SIH; FiO_2: 10%, 8h/day) in a device optimized to avoid movement restriction and to ensure an even distribution of gaseous flow. Control animals were maintained in normoxia (NOR). In both groups, a CTX (Cardiotoxin) injection was performed in the fast-twitch TA muscle to induce damage–regeneration processes. Muscle lesions, structural changes, and expression of myogenic markers were investigated at 3, 7, 14, 21, and 28 days post-injection. In parallel, to investigate the myogenic process, a cellular model allowing physioxia (PO2 5%)/hypoxia (PO2 1%) exposure was implemented. Murine myoblast proliferation was assessed (EdU), as well as early (day 2, Myogenin+ nuclei) and late differentiation (day 4, MFI, MyHC+ area).

SIH exacerbated TA muscle damage area (Heidenhain blue+), particularly at early time points (3, 14 days post-injection). Regarding cross-sectional area (CSA) morphometric analyses, a reduced fibre size is observed in CTX mice, both in NOR-CTX and SIH-CTX groups at 7 days, mainly in type IIb myofibers. At 28 days post-injection, TA total CSA and type IIb myofiber CSA remain smaller in SIH-CTX compared to the uninjected NOR group. The expression of myogenic markers increased over time but was not markedly altered by SIH. In C2C12 murine myoblasts acclimatized to physioxia, hypoxia exposure affected proliferation, Myod and Myf5 expression, and myogenic differentiation (decreased number of Myogenin+ nuclei and MyHC area).

In conclusion, SIH aggravates CTX-induced muscle damage at early time points and alters the subsequent recovery, as shown by the remaining atrophy at late time points. Further studies are needed to attribute those defects to impaired regeneration. In vivo, myogenic markers are not drastically impacted by SIH. However, our finding in vitro supports the hypothesis of a hypoxia-mediated alteration in the myogenic process.

SESSION POSTERS 5 - 77*

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A 2D human skeletal muscle model to predict mRNA vaccine reactogenicity in vitro

mRNA vaccines induce transient inflammation that promotes effective immune responses but can also cause local and systemic reactogenicity. As these vaccines are administered intramuscularly, skeletal muscle cells and their local environment may contribute to inflammatory response, yet their role remains poorly understood. This study aims to develop an in vitro human skeletal muscle model to identify inflammatory biomarkers and pathways associated with mRNA vaccine reactogenicity.

Human primary myoblasts and differentiated myotubes were exposed for 24 hours to four mRNA/LNP vaccine formulations, selected for their distinct reactogenicity profiles evaluated in clinical trials and differing in both LNP composition and mRNA sequence, as well as to control medium or IFN-β as a positive control. Cell viability was preserved across conditions. mRNA formulations increased MHC class I and ICAM-1 expression in human myoblasts, with no substantial change in MHC class II expression, and induced the secretion of CCL3, CCL4, CXCL10, and MCP-1 by both myoblasts and myotubes. The magnitude of these cytokine responses positively correlated with the blood reactogenicity profiles of the mRNA formulations. Bulk RNA-seq further revealed enrichment of inflammatory pathways, including IFN-α and IFN-γ responses, TNF-α signaling via NF-κB, complement, inflammatory response, IL-6 JAK-STAT3 signaling, and IL-5 STAT2 signaling in both cell types. Notably, up-regulation of several inflammatory pathways was reduced with less reactogenic mRNA formulations, highlighting an association between the breadth and magnitude of the inflammatory transcriptional response and vaccine reactogenicity. For the most reactogenic formulations, the transcriptional response was broadly similar to that induced by IFN-β, suggesting that type I IFN signaling may be a key driver of the muscle response to mRNA vaccines.

Overall, these findings identify muscle-derived inflammatory mediators associated with mRNA vaccine reactogenicity and support a simple 2D in vitro skeletal muscle model for investigating mechanisms underlying vaccine-associated inflammation and predicting reactogenicity.

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SESSION POSTERS 5 - 83

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Long-Term Safety of Givinostat in Patients With Duchenne Muscular Dystrophy: Interim Results From an Open-Label Extension Study

The safety and efficacy of givinostat were evaluated in patients with Duchenne muscular dystrophy (DMD) in the phase 3 EPIDYS study (NCT02851797). An ongoing open-label extension (OLE) is evaluating the long-term safety, tolerability, and efficacy of givinostat in these patients who completed, or were screened but not randomized, in prior givinostat studies (NCT03373968). This interim analysis aimed to characterize the safety data observed to date in the OLE.

At data cutoff (December 31, 2023), 207 patients had enrolled: givinostat (n=119; mean [SD] age: 11.6 [2.1] y), delayed givinostat (placebo in prior study) (n=58; 11.5 [2.1] y), and naïve givinostat (not included in prior studies) (n=30; 10.5 [2.3] y) groups. All patients received weight-based givinostat and corticosteroids. Safety was evaluated in patients who received ⩾1 dose of givinostat.

The mean (SD) givinostat exposure was 1256.0 (522.9), 1134.9 (346.4), and 1073.7 (260.2) days in the givinostat, delayed givinostat, and naïve givinostat groups, respectively. Overall, 98.1% reported ⩾1 treatment-emergent adverse event (TEAE; 2793 events, mostly mild (2294) or moderate (445)), with similar incidence across groups. Diarrhea occurred in 27.7%, 36.2%, and 36.7%, and falls in 31.9%, 10.3%, and 33.3%. Thrombocytopenia was observed in 14.3%, 24.1%, and 13.3%, and decreased platelet count in 12.6%, 19.0%, and 10.0%, respectively. Increased blood triglycerides occurred in 18.5%, 19.0%, and 40.0%, and pyrexia occurred in 29.4%, 24.1%, and 13.3%, respectively. Decreased platelets and increased triglycerides during the first 2–4 weeks stabilized in the delayed and naïve groups and remained stable in the givinostat group.

These results align with the known safety profile of givinostat. Early platelets decrease and triglyceride increase stabilized over time. No new safety signals emerged in patients continuing givinostat. These data further support the favorable safety and tolerability profile of givinostat with long-term treatment.

SESSION POSTERS 5 - 89

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Antioxidant treatment can improve RyR1-related myopathies due to a decrease in RyR1 protein amount

We have developed a muscle-specific and inducible RyR1-KO mouse model (RyR-Rec), characterized by an approximately 50% reduction in RyR1 protein levels in skeletal muscle. This model recapitulates several key features of Central Core Disease (Pelletier et al., 2020), including reduced RyR1-mediated calcium release, muscle structural alterations, fiber atrophy, muscle weakness, abnormal mitochondrial distribution, and membrane remodeling. Further investigation of the molecular alterations in RyR-Rec muscles revealed a marked disruption of redox homeostasis. In this study, we tested several antioxidant compounds to determine whether restoring redox homeostasis could improve muscle function in RyR-Rec mice. In addition, we investigated potential sources of reactive oxygen species (ROS), with a particular focus on endoplasmic reticulum stress and mitochondrial dysfunction.

SESSION POSTERS 5 - 95*

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Paraspeckle impairment in ALS muscle contributes to altered muscle homeostasis

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease characterized by degeneration of motor neurons and progressive paralysis. Muscles also undergo cellular alterations, such as imbalances in RNA and protein metabolism and mitochondrial homeostasis [1].
Paraspeckles, a nuclear membraneless organelle, regulate these pathways through nuclear RNA and proteins sequestration. NEAT1_2, a long non-coding RNA acts as a scaffold to form paraspeckles by interacting with RNA binding proteins such as FUS and SFPQ that can be mutated in ALS [2]. Paraspeckles accumulate in the motor neurons of ALS patients [3] but their status in ALS muscle is not known. Therefore, we aim to explore their status and their role in the ALS muscle.
In primary myotube cultures from sporadic ALS patients, we show alterations of paraspeckle number and size independently from NEAT1_2 expression, suggesting paraspeckle malformation. Moreover, paraspeckles lost their stress sensing function in ALS myotubes. By depleting paraspeckles in control myotubes, we uncovered that paraspeckles are involved in the regulation of major muscular pathways such as muscular contraction, oxidative phosphorylation and thermogenesis. Therefore, paraspeckle alteration could be involved in muscle impairment in ALS. We are currently investigating whether genes that were differentially expressed after paraspeckle depletion in control muscle cells, are dysregulated in ALS myotubes and whether paraspeckles contribute to their dysregulation.
Altogether, our findings identify paraspeckles as contributor to ALS pathophysiology. The observed alterations suggest that paraspeckle dysfunction may actively participate in muscle impairment rather than merely reflecting disease progression.

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SESSION POSTERS 5 - 101

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La commission diagnostique FILNEMUS : innovations génomiques, approches fonctionnelles et accélération de l'accès aux traitements

La filière de santé maladies rares FILNEMUS coordonne les acteurs du diagnostic et de la prise en charge des maladies neuromusculaires rares. Sa sous-commission « Génétique moléculaire » œuvre à harmoniser les stratégies diagnostiques, intégrer les innovations génomiques et réduire l'errance diagnostique avec 4 sous-groupes : maladies mitochondriales, neuropathies périphériques héréditaires, myopathies et amyotrophies spinales.
Les travaux du Plan France Médecine Génomique 2025 (PFMG2025) ont donné lieu à une publication dans Génome Medicine (2026), montrant l'amélioration du rendement diagnostique du séquençage du génome (WGS) par rapport aux panels de gènes et à l'exome dans les myopathies. Des travaux complémentaires menés par le groupe neuropathies sur la même thématique sont en cours. L'actualisation du consensus national sur les listes de gènes des myopathies, publiée en 2026 dans le Journal of Neuromuscular Diseases, contribue à harmoniser les analyses. L'accès à l'analyse de l'ADN mitochondrial sur AURAGEN et SEQOIA depuis 2025 complète ces avancées.
Le développement de tests fonctionnels et le lien avec la recherche sont une priorité, avec un projet pilote consacré aux maladies mitochondriales (PNMR4) et la mise en place de RCP post génomiques.
La mise à jour des gènes actionnables impliqués dans les myopathies ainsi que l'intégration des gènes FILNEMUS dans la base de données TREATABOLOME, renforcent le lien entre diagnostic moléculaire et accès aux thérapeutiques. Le recensement national des patients atteints d'un déficit en thymidine kinase (TK2), maladie mitochondriale traitable, vise à favoriser un diagnostic précoce.
FILNEMUS a contribué à la mise en place, en septembre 2025, du dépistage néonatal moléculaire de l'amyotrophie spinale (SMA), facilitant un diagnostic précoce et un accès rapide au traitement.
Dans le cadre du projet PERIGENOMED-CLINICS, les GT clinico-biologiques FILNEMUS des différents sous-groupes ont pu valider une liste de maladies neuromusculaires candidates au dépistage génomique néonatal. La sous-commission actualise les arbres décisionnels du diagnostic moléculaire des myopathies, maladies mitochondriales et neuropathies, et diffuse des recommandations sur le dépistage du statut de porteur hétérozygote dans les myopathies rares autosomiques récessives.
Ces actions visent à améliorer le diagnostic et à accélérer l'accès aux traitements.

SESSION POSTERS 5 - 106

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Endothelial cell fate during muscle regeneration is governed by HIRA histone chaperone

Endothelial cells are essential for proper skeletal muscle homeostasis and regeneration, having a structural role and crosstalk with myogenic cells. To understand how endothelial cell fate decisions are determined during regeneration is crucial for muscle repair. In this study, we investigated the role of the histone chaperone HIRA in endothelial cells using a Cdh5 driven endothelial specific conditional mutant model crossed with Hira floxed mice. Following muscle injury, we observed a significant reduction in vascular density 7 days post-injury (dpi), with a decrease in Tomato lineage traced endothelial cells and CD31 positive cells, suggesting a delay in angiogenic response, as endothelial cells numbers returned to control levels 28 dpi. This vascular defect was accompanied by a significant increase in the number of VEGFR2 positive endothelial which is consistent with a delay of activation of angiogenesis. As VEGFR2 is expressed by the leading tip cells during the sprouting step of angiogenesis, this can indicate that the process of angiogenesis itself got delayed, Interestingly, the proliferation of endothelial cells remains unchanged between the control mice and the conditional knock-out (cKO), which indicates that the reduction of the vascular density does not result from a proliferative defect.

In parallel, we analyzed Myosin Heavy Chain 3 (MYH3), a marker for muscle regeneration as it is expressed by regenerative and newly formed fibers. The number of MYH3+ fibers was increased in the cKO muscles, consistent with the hypothesis of delayed regeneration.

Together, these results suggest that HIRA in endothelial cell is required for proper early angiogenic dynamics during muscle regeneration and may influence the timing of myogenic repair.

SESSION POSTERS 5 - 110*

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Regulation of muscle stem cell fusion in the context of myonuclear accretion

Skeletal muscle stem cells (MuSCs) contribute to muscle homeostasis and plasticity by fusing with adult myofibres and donating their cellular content – a process known as myonuclear accretion. However, the transcriptional role and underlying regulatory mechanisms of myonuclear accretion remain largely unexplored.

We previously identified AMPKα2 as a MuSC-intrinsic regulator of myonuclear accretion. Here, we performed a deeper analysis of two of its phosphotargets 'BAIAP2' and 'NCKAP1', in vitro in primary mouse MuSCs.

BAIAP2 and NCKAP1 were silenced in MuSCs using siRNA. After confirmation of silencing at the transcript level, cells were differentiated for 48h. In fixed cells, we measured the fusion index, demonstrating no effect of the absence of NCKAP1, and a decrease in fusion in absence of BAIAP2. Furthermore, live cells were tracked for 48h after silencing using holotomography (imaging based on the refractive index), which allowed us to visualize the fusion events and the formation of membrane protrusions, confirming the role of BAIAP2 infusion, and suggesting a potential effect of membrane protrusions.

Future work aims at identifying the upstream activators of the AMPKα2-BAIAP2 signalling axis, as well as characterizing the downstream molecular partners and consequences of BAIAP2-mediated regulation of myonuclear accretion.

SESSION POSTERS 5 - 113

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Fatty acid metabolism in muscle stem cells: a potential regulator of muscle regeneration

Skeletal muscle stem cells (MuSCs) play a central role in muscle homeostasis and regeneration. To fulfil these functions, MuSCs undergo profound changes in their cellular state, accompanied by major metabolic adaptations. While the contribution of glucose and amino acid metabolism to MuSC function has been extensively investigated, the role of fatty acid metabolism remains poorly understood.
The aim of this project is to characterize fatty acid (FA) remodeling during MuSC activation, identify genes involved in this process, determine the contribution of specific FAs to the myogenic program, and ultimately develop culture media with defined FA compositions for MuSCs.
Using transcriptomic analyses, we first found that MuSC activation is associated with increased expression of genes involved in FA uptake, while, surprisingly, genes involved in FA oxidation (FAO) are downregulated. To investigate whether these transcriptional changes are associated with functional metabolic adaptations, we used an in situ metabolic profiling approach that enables the measurement of metabolic enzyme activities directly in MuSCs within their native muscle environment. Consistent with the transcriptomic data, we found that the activity of a key enzyme involved in FAO decreases during MuSC activation.
These findings suggest that the increased uptake of FAs during MuSC activation may serve functions beyond energy production, potentially contributing to the remodeling of cellular lipid composition. We therefore investigated changes in the lipid profile of MuSCs during activation and observed substantial remodeling of their cellular lipid composition, supporting the hypothesis that FA metabolism is actively reorganized during the myogenic process.
Finally, using primary MuSC cultures, we investigated the functional consequences of altering FA availability. We found that supplementation with different FAs modulates MuSC entry into the cell cycle, suggesting that individual FAs may directly influence MuSC behavior.
Together, these results highlight the dynamic remodeling of FA metabolism during MuSC activation and support a potential regulatory role for FAs in the myogenic program. This work may contribute to the identification of metabolic pathways that could be targeted to modulate MuSC function and ultimately improve muscle regeneration in pathological conditions.

SESSION POSTERS 5 - 116

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Comparative analysis of long-term effectiveness of vamorolone vs standard of care glucocorticoid (SoC GC) treatment in boys with DMD

Background: Vamorolone has demonstrated efficacy for the treatment of DMD in short-term studies; however, the long-term durability remains unknown.

Objective: To assess the long-term effectiveness and changes in anthropometric measures in DMD boys treated with vamorolone compared to SoC GCs.

Methods: Corticosteroid-naïve children with DMD who initiated vamorolone between 4-7 years of age as part of VISION-DMD (NCT03439670) and VBP15-002/003/LTE (NCT02760264/NCT02760277/NCT03038399) studies and continued through various access programs until enrolling into GUARDIAN (NCT06713135). Patients had > 1 year of drug exposure and follow-up. Results were compared to pooled data from external studies (FOR-DMD [NCT01603407]; CINRG Duchenne Natural History Study [NCT00468832]) using propensity score matching. Loss of ambulation (LoA) was analysed by time to event (TTE) approach; slope analysis was used for anthropometry.

Results: The mean (SD) baseline age for TTE analysis was 5.8 (1.0) (vamorolone; N=81) and 6.1 (1.2) years (GCs; N=287), and for anthropometric analysis 5.8 (1.0) (vamorolone; N=110) and 5.9 (1.1) years (GCs; N=199). Both vamorolone cohorts had median drug exposures of ~5 years vs ~4.5 years for both SoC-GC cohorts. All drug exposures were daily. Majority of both vamorolone cohorts received 4-6mg/kg/day vamorolone, with exposures of 306 (TTE) and 410 (anthropometric) patient-years and 84 (TTE) and 107 (anthropometric) for 2 mg/kg/day. No statistically significant difference was seen in time from treatment start to LoA between vamorolone and pooled SoC GCs (nor deflazacort or prednisone separately), with Hazard Ratios (HR) of 1.05 (95% CI 0.53; 2.10), p=0.9041; 1.22 (0.57; 2.60), p=0.6544 and 0.92 (0.44; 1.94), p=0.8587. Vamorolone patients maintained normal growth whereas growth stunting (height Z-score < -2.0 SD) was observed on SOC-GCs (p<.0001). There was no difference in increase in BMI Z-scores between vamorolone and SoC-GCs over time or in weight-to-height trajectories.

Conclusions: Our results suggest comparable effectiveness of approximately 5 years of vamorolone to SoC-GCs while preserving growth.

SESSION POSTERS 5 - 119*

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Impact of a heat wave on skeletal muscle homeostasis and regeneration

Climate change represents a global health issue, with heat waves emerging as a critical environmental stressor. These extreme heat events often lead to severe fatigue, excessive sweating, nausea, headaches, cardiac and renal dysfunctions. However, the cellular and molecular impacts of heat waves on skeletal muscle remain poorly understood, despite its pivotal role in thermoregulation.
In this study, we investigated how acute heat wave exposure impacts skeletal muscle homeostasis and regeneration. Eight-week-old male C57BL6 mice were subjected to cardiotoxin-induced injury of the tibialis anterior (TA) muscle or left uninjured. They were then immediately exposed to a heat wave protocol (36°C at night, 26°C during the day) for five consecutive days, followed by a return to normal housing (22°C). Control mice remained in normal housing condition. Our results demonstrate that both uninjured or injured mice showed elevated nighttime body temperatures during the heat wave. During the heat wave, body weight fluctuated inversely to controls: nocturnal weight loss was partially recovered during the day, leading to overall weight loss, likely due to reduced food and water intake, especially at night. Under homeostatic conditions, TA muscle architecture (fiber size, satellite cell number and capillary density) remained unchanged in heat-exposed mice, both immediately after the heat wave (day 5) and two weeks later (day 14). After muscle injury, heat-exposed mice exhibited delayed satellite cell proliferation (PAX7+ KI67+ cells), along with the formation of smaller regenerating fibers from day 7 to day 30 post-injury. Surprisingly, regenerated muscles in heat-exposed mice were heavier and showed increased fibrosis 30 days post-injury.
Altogether, these findings indicate that acute heat wave exposure does not disrupt muscle homeostasis but impairs satellite cell function, increases interstitial fibrosis and delays skeletal muscle repair upon injury.

SESSION POSTERS 5 - 122*

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Primary cilia-targeted proteomics reveal dynamics in ciliary actin-binding proteins and Rho GTPases at different stages of the myogenic lineage

Adult muscle stem cells (MuSCs) are essential for skeletal muscle regeneration. Upon injury, normally quiescent MuSCs undergo extensive cytoskeletal remodeling to activate, re-enter the cell cycle, and proliferate to generate either lineage-committed myocytes or self-renewing reserve MuSCs. Quiescent MuSCs display a primary cilium, a microtubule-based organelle that protrudes from the cell surface and serves as a hub for chemical and mechanical signal transduction. The primary cilium is dynamically regulated and contributes to MuSCs lineage progression and self-renewal, notably through Hedgehog signaling. Interestingly, Hedgehog-related factors display differential localization in the primary cilium as MuSCs progress in their lineage, suggesting that ciliary protein content varies during this process. However, whether the ciliary proteome, and signaling activity, influence MuSC quiescence and fate beyond Hedgehog remains unclear.

Here we perform cilia-targeted biotinylation coupled with mass spectrometry to define the cilia proteome of proliferating and self-renewing muscle cells. Besides identifying core ciliary components shared across cell state, we find that primary cilia of proliferating and reserve MuSCs are enriched in actin cytoskeleton regulators, including Rho GTPases signaling effectors. Additionally, we could highlight distinctions between the proteome obtained for proliferating and reserve cell. These findings raise the hypothesis that primary cilia could contribute to cytoskeletal remodeling associated with MuSC self-renewal and return to quiescence. Consistently, conditional and tamoxifen-inducible ablation of primary cilia in the Pax7(CreERT2/+); Ift88(fl/fl); R26(mTmG/+) mouse model affects quiescent MuSC cytoskeleton and impairs MuSC capacity to activate, proliferate and self-renew. Together, our findings suggest that modulation of primary cilium composition may drive MuSC quiescence and fate decisions.

SESSION POSTERS 5 - 125*

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Characterization of the skeletal muscle triadome: identification of new structural and functional actors in triads

INTRODUCTION: Triads are specialized membrane structures essential for skeletal muscle contraction, formed by a transverse tubule flanked by two terminal cisternae of the sarcoplasmic reticulum. This close membrane apposition allows direct interaction between voltage sensors and calcium release channels (located respectively in the tubular and cisternal membranes), triggering the calcium release that drives contraction. Although this architecture must withstand the mechanical stress of contraction, the proteins ensuring its formation and maintenance remain poorly characterized. This membrane proximity also defines the triad as a membrane contact site, a class of structures that typically feature tethering proteins as well as proteins involved in other functions, such as lipid transport or cell signaling. To date, triad proteins have been studied almost exclusively for their role in calcium release, and the existence of proteins involved in other functions remains unexplored.

OBJECTIVES: This project aims to 1) establish the complete triad proteome and 2) determine whether newly identified proteins contribute to triad architecture and functions beyond calcium release. RESULTS: Using in vivo TurboID-based proximity labeling in adult mouse skeletal muscle, the first triad proteome was established, revealing several hundred proteins previously unknown at this location. Among them, three candidates were selected: while known in other cellular contexts for mediating membrane apposition and lipid transport, their presence at triads has never been reported.

FUTURE DIRECTIONS: Knockdown of these three candidates will be performed to assess their roles in triad formation and maintenance, excitation-contraction coupling efficiency, muscle force generation, and intermembrane lipid transfer. IMPACT: This work will elucidate how triads are assembled and maintained, while offering the first insights into their physiological functions beyond contraction. Given that several muscle disorders stem from mutations in triad proteins, these newly identified actors may provide valuable novel targets for myopathy research.

SESSION POSTERS 5 - 128

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Tolérance et efficacité à long terme de l'efgartigimod PH20 par voie sous-cutanée dans le traitement de la myasthénie généralisée : Résultats finaux de l'étude ADAPT-SC+

Contexte. L'efgartigimod est un fragment Fc d'IgG1 qui bloque le récepteur Fc néonatal. L'étude ADAPT-SC+ a évalué la tolérance et l'efficacité à long terme d'efgartigimod SC (coformulé avec l'hyaluronidase humaine recombinante PH20) dans la MG.

Méthodes. Efgartigimod a été administré en cycles de 4 injections hebdomadaires. Les cycles suivants ont été initiés sur la base d'une évaluation clinique (Année 1, ⩾4 semaines entre les cycles; Année 2 et suivantes, ⩾1 semaine entre les cycles). L'incidence et la gravité des événements indésirables (EI) ont été évaluées ainsi que l'efficacité avec l'échelle MG-ADL, l'impact sur la qualité de vie (QdV) avec le questionnaire MG-QoL15r.

Résultats. 180 participants ont reçu ⩾1 injection d'efgartigimod SC: durée moyenne [écart-type] de l'étude, 2,6 [0,9]ans; 459,4 participants-années de suivi. Les EI étaient majoritairement légers/modérés. Les réactions au site d'injection (RSI) n'ont pas entraîné d'arrêt de traitement et ont diminué au fil des cycles. L'intervalle moyen médian (Q1, Q3) entre les cycles a diminué de 4,8 (4,3, 7,9) semaines à 4,2 (3,0, 6,5) semaines. Efgartigimod a été bien toléré. Des améliorations du score MG-ADL ont été observées chez les participants anti-RACh+ dès la semaine 1 et maintenues jusqu'à la semaine 163; des améliorations similaires ont été observées chez les participants anti-RACh−. Une expression minimale des symptômes (MSE; score MG-ADL, 0-1) a été observée au moins une fois chez 59,2% (n=84) des participants anti-RACh+ et 34,2% (n=13) des participants anti-RACh−. Parmi ceux qui atteignent une MSE, elle a été soutenue chez 88,1% (n=74) des participants anti-RACh+ et 69,2% (n=9) des participants anti-RACh− lors d'évaluations ⩾4 semaines. Des améliorations soutenues du score MG-QoL15r ont été observées.

Conclusion. Le traitement à long terme par efgartigimod SC a été bien toléré, a induit une efficacité et une MSE soutenue et des améliorations de la QdV chez des patients myasthéniques.

SESSION POSTERS 5 - 131*

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Transformations de la pratique professionnelle et de la relation de soin dans la SMA adulte.

L'arrivée des traitements innovants a modifié la prise en charge de l'amyotrophie spinale (SMA) adulte. Au-delà de leurs effets cliniques, ces thérapeutiques constituent un changement de paradigme : la SMA cesse d'être seulement un destin biologique et devient un objet de choix, engageant des possibilités inédites de transformation du devenir corporel. Les cliniciens ne sont plus seulement confrontés à de nouvelles prescriptions : ils accompagnent des patients dont les attentes, espoirs, hésitations, refus ou renoncements redéfinissent les échanges, les décisions et les responsabilités partagées. L'innovation thérapeutique transforme ainsi l'expérience des patients, redéfinit les pratiques médicales et convoque de nouveaux enjeux éthiques et relationnels. Pourtant, si la littérature documente l'efficacité et la sécurité de ces traitements, leurs effets sur les expériences individuelles, les pratiques médicales, les décisions thérapeutiques et la relation de soin demeurent peu explorés.

Objectif : Comprendre comment les traitements innovants reconfigurent les pratiques de prescription et la construction de la décision thérapeutique en transformant conjointement les représentations et l'expérience des patients et des neurologues.

Méthode : Étude nationale multicentrique à méthodologie mixte. Cohorte des neurologues prescripteurs : un questionnaire explorera les pratiques de prescription, les représentations des traitements et les enjeux éthiques et institutionnels associés. Des entretiens semi-structurés approfondiront l'expérience de ces thérapeutiques, les transformations de la pratique clinique et de la relation de soin. Cohorte des patients : un questionnaire destiné aux adultes atteints de SMA (types II à IV) explorera les représentations, les enjeux ainsi que l'expérience de ces traitements. Des entretiens semi-structurés auprès de patients ayant accepté ou refusé un traitement exploreront leur expérience subjective et leur processus décisionnel.

Résultats attendus / Perspectives : Cette recherche visera à comprendre les transformations induites par l'innovation thérapeutique et à identifier les déterminants cliniques, relationnels et institutionnels influençant les pratiques et les choix thérapeutiques. Ces résultats pourront éclairer les pratiques de prescription, les recommandations professionnelles et la réflexion éthique des praticiens. Ils pourront apporter des repères pour d'autres maladies rares confrontées aux innovations thérapeutiques.

SESSION POSTERS 5 - 134*

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Skeletal Muscle Alterations in the Early Stages of Multiple Sclerosis

Background: Muscle weakness is common in people with multiple sclerosis (PwMS). Although mainly studied at the central nervous system level, skeletal muscle alterations have also been reported in PwMS with a long-standing diagnosis. This includes changes in muscle fiber-type composition, muscle hypotrophy, and impaired oxidative metabolism. These alterations may result from physical deconditioning due to a sedentary and inactive lifestyle and/or disease-related mechanisms. This study aimed to characterize skeletal muscle alterations in recently diagnosed PwMS (R-PwMS).

Methods: Twenty-six R-PwMS (disease duration ⩽2 years) and twelve healthy controls matched for age, sex, and body mass index were included. Vastus lateralis muscle biopsies were performed to assess muscle fiber structural characteristics (fiber type distribution and cross-sectional area [CSA]), microvascular characteristics, and enzyme activities of myokinase (MK), creatine kinase (CK), enolase (ENO), citrate synthase (CS), and cytochrome c oxidase (COx).

Results: Muscle fiber type distribution was similar between groups ($p > 0.05$). PwMS exhibited a 14% lower mean surface area covered by 100 muscle fibers, accounting for fiber type distribution, than controls ($p = 0.043$) driven by lower CSA in type IIa (−16%, $p = 0.040$) and type IIx fibers (−27%, $p = 0.011$), while type I fiber CSA was preserved ($p > 0.05$). Microvascular characteristics were similar between groups ($p > 0.05$), except for a reduced number of capillaries around type IIa fibers in PwMS (-14%, $p = 0.049$). Whole-fiber COx activity did not differ between groups. However, PwMS exhibited reduced COx activity in the subsarcolemmal ($p = 0.004$) and intramyofibrillar ($p = 0.016$) regions of type I fibers, with no differences in type IIa or IIx fibers ($p > 0.05$). CS, ENO, and MK activities were similar between groups, whereas CK activity was 9% lower in PwMS ($p = 0.033$).

Conclusion: Compared to healthy individuals, PwMS exhibited structural and metabolic alterations in their skeletal muscle, these changes being characterized by selective hypotrophy of type II fibers, reduced COx activity in type I fibers, and decreased CK activity. These findings suggest that skeletal muscle alterations emerge early in the disease course, potentially reflecting disease-related mechanisms, including the chronic systemic inflammatory environment associated with MS, rather than chronic physical deconditioning alone.

SESSION POSTERS 5 - 137

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Senescent cells orchestrate macrophage responses to promote skeletal muscle regeneration

Cellular senescence is a stress response characterized by stable cell cycle arrest and acquisition of a robust secretory phenotypes, which primarily mediate the communication between senescence and microenvironment. There is a transient senescence induction during muscle regeneration, and suppression of the senescent program in geriatric MuSCs (Muscle Stem Cells) restores their regenerative capacity. We observed that in both young and old regenerative muscle, fibro-adipogenic progenitors (FAPs) represent the main cellular population to become senescence. While they exhibit an inflammatory and immune-associated state in aged context, senescent young FAPs formed a major senescence-associated stromal population with a regeneration-associated program, that is beneficial for efficient muscle repair. This different transcriptomic signature suggests that senescent cells potentially communicate differently with microenvironment within young and old regenerative muscle. Thus, we asked how senescent cells communicate with the cellular environment and particularly with immune system in the context of muscle regeneration. Transcriptomic analysis and functional in vitro experiments point out that secreted factors from senescent cells induces a pro-differentiation/fusion response in macrophages toward young and old MuSCs, facilitating the formation of multinucleated myotubes. Interestingly, old macrophages are not able to adopt this pro-regenerative phenotype. Therefore, our results suggest a crosstalk between senescent cells and macrophages involved in efficient muscle repair, that is dysregulated in aged context.

SESSION POSTERS 5 - 140

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Effect of vamorolone and prednisone on glucose and lipid metabolism in boys with Duchenne Muscular Dystrophy (DMD)

Background: Prednisone (PRED) is known to increase insulin resistance and serum triglyceride levels. Vamorolone (VAM) is a dissociative corticosteroid with a unique mode of action that may modify its metabolic safety profile.

Objectives: Compare the effect of VAM and PRED on glucose and lipid metabolism.
Methods: VISION-DMD (VBP15-004) was a randomized double-blind study assessing PRED 0.75mg/kg/d or VAM 6 mg/kg/d in corticosteroid naïve, 4-⩽7y boys with DMD. Fasting glucose, insulin, hemoglobin A1c (HbA1c), triglycerides (TG), and total-, LDL-, and HDL-cholesterol were assessed after 24 weeks of treatment. GUARDIAN (SNT-IV-VAM-011) is assessing the long-term safety and effectiveness of VAM in boys with DMD who have completed prior studies.

Results: In VISION-DMD, fasting insulin levels increased after 24 weeks of treatment with both PRED and VAM (Change from baseline CBL [mean±SEM] +43±16 vs +53±14 pmol/L, respectively), without increasing fasting glucose or HbA1c. TG increased more with PRED than with VAM (CBL mean±SEM: 0.581±0.132 vs 0.287±0.110 mmol/L). HDL-cholesterol increased after treatment with PRED and VAM (CBL mean±SEM: 0.127±0.026 vs 0.098±0.035 mmol/L). LDL cholesterol decreased by ~5-10% after treatment with both. In GUARDIAN, mean HbA1c was 5.4% (ref 4,4-5,7%), mean±SEM total cholesterol was 4.2±0.11 mmol/L, and mean±SEM LDL-cholesterol was 2.3± 0.11 mmol/L (1 patient above the normal range) at baseline (mean duration of treatment 5.2 y; mean daily dose 4.7 mg/kg/d). Low HDL-cholesterol was observed in 21% of patients; mean±SEM TG was 1.4±0.1 mmol/L, with 26% of patients above the normal range.

Conclusion: VAM does not change fasting blood glucose or HbA1c levels even after longterm use and has less impact on serum triglycerides than PRED.

SESSION POSTERS 5 - 143

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Thyroid dysfunction in FSHD: prevalence and associated factors in the French FSHD registry

Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common muscular dystrophies. FSHD1 and FSHD2 have distinct molecular causes but share aberrant expression of the transcription factor DUX4. Marked inter- and intrafamilial clinical variability suggests that additional factors may modulate disease expression. These may include comorbidities with overlapping symptoms, particularly autoimmune disorders, which can complicate clinical assessment and management. Thyroid dysfunction, potentially autoimmune in origin, is one such condition: it can cause muscle weakness, myalgia, and exercise intolerance, yet its prevalence and associated factors in FSHD remain poorly characterized. Using the French national FSHD registry, we assessed its prevalence and associations with demographic, clinical, and molecular characteristics.

Uni- and multivariable cross-sectional analyses were used to assess factors associated with thyroid dysfunction. For trend analyses, based on the proposed FSHD1–FSHD2 continuum, molecular categories were ordered by increasing D4Z4 repeat count in FSHD1, with FSHD2 treated as a separate category following the 8–10 repeat unit (RU) group.

Among 1,252 patients, thyroid dysfunction was recorded in 10.3%, with a higher prevalence in females than males (16.7% vs 4.8%). In univariable analyses, female sex and older age were associated with higher odds of thyroid dysfunction (both $p < 0.001$). A trend toward higher prevalence across molecular categories was significant in females (p for trend = 0.011) but not in males. In a multivariable model including an age-by-molecular-group interaction, patients with FSHD1 carrying 8–10 RUs or with FSHD2 had higher odds at the mean age than those with FSHD1 carrying <8 RUs (OR 1.76, 95% CI 1.06–2.91). The age-related increase in odds was weaker in the 8–10 RU/FSHD2 group (interaction OR per 10-year increase 0.63, 95% CI 0.46–0.86).

These findings highlight the importance of considering thyroid dysfunction when assessing patients with FSHD. Further characterization of these disorders, particularly whether they are of autoimmune etiology, could help clarify the observed association with molecular characteristics. Confirmation of this age-dependent association in independent cohorts would provide a stronger basis for exploring its biological underpinnings and clinical implications.

This work was supported by the AFM-Téléthon.

SESSION POSTERS 5 - 146

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Cumulative clinical safety experience with Genethon's AAV8 microdystrophin gene therapy (GNT0004) from an ongoing trial in ambulant boys with Duchenne muscular dystrophy

Duchenne Muscular Dystrophy (DMD) is a rare, X-linked, severe disease caused by mutations in the dystrophin gene. DMD is characterized by a heterogeneous clinical course and progressive muscle loss, resulting in impairment of respiratory and cardiac functions, and early death. Despite advances in multidisciplinary care and steroid treatments, no curative therapy currently exists in Europe, and a substantial unmet medical need remains.
GNT0004 is a microdystrophin gene therapy for DMD that completed phase I/II (Part 1 of GNT-016-MDYF trial; CTIS number: 2020-002093-27) and is being evaluated in an ongoing phase III study in ambulant boys aged 6-10 years (Part 2).
We report safety data from 15 patients dosed (cut-off date: Apr 22, 2026): 5 enrolled in Part 1 (1×10^{13} vg/kg, n=2; 3×10^{13} vg/kg, n=3) and 10 enrolled in the ongoing placebo-controled Part 2 (3×10^{13} vg/kg). Prophylactic immunomodulation consisted of a 3-month corticosteroid regimen (on top of background steroid treatment for DMD), and 2 months of sirolimus (trough levels 4-8 ng/ml).
At 3×10^{13} vg/kg (mean follow-up: 15.7 [SD 20.7]; range: 2 to 61 months), GNT0004 was well tolerated. No deaths, acute liver injury (ALI) or acute liver failure (ALF) were reported. The most frequently reported adverse reactions (ADR) were mild to moderate hepatic reactions, asymptomatic elevations of liver enzymes, and were reported in 2of 13 patients (15%). Bilirubin levels remained within the normal range. One patient experienced an infusion-related reaction (IRR). No criteria for a severe anaphylactic reaction have been observed (no hypotension, no altered alertness, no diarrhea, no breathing difficulties, no sign of shock). No significant tolerability concerns related to sirolimus were reported, and no severe infection occurred during the prophylactic treatment or tapering periods.
These findings support the premise that a comparatively low vector dose, together with transient sirolimus prophylaxis and close monitoring, may optimize the benefit-risk profile of systemic AAV gene therapy.

SESSION POSTERS 5 - 149

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Tubulin isotype diversity as a driver of skeletal muscle architecture

Skeletal muscle contraction relies largely on the functional organization of muscle cells. In particular, the microtubule network plays an essential role in muscle development, intracellular organization and contractile function. Its organization is regulated by several microtubule-associated proteins (MAPs), tubulin post-translational modifications (PTMs) and tubulin isotypes. However, the specific contribution of individual tubulin isotypes to muscle cell differentiation and homeostasis remains poorly understood. Recently, an α-tubulin isotype, Tuba4a, was identified as causing myofibrillar myopathy when mutated.

To investigate the role of Tuba4a in skeletal muscle cells, we used isolated muscle fibers and primary muscle cell cultures derived from Tuba4a knockout (KO) animals, as well as Tuba4a overexpression and depletion approaches in wild-type (WT) cells. Our preliminary results reveal stage-dependent effects of Tuba4a on muscle cells, with distinct consequences during early differentiation and in mature muscle fibers. These findings suggest that Tuba4a contributes differently to microtubule organization and function throughout muscle cell development and maturation.

Interestingly, these observations are consistent with phenotypes reported in patients carrying TUBA4A mutations, supporting a link between altered tubulin isotype function, microtubule organization and muscle dysfunction. Together, this work aims to elucidate the stage-specific role of Tuba4a in skeletal muscle and to better understand how the regulation of a single tubulin isotype contributes to the establishment and maintenance of a functional muscle microtubule network.

SESSION POSTERS 5 - 152

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Myopathie lipidique subaiguë sévère après prise transitoire de sertraline

Introduction : des formes tardives de troubles de la beta-oxydation des acides gras de type MADD ont récemment été décrites chez des patients sous sertraline, porteur ou non de mutations génétiques des gènes ETFA, ETFB et ETFDH. Nous rapportons le cas d'une patiente présentant une forme grave et sévère de lipidose musculaire, progressant après la prise temporaire de sertraline, et d'évolution favorable sous riboflavine.
Cas clinique : une femme de 74 ans, suivie pour un méningiome de l'angle ponto-cérébelleux gauche traitée par radiothérapie et une hypoparathyroidie, a présenté un tableau de tremblement puis de tétraparésie d' aggravation progressive avec perte de la marche en 4 mois, troubles de la déglutition avec perte de poids et cervicalgie. Elle souffre d' asthénie et de troubles de la déglutition douloureux. L'examen clinique retrouve une tête tombante, une faiblesse musculaire diffuse à prédominance proximale, sans amyotrophie ; les ROT sont faibles aux membres inférieurs. Elle est dépendante pour tous les actes de la vie quotidienne (transfert, habillage). Le bilan paraclinique retrouve des CPK à 239 U/L (Norme < 170) et la présence d'un syndrome myogène à l'EMG. La biopsie musculaire montre une myopathie lipidique vacuolaire et le profil des acylcarnitines plasmatiques est en faveur d'un MADD. Sur le plan génétique, identification d'un variant à l'état hétérozygote dans le gène ETFDH ne permettant pas de retenir l'hypothèse d' une forme génétique de MADD. Evolution favorable des symptômes après mise en place d' un traitement par Riboflavine dans un 1er temps, puis l'ajout de Levocarnil. La prise d'un traitement par sertraline a été retrouvé de façon transitoire (2-3 semaines), au début de l'aggravation de la fonction motrice.
Conclusion : ce cas illustre la nécessité de rechercher un antécédent de prise de sertraline et de traiter systématiquement par vitamine B2 tout patient symptomatique présentant une myopathie lipidique.

SESSION POSTERS 5 - 155

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Drosophila model reveals Myo-miR-1 dependent gene deregulations in DM1

Steinert disease, or myotonic dystrophy type 1 (DM1), is a multisystemic disorder characterized by myotonia and muscle degeneration. Congenital myotonic dystrophy (CDM) is the most severe form of myotonic dystrophy type 1 (DM1), leading to developmental disabilities with motor and cognitive impairments. Both are caused by a toxic RNA gain-of-function mechanism resulting from the expansion of CTG repeats in the 3βuntranslated region of the DMPK gene. The mutant DMPK transcripts containing expanded CUG form nuclear foci and sequester the Muscleblind-like 1 splicing factor, resulting in mis-splicing of its targets. The sequestration of MBNL proteins also disrupts processing and leads to down-regulation of the muscle- and heart-specific miRNA, miR-1. Here, we use Drosophila DM1 models to explore the role of miR-1 during embryonic muscle formation and its impact on larval mobility and muscle structure. We combined in silico screening for miR-1 targets with transcriptional profiling of DM1 muscle to identify miR-1 target genes with potential roles in CDM. We identified Mical as a miR-1 target involved in DM1. Mical encodes a multi-domain flavoprotein monooxygenase, which oxidizes actin, resulting in disassembly of actin filaments. We report a functional analysis of embryonic muscle and larval defects in Drosophila CDM model and show that reduced miR-1 levels and overexpression of its target Mical contribute to pathogenic CDM muscle anomalies.

SESSION POSTERS 6

Vendredi 20 Novembre
10h30 - 11h00

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Vendredi 20 novembre de 10h30 à 11h00

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18	*	MESBAH	Marvin	Investigation and Therapeutic Targeting of Ferroptosis in Dystrophin-Deficient Rats
24		METAY	Corinne	Etude de la relation génotype – phénotype et des impacts fonctionnels de variants du gène PLOD1 dans une cohorte de 15 patients atteints du syndrome d'Ehlers-Danlos cyphoscoliotique
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66		SOUVANNANORATH	Sarah	Un nouveau variant du gène KBTBD13 élargit le spectre clinique et pathologique de la myopathie congénitale à batônnets de type 6 (NEM6).
72		STOCKHOLM	Daniel	MuscleJ2 evolved: an enhanced platform with AI-assisted tools for quantitative analysis of skeletal muscles
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SESSION POSTERS 6 - 6*

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Fertilité sous Risdiplam : exemples d'attitudes conservatrices de gamètes à partir de 3 situations cliniques, en l'absence de recommandation scientifique établie

L'amyotrophie spinale (AMS) est une affection pouvant elle-même être pourvoyeuse d'infertilité par plusieurs mécanismes suspectés, potentiellement aggravée par l'exposition au Risdiplam avec un effet suposé réversible.
Nous présentons trois situations cliniques distinctes, afin d'illustrer diverses attitudes conservatrices de gamètes.
Cas 1 : Jeune homme âgé de 20 ans présentant une AMS type III. Initiation d'un traitement par Nusinersen à 11 ans, avec une substitution en faveur du Risdiplam, à l'âge de 14 ans devant une stagnation fonctionnelle mesurée. Après obtention d'une puberté clinique à l'âge de 16 ans, arrêt du Risdiplam durant 4 mois puis réalisation d'une conservation de gamètes avant reprise du traitement (10 paillettes contenant environ 2,2 millions de spermatozoïdes, mobilité progressive 30 %). Patient actuellement sous Risdiplam et Apetigromab.
Cas 2 : Patient âgé de 17 ans, présentant une AMS type III diagnostiquée à l'âge de 14 ans, traitée initialement par Nusinersen. Devant des effets secondaires (syndromes post-PL récurrents), substitution au profit du Risdiplam. Réalisation d'une conservation de gamètes (18 paillettes, de 3,5 millions de spermatozoïdes à 12 millions de spermatozoïdes, mobilité progressive 40 à 45 %), puis initiation du Risdiplam au décours.
Cas 3 : Patient âge de 29 ans présentant une AMS de type II, en activité professionnelle, vivant en couple avec projet de paternité exprimé dès 2021 avant la validation en RCP d'un traitement par Risdiplam. Pas de conservation possible de spermatozoïdes avant introduction du Risdiplam. Après 3 ans sous Risdiplam ; oligospermie sévère à 0,2 millions/mL de spermatozoïdes (mobilité progressive 34%) sur le spermogramme. Début d'une procédure d'AMP avec conservation de gamètes : après arrêt du traitement, réalisation de 2 spermogrammes de contrôle à 5 et 7 mois sans exposition retrouvent respectivement, une oligospermie à 1 millions/mL (hypomobilité progressive 40%) et à 16 millions de spermatozoïdes/mL (mobilité progressive 60%) permettant une FIV.
Ces trois observations cliniques illustrent les divers schémas préventifs de conservation de gamètes proposés chez les patients de sexe masculins, quel que soit les âges, atteints d'une AMS. L'impact du Risdiplam sur la spermatogénèse est repris sur le plan physiopathologique.

SESSION POSTERS 6 - 12

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The SOLAR study: Phase 3 Study to Evaluate the Efficacy and Safety of Salanersen in Participants Aged 15-60 Years with Spinal Muscular Atrophy

Salanersen is a novel, intrathecally administered antisense oligonucleotide in development for spinal muscular atrophy (SMA). Salanersen corrects splicing of survival motor neuron 2 pre-mRNA by binding to a region also targeted by nusinersen and is designed to increase survival motor neuron protein. Salanersen has a new backbone chemistry that leads to high potency, enabling the potential for high efficacy with once yearly dosing. The SOLAR study is an open-label, Phase 3 study designed to investigate the efficacy, safety, and pharmacokinetics of salanersen in participants aged 15–60 years with SMA who are either treatment-naïve or risdiplam-treated.

The SOLAR study includes two cohorts: participants who are treatment-naive and those who have previously received risdiplam. Key study eligibility criteria include a baseline Hammersmith Functional Motor Scale – Expanded (HFMSE) total score of 10 to 54 to define a study population with the potential to evaluate changes in motor function over time. All participants will receive salanersen 80 mg by intrathecal lumbar puncture every 12 months for approximately 5 years.

The primary efficacy endpoint is change from baseline in HFMSE total score at 12 months in the treatment-naive cohort, based on the progressive decline expected in this population without treatment. Key secondary efficacy endpoints will be evaluated in both treatment-naive and risdiplam-treated cohorts and include change from baseline and responder analyses in HFMSE total score, Revised Upper Limb Module total score, and 6-minute walk test total distance walked. Other efficacy endpoints include compound muscle action potential, respiratory function, bulbar function, fatigability, and activities of daily living assessed over the study period. Additionally, safety, tolerability, and pharmacokinetics of salanersen will be evaluated.

As the SOLAR study represents a broad population of older teens and adults with SMA, in both age and disease subtype, data from the study may help inform both initiation of therapy and transitions between therapies in clinical practice.

SESSION POSTERS 6 - 18*

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Investigation and Therapeutic Targeting of Ferroptosis in Dystrophin-Deficient Rats

State of the art:
Duchenne muscular dystrophy (DMD) is a lethal pediatric neuromuscular disorder caused by dystrophin deficiency, resulting in chronic myonecrosis and progressive loss of muscle function. Although necroptosis contributes to myofiber death in DMD, the involvement of ferroptosis remains poorly understood. Ferroptosis is a regulated cell death pathway driven by iron-dependent lipid peroxidation and counteracted by GPX4. We hypothesize that ferroptosis contributes to DMD myonecrosis and that its inhibition may have therapeutic potential.

Objectives and methods:
We aimed to characterize ferroptosis in DMD rat muscle, model ferroptotic cell death in vitro and evaluate its pharmacological inhibition in vivo. Ferroptosis-related markers were assessed by RT-qPCR, protein analysis, glutathione quantification, 4-HNE assays and BODIPY C11 imaging. Ferroptosis was induced in C2C12 myoblasts using RSL3 or Erastin, with or without ferroptosis inhibitors. Two preclinical trials tested UAMC-3203 (5 mg/kg/day) in DMD Dup10-17 rats, using daily intraperitoneal injections or continuous subcutaneous delivery via osmotic pumps.

Results:
DMD muscles showed decreased GPX4 and glutathione, alongside increased ACSL4 and ALOX12. Preliminary 4-HNE and BODIPY C11 analyses suggested enhanced lipid peroxidation, particularly at the sarcolemma. In C2C12 cells, RSL3- and Erastin-induced death was rescued by Ferrostatin-1, Liproxstatin-1 or UAMC-3203. In vivo, daily UAMC-3203 treatment produced no significant molecular or functional improvement, although 4-HNE tended to decrease. Continuous delivery was then tested to address the compound's short half-life, but was stopped at day 17 due to apparent toxicity. Analyses are ongoing to assess its effect on lipid peroxidation.

These findings support ferroptotic susceptibility in DMD muscle and motivate further testing of ferroptosis inhibition as a therapeutic strategy.

SESSION POSTERS 6 - 24

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Etude de la relation génotype - phénotype et des impacts fonctionnels de variants du gène PLOD1 dans une cohorte de 15 patients atteints du syndrome d'Ehlers-Danlos cyphoscoliotique

Le syndrome d'Ehlers-Danlos cyphoscoliotique (SEDcyp) appartient à un groupe cliniquement et génétiquement hétérogène de maladies du tissu conjonctif. Il est caractérisé par une hypotonie musculaire congénitale associée à une atteinte cyphoscoliotique, une hyperlaxité articulaire, ainsi qu'une fragilité accrue de la peau et des parois vasculaires. Le gène PLOD1 est un gène majeur du SEDcyp, codant pour la lysyl hydroxylase 1 (LH1 / PLOD1) impliquée dans l'hydroxylation post-traductionnelle de résidus lysine du procollagène. LH1 agit sur la résistance de la matrice extracellulaire en contrôlant la réticulation des fibres de collagène. A ce jour, une centaine de variants – tous de transmission récessive – est rapportée responsable du SEDcyp-PLOD1. L'absence de cohortes étendues de patients SEDcyp-PLOD1 limite l'avancement des connaissances cliniques, relatives à l'évolution de la maladie et aux mécanismes physiologiques sous-jacents.
Nous décrivons ici les caractérisations clinique, moléculaire et biochimique d'une cohorte internationale regroupant 16 cas index et 3 apparentés SEDcyp-PLOD1. Nous précisons ainsi les atteintes cliniques majoritaires et sporadiques. Les études de séquençage de gènes mettent en évidence 14 variants différents présents à l'état homozygote ou hétérozygote composite, dont 6 non publiés à ce jour.
L'impact physiologique de plusieurs de ces variants est évalué par des tests fonctionnels complémentaires : effet sur l'épissage (RNAseq), dosages urinaires des marqueurs lysylpyridinoline/hydroxylysylpyridinoline impliqués dans la réticulation du collagène, études protéiques quantitatives (Slot blot et western blot sur milieux de culture et extraits protéiques) et qualitatives (immunomarquages) et la capacité contractile (gels de collagène) de cultures de fibroblastes.
L'analyse des données cliniques, génétiques et fonctionnelles de cette cohorte de patients SEDcyp-PLOD1 permet d'apporter de nouveaux éléments dans la corrélation génotype-phénotype, dans les mécanismes fonctionnels à l'origine du SEDcyp-PLOD1 et dans l'évolution des atteintes phénotypiques au cours de l'âge. Cette étude, basée sur la plus grande cohorte SEDcyp-PLOD1 jamais décrite, servira à l'amélioration du diagnostic génétique et à la prise en charge des patients. L'analyse des mécanismes physiopathologiques impliqués dans le développement et la progression de la maladie permettra le développement de nouvelles stratégies thérapeutiques.

SESSION POSTERS 6 - 30*

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Development of therapeutic strategies for Volumetric Muscle Loss repair based on innovative biomimetic hydrogels

Adult skeletal muscle has remarkable regenerative capacity relying on resident muscle stem cells (MuSC). Upon injury, MuSC supported by the other cell types of their surrounding niche are able to repair damaged muscle. However, in case o massive ablation of muscle mass, also known as Volumetric Muscle Loss (VML), the biophysical and cellular cues orchestrating the muscle regenerative process are lost, leading to the replacement of muscle tissue by fibrosis and functional deficits. To date, treatment options for these injuries remain limited and most of the patients suffer from chroni disability. We are developing strategies aiming at developing biocompatible hydrogels mimicking the topographic and biomechanica properties of the native muscle and favoring the fusion and the maturation of myogenic cells. We thus sought to investigat whether these hydrogels could have a beneficial effect for VML repair. We generated and characterized a surgical mouse model of VML that enables the reproducible removal of 20% of the quadriceps muscle. Two-weeks post-injury significant loss of muscle mass and function with persistent fibrosis up to one month post injury was observed thus validating our model of VML. We transplanted the hydrogels directly after the VML and analyzed muscle regeneration after 7 days, 2 weeks and 1 month. Cellular dynamics mediated by these hydrogels were investigated by single nuclei RNAseq and we noticed a high proportion of regenerating myonuclei and MuSC cells in transplanted muscle at 7 days. At 2 weeks transplanted muscles exhibited islets of regenerating myofibers within the injury that were totally absent in nontransplanted muscles. In addition, by 3D imaging, we showed that hydrogel transplantation improved re-vascularization o the injured muscle. Our findings demonstrate that our biomimetic hydrogels stimulate MuSC recruitment and muscle regeneration, suggesting that they could be of great interest for regenerative medicine approach.

SESSION POSTERS 6 - 36

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Analytical assessment of ME&MGTM digital biomarkers to monitor generalized Myasthenia Gravis symptoms in the DOMYA study

Generalized Myasthenia Gravis (gMG) is an autoimmune disease characterized by fluctuating muscle weakness, making it critical to assess symptoms outside of clinic visits. ME&MG is a software as a medical device allowing objective self-assessment of ptosis, dysarthria, breathing, upper and lower limb muscle weakness. In the ME&MGopen decentralized study, proof-of-concept was established with digital biomarkers (dBMKs) correlating with clinically validated patient-reported outcomes. The ongoing global DOMYA study (NCT05564936) aims to validate ME&MG clinical performance. This interim analysis describes patient demographics and baseline analytical assessments of dBMKs scores.

Patients with anti-acetylcholine receptor antibody-positive gMG were recruited in the USA and France to be monitored for one year, performing ME&MG tests in clinic and at-home. ME&MG assessments were completed during inclusion (D0) and in the morning and evening of the following day (D1). Collected tests and derived dBMKs were evaluated for data quality (empty files, deviations or noise), reliability and analytical effectiveness (independent manual annotation by data scientists and correlation with clinicians' measures).

The cohort included 86 patients (France: 44; USA: 42). Patients were 51.2% female with mean age 53.9±14.5, mean disease duration 8.6±9.8 and mean MG-ADL score 3.4±2.5. A total of 1177 tests were collected amongst the five domains assessed, with 81.5-100% of them suitable for dBMKs analysis. D0 and D1 dBMKs measurements displayed strong agreement (all ICC$\geq$0.54, $p<0.001$) and all assessable measures associated with manual annotations (all $r\geq0.67$, $p<0.001$). ME&MG dysarthria and ptosis scores correlated weakly and moderately, respectively, with clinicians' assessments of the corresponding functional domains. ME&MG breathing, upper limbs, and lower limbs scores showed strong correlations with corresponding clinician-rated assessments (all $r\geq0.80$, $p<0.001$).

These analyses confirm ME&MG dBMKs quality, reliability and analytical validation. Assessing the clinical relevance of ME&MG with the full study readout will further support their adoption for remote monitoring of gMG manifestations in routine clinical practice or research settings.

SESSION POSTERS 6 - 42

SESSION POSTERS 6 - 48

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Decoupling Growth and Loss of Ambulation in Duchenne Muscular Dystrophy (DMD): Long-Term Outcomes With Vamorolone

Background: Vamorolone is a dissociative corticosteroid approved for DMD, with efficacy comparable to classic corticosteroids, and a more favourable safety profile.
Objectives: Explore association between height and loss of ambulation for vamorolone vs classic corticosteroids (CS).

Methods: Longitudinal changes in growth and time to loss of ambulation from treatment initiation to last observation were evaluated in boys from vamorolone clinical program with >1 year of treatment exposure and follow-up, compared with weighted propensity score matched classic CS-treated patients from pooled CINRG and FOR DMD. Height z-scores were analysed using random-coefficient linear mixed-effects model with predictors for time on treatment, treatment group, loss of ambulation (LoA) and interaction terms.

Results: Anthropometric and effectiveness data were available for 113 and 83 boys on vamorolone, and 199 and 287 boys on classic CS, respectively. Mean±SD age at treatment initiation was 5.8±1.0 vs 6.1±1.2 years (effectiveness data) and 5.9±1.0 vs 5.9±1.1years (anthropometric data) for vamorolone and classic SoC CS, respectively. Median treatment duration was ~5 years with mean±SD daily dose 4.5±1.2 mg/kg/day for vamorolone and ~4.0-4.5 years for classic CS; all treatments were daily.
Vamorolone patients maintained normal growth whereas growth stunting (defined as height z-score < -2.0 SD) was observed on classic CS (p<.0001). Treatment with vamorolone showed no difference in time to LoA vs classic CS (HR 1.2; 95% CI 0.63–2.30; p = 0.6307). Height was not associated with ambulatory status with vamorolone (p = 0.815), whereas lower height was significantly associated with retained ambulation on classic CS (p = 0.0039).

Conclusion: Growth trajectories remained stable on vamorolone without increased risk of LoA compared with classic CS. Shorter stature was associated with retained ambulation on classic CS, as previously reported.

SESSION POSTERS 6 - 54*

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Genetically encoded reporters of actin filament organization in living cells and tissues

The cytoskeletal protein actin is one of the most abundant and conserved macromolecules throughout eukaryotes, crucial for cell shape and integrity. Actin filaments are generated through polymerization of actin monomers and mediates a variety of essential biological functions, including cell division, tissue morphogenesis and muscle contraction. These numerous activities are achieved through the ability of actin filaments to be arranged into precise architectures. The sarcomere arrangement and therefore its ability to contract and relax, for example, relies on the proper organization of the thin actin and thick myosin filaments. The precise geometrical organization of actin filament assemblies, i.e. how actin filaments are physically oriented in space and to what extent they are aligned to each other is crucial to generating motor forces from the myosin-actin interaction in the sarcomere that can be directly related to muscle strength. Fluorescence polarization microscopy, named polarimetry, is ideally placed for measuring actin filament organization in living cells by exploiting the sensitivity of polarized light excitation to the orientation of fluorophores attached to actin filaments. Fluorescence is maximized when polarized light is aligned with the excitation dipoles of the fluorophores. Thus, an ensemble of fluorophores will be excited more efficiently in preferred directions depending on their distribution. By measuring the modulation of fluorescence induced by the rotation of the polarized light in the sample plane, we can extract independently the mean orientation of the fluorophores within the focal volume (angle rho, β and the in-plane projection of the angle explored by these fluorophores, (angle psi, β. If the fluorophores are linked to actin filaments in a constrained manner, the measured parameters reflect directly the molecular-scale organization of the labeled filaments in living cells at each pixel location, with βtheir mean orientation, and βtheir degree of alignment. By engineering fusions of widely used actin localization reporters to fluorescent proteins with constrained mobility, we have succeeded in developing genetically-encoded, green- and red-fluorescent protein- based reporters for non-invasive, quantitative measurements of actin filament organization in living cells and tissues by fluorescence polarization microscopy.

SESSION POSTERS 6 - 60

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Minimal symptom expression in myasthenia gravis: A post hoc analysis of phase 3 rozanolixizumab studies

Introduction: In the Phase 3 MycarinG study (NCT03971422) and its open-label extensions, Myasthenia Gravis Activities of Daily Living (MG-ADL) responder rates (≥2-point improvement in score) of ≥63.7% were observed in Cycles 1–13 of rozanolixizumab treatment in patients with generalised myasthenia gravis (gMG). Attaining minimal symptom expression (MSE), defined as an MG-ADL score of 0 or 1, is considered a treatment goal in gMG.

Objective: Assess achievement of MSE in patients across rozanolixizumab treatment cycles, based on their Cycle 1 response.

Methods: In MycarinG, patients were randomised to once-weekly placebo, rozanolixizumab 7mg/kg or rozanolixizumab 10mg/kg for 6 weeks. In MG0004 (NCT04124965), patients received once-weekly rozanolixizumab 7 or 10mg/kg for ≤52 weeks. In MG0007 (NCT04650854), after an initial 6-week cycle of rozanolixizumab 7 or 10mg/kg, further cycles were administered on symptom worsening (investigator's discretion). Final efficacy data were pooled across MycarinG, MG0004 (first 6 weeks) and MG0007 for patients with ≥2 symptom-driven rozanolixizumab cycles. The proportion of patients who achieved MSE (MG-ADL score: 0 or 1) at any time during treatment or observation in each symptom-driven cycle up to Cycle 13 was analysed post hoc based on Cycle 1 MSE achievement.

Results: Overall, 129 patients were assessed. In Cycle 1, 27.9% (36/129) of patients were MSE responders. Among these, subsequent MSE rates were ≥60.0% in each cycle in Cycles 2–13. Among Cycle 1 MSE non-responders, 19.4% achieved MSE in a subsequent cycle (up to Cycle 13; median number of additional cycles received: 6). In every cycle (1–13), almost all patients who achieved MSE did so within the 6-week treatment period; rapid onset (1 week) was seen in some patients.

Summary/Conclusion: In each of Cycles 2–13, among those who achieved MSE in Cycle 1, the majority of patients achieved MSE, suggesting consistent efficacy with long-term rozanolixizumab treatment.
Funding: UCB.

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Un nouveau variant du gène KBTBD13 élargit le spectre clinique et pathologique de la myopathie congénitale à batônnets de type 6 (NEM6)

Introduction : La myopathie congénitale à batônnets associée à des mutations du gène KBTBD13 (NEM6) est caractérisée par une faiblesse lentement évolutive, à prédominance proximodistale et axiale, et des mouvements lents débutant dans l'enfance. Nous rapportons le cas d'un patient atteint d'une NEM6 due à un variant non rapporté du gène KBTBD13, présentant un phénotype clinique plus sévère.
Cas clinique : un homme de 60 ans a présenté une fatigabilité des membres inférieurs avec course lente et chutes dans l'enfance, chirurgie de pieds varus equins à 23 ans, faiblesse et marche dandinante à 26 ans. Aggravation progressive avec perte de la marche à 43 ans et incapacité à tenir debout à 53 ans. L'examen neurologique montre une faiblesse musculaire diffuse sévère associée à une hypertrophie musculaire et des rétractions, des contractures musculaires parfois douloureuses des membres, une chute de la tête et une ouverture buccale limitée, un palais ogival. Insuffisance respiratoire traitée par VNI nocturne chez ce patient obèse et fumeur. Sur le plan paraclinique, élévation des CPK à 2 fois la normale ; tracé myogène à l'EMG ; remplacement graisseux diffus de la quasi-totalité des loges musculaires à l'IRM. La biopsie musculaire a révélé d'abondants bâtonnets, mais l'absence de cores. L'analyse génétique a identifié un nouveau variant hétérozygote du gène *KBTBD13*, c.1267C>G (p.Leu423Val), absent chez sa mère et son fils asymptomatiques.
Conclusion : Le phénotype de notre patient partage des caractéristiques similaires avec les cas de NEM6 précédemment décrits, mais aussi des particularités cliniques (contractures musculaires douloureuses, hypertrophie et rétraction), une évolution clinique apparemment plus sévère et l'absence de « cores ». Ainsi, ces données élargissent le spectre clinique et paraclinique des NEM6.

SESSION POSTERS 6 - 72

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MuscleJ2 evolved: an enhanced platform with AI-assisted tools for quantitative analysis of skeletal muscles

Quantitative analysis of skeletal muscle histology requires accurate myofiber segmentation, particularly in developing or pathological tissues where fiber morphology can be highly heterogeneous. MuscleJ2 provides a user-friendly environment for multiparametric histological analysis. However, the heterogeneity of muscle biopsies, combined with technical challenges associated with tissue sectioning and variability in immunostaining quality, can limit the ability of MuscleJ2 to accurately discriminate all myofibers in certain muscle sections. To address these limitations, we are expanding MuscleJ2's capabilities by integrating state-of-the-art AI-based segmentation methods while preserving its user-friendly interface and accessibility to biologists without programming expertise.
This development relies on integration with QuPath, an open-source bioimage analysis platform providing access to deep-learning segmentation methods, including Cellpose-SAM. An important advantage is the possibility of interactive quality control, allowing users to visually inspect AI-generated segmentations, identify errors and manually refine individual myofiber boundaries. A dedicated extension is being developed to streamline the exchange of annotations and regions of interest (ROIs) through graphical commands, without requiring users to write or modify code. AI-derived contours can subsequently be used for MuscleJ2 whole-fiber and region-specific measurements. The workflow is also being expanded with improved graphical representations, including boxplots displaying individual observations and fiber-size distribution profiles with means and standard deviations.
The approach was tes

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Accompagnement de la grossesse chez les patientes atteintes d'amyotrophie spinale : proposition de parcours issue d'un groupe de travail pluridisciplinaire intégrant le point de vue des patientes

Introduction : Les avancées thérapeutiques récentes ont modifié le pronostic de l'amyotrophie spinale (SMA), améliorant l'espérance de vie et l'autonomie des patients. Ces progrès ouvrent de nouvelles perspectives, dont des projets de maternité : dans une étude française récente, 30 grossesses ont été rapportées chez 22 patientes atteintes de SMA. Ces grossesses présentent des enjeux spécifiques pour les futures mères, notamment moteurs et respiratoires. Un excès de prématurité est rapporté, corrélé à la sévérité de l'atteinte respiratoire maternelle. Ce travail vise à formaliser un parcours dédié afin d'anticiper les besoins, guider les équipes et sécuriser la prise en charge du binôme mère-enfant.

Méthodes : Un groupe de travail pluridisciplinaire de 12 personnes a été constitué, associant experts cliniques et paramédicaux, deux patientes atteintes de SMA ayant mené une grossesse à terme et un partenaire associatif. Données de la littérature et recommandations nationales (PNDS) ont été confrontées aux pratiques de terrain et au vécu des patientes.

Résultats : Le groupe a formalisé un parcours en quatre étapes : 1) Projet parental : intégration précoce dans le suivi, conseil génétique systématique et coordination des intervenants ; 2) Avant la grossesse : bilan préconceptionnel des facteurs de risque, notamment respiratoires, et optimisation de l'état maternel ; 3) Pendant la grossesse : surveillance rapprochée avec suivi gynécologique mensuel minimum, intensifié au 3e trimestre, suivi neurologique et fonctionnel trimestriel, préparation de l'accouchement et anticipation des aides ; 4) Après l'accouchement : sécurisation du post-partum, réhabilitation fonctionnelle, adaptation des aides humaines et techniques, et soutien psychologique.

Conclusion : Ce parcours, intégrant expertises médicales et vécu des patientes, propose un cadre global de la préconception au post-partum. Il souligne l'importance d'une anticipation précoce, d'une coordination pluridisciplinaire et d'adapter le lieu d'accouchement pour limiter les situations d'urgence. Sa diffusion devrait contribuer à l'harmonisation des pratiques et à un accompagnement individualisé.

SESSION POSTERS 6 - 84

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New molecules impacting skeletal muscles behavior in SMA

SMA (Spinal muscular atrophy) is the most frequent genetic cause of muscle atrophy. Motoneuron death is the primary cause of the disease. Disruptive treatments have recently accessed the market save SMA children from death, but do not cure the disease and children remain with a heavy handicap mostly caused by muscle atrophy and insufficient force production by muscles. RHU consortium (SMART) aims to develop add-on treatments to prevent muscle atrophy in treated SMA patients. We developed an efficient drug screening assay using muscle cells from human SMA patient cells (16 000 drugs pre-screened by CyTOO company). We selected 180 drugs and test their efficiency in various culture conditions: controls cells lines, SMA patients cell lines and co-cultures models (SMA myotubes with motoneurons from ipSC). Our work highlighted four drugs that strongly enhance fusion/hypertrophic phenotype. Altogether, we aim to better understand the physiopathology of treated SMA patients and initiate the development of pharmaceutical strategies to remediate muscle atrophy in SMA.

SESSION POSTERS 6 - 90*

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Interdependence between Muscle Stem Cell and Motor neuron pools: new insights into Spinal Muscular Atrophy physiopathology

Proximal spinal muscular atrophy (SMA) results from biallelic loss-of-function variants in SMN1 gene, leading to insufficient Survival of Motor Neuron (SMN) protein. Although motor neuron (MN) degeneration is the primary hallmark of the disease, SMN is ubiquitously expressed and its deficiency also affects peripheral tissues, including skeletal muscle tissue and its resident Muscle stem cells (MuSC). Using a tamoxifen (TMX)-inducible conditional knockout mouse model (Pax7CreERT2; Smn floxed), we showed that quiescent MuSC in adult muscle, have high requirement for SMN. Indeed, targeted reduction of SMN in MuSC, led to rapid MuSC death, followed by Neuromuscular Junctions (NMJ) remodeling and ultimately a non-cell autonomous loss of part of the MN. These data reveal a previously uncharacterized interdependence between MuSC and MN pools and identify MuSC as crucial therapeutic targets for the long-term preservation of neuromuscular system integrity. To gain further insights into the contribution of MuSC to SMA physiopathology, we are now investigating whether quiescent MuSC show location-dependent vulnerability to SMN deficiency relative to the NMJ and whether a specific subset of MN is affected by MuSC pool depletion, by 3D imaging and omics approaches. Our preliminary data suggest that SMN expression is heterogeneous within the MuSC pool and that MuSC located close to the NMJ may be more sensitive to SMN deficit. Moreover, we are exploring whether current disease modifying treatments can preserve the MuSC pool; single-nucleus RNA- sequencing of SMA treated and untreated patients showed a reduced proportion of quiescent MuSC in untreated SMA samples compared to the controls. Conversely, we found that treated SMA muscles showed similar proportion of quiescent and activated as control muscles. In vitro, our preliminary observations suggest that Risdiplam treatment may impair myogenic cell differentiation and fusion capacity, despite increasing SMN protein levels. Overall, our study will provide new insights into the pathophysiology of SMA as well as crucial information for the design of next generation therapies.

SESSION POSTERS 6 - 96

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Du Centre de Référence MNM au territoire : une journée régionale pour renforcer le lien ville-hôpital en maladies neuromusculaires

Contexte : Les patients atteints de maladies neuromusculaires nécessitent une prise en charge multidisciplinaire impliquant des professionnels hospitaliers, libéraux et médico-sociaux. Afin de renforcer les compétences des acteurs de proximité et de favoriser la coordination des parcours de soins, le Centre de Référence des Maladies Neuromusculaires (CRMNM) AOC enfants et adultes du CHU de Montpellier organise, en partenariat avec le Service Régional de l'AFM-Téléthon, une journée annuelle de formation.
Objectif : Décrire l'organisation et les objectifs de cette action de formation continue, qui vise à améliorer la qualité des prises en charge en favorisant la coordination du réseau régional par un apport de connaissances sur les pathologies, par l'identification des acteurs impliqués dans la prise en soins et l'accompagnement des malades et de leur famille et par la mise en lien direct entre ces acteurs.
Méthodes : Depuis 13 ans, une journée de formation est proposée aux professionnels hospitaliers, libéraux et médico-sociaux, initialement du secteur de l'ancien Languedoc-Roussillon, désormais élargi à la région Occitanie. Les thématiques sont définies par un comité de pilotage (CRMNM–AFM-Téléthon) à partir d'une part des besoins identifiés à travers les situations des malades et d'autres part des besoins exprimés par les professionnels dans un questionnaire d'évaluation diffusé après chaque édition.
Résultats : La participation a progressivement augmenté pour atteindre 137 professionnels par an. Cette formation favorise l'actualisation des connaissances, l'harmonisation des pratiques entre l'hôpital et la ville, la diffusion des recommandations de bonnes pratiques, le développement des échanges interprofessionnels et le renforcement de la coordination des parcours de soins.
Conclusion : Bien que non reconnue au titre du Développement Professionnel Continu (DPC), cette formation constitue un levier efficace pour structurer le réseau régional des maladies neuromusculaires et contribuer à l'amélioration de la qualité et la prise en charge des patients.

SESSION POSTERS 6 - 102*

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Modeling, modulating, and monitoring intramuscular fibro-fatty infiltrates

Maintaining muscle mass is important to support life's activities that require mobility, strength, and power. Skeletal muscles possess a remarkable capacity for regeneration. However, in chronic pathological conditions such as muscular dystrophies, this process can follow maladaptive mechanisms. Instead of efficiently restoring muscle tissue, the muscle mass is progressively rplaced by fibro-adipose deposits, severely impairing muscle contractile function.
My PhD project aims to understand the molecular mechanisms underlying the formation of intramuscular fibroadipose tissue, which originate from a population of cells known as fibro-adipogenic progenitors (FAPs). To address this question, I am using an experimental approach combining CRISPR technology with adeno-associated viral (AAV) vectors, to modulate in vivo the expression of candidate genes in FAPs.
The approach is done in the context of glycerol-induced muscle injury, which triggers muscle regeneration while leading to persistent fibro-adipose tissue formation. We use AAV5 serotype to specifically target FAPs (and drive expression of CRISPR components), taking advantage of their transient expansion after injury. We use a mouse model with FAP-specific expression of a tagged dCas9 protein, and use AAVs to drive in FAPs expression of gRNAs targeting the promoter of candidate genes, as well as a tag-binding effector protein which can silence or enhance transcription. This can be done in non-pathological situations, but also using pathological mouse models. In the lab, we use a mouse model based on inactivation in FAPs of the Fat1 gene, a situation which exacerbates glycerol-induced intramuscular adipose tissue expansion (Ferracci & Helmbacher, 2026).
As first candidate gene, I assessed the relevance of the transcription factor ZEB1, known as inducer of EMT, or fibrosis and adipogenesis, expression of which is induced after injury in myogenic cells and FAPs, and is enhanced in Fat1-deficient FAPs. Owing to ZEB1 antibodies, I have validated the efficiency of our system in silencing ZEB1 expression in infected FAPs. Furthermore, by monitoring adipogenesis with Perilipin1 antibodies, I was able to confirm that ZEB1 activity is necessary for intramuscular adipogenesis induced by glycerol injury. I next aim to explore the effect of enhancing ZEB1 expression, to assess whether gain of ZEB1 is sufficient to promote intramuscular fibrosis and adipogenesis.

SESSION POSTERS 6 - 107

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Errance diagnostique et parcours pré-diagnostique dans la maladie de Duchenne en France

La dystrophie musculaire de Duchenne (DMD) est une affection neuromusculaire sévère débutant dès la petite enfance. Bien que les manifestations motrices initiales apparaissent généralement chez le jeune enfant, le délai diagnostique demeure important, limitant l'instauration précoce d'une prise en charge multidisciplinaire adaptée. Dans le cadre de l'étude EpiDuch, une analyse exploratoire s'est attachée à caractériser la trajectoire de soins et l'errance diagnostique des patients au cours des deux années précédant le diagnostic.

L'étude rétrospective repose sur un appariement indirect déterministe par itération entre le registre de la BNDMR et les données médico-administratives du SNDS (taux de chaînage de 74 %, N=939). L'analyse exploratoire de l'errance diagnostique a porté sur le sous-groupe de 216 patients masculins appariés diagnostiqués à partir de 2016 et âgés d'au moins 2 ans au moment du diagnostic, afin d'assurer un recul historique d'au moins deux ans complets avant la confirmation de la maladie (années N-2 et N-1).

Lors de la survenue des premiers symptômes, l'âge moyen des 669 patients avec une date de diagnostic, était de 2,8 ± 2,0 ans (avec 69,3 % des garçons présentant des manifestations cliniques entre 0 et 3 ans), alors que l'âge moyen lors du diagnostic confirmé s'élevait à 4,6 ± 3,6 ans, concrétisant un délai diagnostique moyen de deux années. Durant la phase pré-diagnostique, le volume annuel moyen de consultations médicales ambulatoires est demeuré stable entre l'année N-2 et l'année N-1 (5,5 vs 5,1 consultations pour un diagnostic posé entre 2 et <4 ans ; 3,1 vs 3,7 consultations à 4 ans ; 2,6 vs 2,6 consultations à ⩾5 ans), les médecins généralistes assurant l'essentiel de ces visites. À l'opposé, le recours aux soins paramédicaux a connu un accroissement remarquable lors de l'année N-1 précédant immédiatement le diagnostic (nombre moyen de jours de soins : 3,3 à N-2 vs 7,5 à N-1 pour un diagnostic à 2-<4 ans ; 3,7 vs 12,0 à 4 ans ; 8,0 vs 12,4 à ⩾5 ans). Cette augmentation était principalement tirée par la kinésithérapie (3,2 vs 6,4 jours ; 3,1 vs 8,4 jours ; 5,4 vs 7,8 jours). Les hospitalisations toutes causes ont augmenté au cours de l'année N-1 (0,1 vs 0,7 ; 0,3 vs 0,8 ; 0,3 vs 0,8).

L'étude EpiDuch confirme la persistance d'une errance diagnostique de deux ans en France. Ceci renforce l'importance de sensibiliser les médecins généralistes et les kinésithérapeutes afin d'accélérer le parcours de diagnostic.

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Merci de vous référer au programme pour connaitre l'horaire exact de votre session.	

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PS1	144		CIUMAS	Mariana	Impact cardiovasculaire chez les patients atteints de myasthénie en France : une étude rétrospective à partir de la base de données de l'Assurance Maladie française
PS2	14		CIUMAS	Mariana	Efficacité clinique durable et tolérance à long terme de l'efgartigimod intraveineux dans le traitement de la myasthénie généralisée : ADAPT NXT Partie B

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PS2	50		DI GALLO	Maxime	FLASH: Innovative Integrated Enzymatic-Fluorescent Labeling for Automated Muscle Fiber Typing, Metabolic and Morphometric Analysis
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