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Report of the XXI Meeting of the Interuniversity Institute of Myology and preview of the XXII edition

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Abstract

The 21st Annual Meeting of the Interuniversity Institute of Myology (IIM), held in Assisi, Italy, from September 4–7, 2024, gathered 123 experts, including basic and clinical myologists, pharmaceutical representatives, and patient organizations from Italy, Europe, Canada, and USA. The meeting fostered a proactive, collaborative and dynamic atmosphere, promoting scientific exchange and international partnerships focused on muscle research, from physiology to disease mechanisms, and eventually therapeutic approaches. The 21st IIM Meeting featured 6 main scientific sessions, showcasing 30 oral presentations and 45 always-on-display posters, all reporting original and unpublished research. The program was enriched by four keynote lectures from internationally renowned speakers and talks from delegates of the Société Française de Myologie, adding depth to the scientific discussions. As part of the IIM Meeting organization, this year there was also a free-access educational convention titled "Physical exercise as prevention". Leading IIM experts shared insights on exercise-based lifestyle interventions aimed at improving public health, with the participation of the Italian former boxer Roberto Cammarelle. The event drew a large in-person and online audience. This IIM Meeting edition strongly emphasized the involvement and growth of young researchers, with 50% of the attendees being <35, reinforcing IIM's commitment to fostering the next generation of myologists. Along this line, and to further support young researchers, awards for Best Talk, Best Poster Blitz, and Best Poster were presented. The winners joined the IIM Young Committee, contributing to the scientific organization of future IIM meetings together with the IIM Scientific Committee. The meeting was also integrated into the "Advanced Myology Update 2024" high-training course, organized by the University of Perugia in collaboration with IIM. The 11 trainees enrolled in the course participated in dedicated roundtables and exclusive lessons led by IIM's invited speakers. In this report are included the abstracts of both oral and poster presentations, with some being withheld for patent-related reasons. Through its annual congress and educational initiatives, IIM played a crucial role in shaping the future of myology research, fostering innovation, collaboration, and scientific excellence on an international scale. We invite you to save the date for the 22nd IIM meeting that will be held in the beautiful Assisi, September 11-14, 2025. We can't wait to welcome you!

Key Words: skeletal muscle; heart; genetics, epigenetics, development and regeneration; wasting; cachexia; neuromuscular diseases.

XXI Meeting of the Interuniversity Institute of Myology

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The Interuniversity Institute of Myology (IIM) (iimmyology.it) was established in 2004, inspired by Giorgio Fanò-Illic (then at the University of Chieti-Pescara, Italy). Initially created to bring together Italian university scientists in the field of myology, organizing an annual meeting on muscle research, the IIM Meeting has since then expanded into a globally recognized scientific event. Today, the IIM Meeting welcomes researchers from universities and institutes worldwide, fostering studies on muscle physiology and diseases, including myogenesis, muscle regeneration, muscle function, muscle atrophy, and muscular dystrophy. The IIM is a non-profit organization based on voluntary activity of an elected Director (Prof. Guglielmo Sorci) and two scientific committees (senior and young), fostering muscle research through collaboration, mobility, and knowledge exchange to advance myology. The IIM is committed to equity, inclusivity and balance. The senior scientific committee, formed by 12 established researchers (6 males, 6 females) from Italy, France and USA is mirrored by the young scientific committee formed by 7 early career myologists (2 males, 5 females). Both committees take independent actions for organizing the annual meeting, dissemination, social and public engagement activities.

In 2024, the proactive and inclusive atmosphere encouraged scientific discussions, networking, and international collaborations among the 123 attendees (74 females, 49 males), solidifying the IIM meeting as a premier platform for young researchers in muscle biology, disease mechanisms, and therapeutic strategies. For the XXI IIM Meeting 4 internationally recognized researchers in the muscle field were invited: Prof. Leonardo F. Ferreira from the Duke University (USA), Prof. Michael Rudnicki from the Ottawa Hospital Research Institute (Canada), Prof. Julia von Maltzahn from the Brandenburg University of Technology (Germany) and Prof. Denis C. Guttridge from the Medical University of South Carolina (USA). Also this year, the IIM confirmed the collaboration with the Societé Française de Myologie (SFM), inviting three representatives, Charlotte Gineste, Alexis Boulinguiez and Alexis Osseni to give talks in the meeting.

In addition to the lectures by the invited international speakers, the Scientific Committee selected presenters from the submitted abstracts for each session, with a strong focus on supporting young researchers, resulting in 15 out of 30 speakers being under the age of 35.

The meeting started with the lecture of Prof. Leonardo F. Ferreira (Duke University, Durham, NC, USA) presenting an overview on the state of the art of molecular and biophysical basis of skeletal muscle dysfunction in heart failure, pointing at redox homeostasis and mitochondrial bioenergetics as key elements involved in the pathology.

The congress proceeded with the first session focused on "Muscle function and weakness", where 4 different selected speakers, form Italy and France exposed their latest results on key molecular players involved during muscle contraction, mechanisms involved in myopathies and possible therapeutic targets and strategies. The following session was dedicated to "Muscle diseases and regenerative medicine". For this section, two Italian and two France selected speakers presented innovative approaches to study and treat Duchenne Muscular Dystrophy. The session concluded with an oral participation of a delegate of the Parent Project Association (https://www.parentproject.it/), which presented how patients' associations can play a key role in promoting European multi-partner projects aimed at the identification of novel therapeutic strategies for patients affected by neuromuscular disorders. The first day of the congress ended with an informal dinner for all participants, during which the first round table of the "Advanced Myology Update 2024" high-training course took place. This special gathering provided a mentoring opportunity for students enrolled in the course to engage in informal discussions with the invited speakers, who shared valuable insights on key aspects to consider for their scientific career advancement.

The second day of the meeting continued with the session dedicated to "Muscle diseases and regenerative medicine", including 4 selected oral presentations of researchers from Italy and the United Kingdom. Molecular mechanisms and possible therapeutic approaches for Fibrodysplasia Ossificans Progressiva, Amyotrophic Lateral Sclerosis, Myotonic dystrophy type 2 and Oculopharyngeal muscular dystrophy were presented and discussed.

The second lecture of the congress was held by Prof. Michael Rudnicki (Ottawa Hospital Research Institute, Ottawa, Canada), who presented the state of the art of the molecular regulation of muscle stem cell function, depicting the importance of muscle stem cell subpopulation during skeletal muscle regeneration. This lecture opened the third session of the XXI IIM congress, which indeed included oral presentation regarding "Muscle stem cells and stem cell niche". The 4 selected speakers (from Italy, United Kingdom and The Netherlands) showed to and discussed with the audience their studies of molecular and cellular regulators of the adult muscle stem cells and skeletal muscle regeneration. The morning was thus concluded with a technical talk held by a delegate of the sponsor Prodotti Gianni/Abcam that described the cutting-edge tools that use recombinant technology for molecular investigation in biomedicine and biology. Finally, one minute video poster blitzes from under35 attendees were shown with the dual aim to convince people to attend the poster sessions and to allow the young to show their science in a modern way, keeping pace with the time changes in communication among the new generations.

The first poster session was dynamic and engaging, showcasing original and unpublished studies in multiple fields of myology. Taking place between lunch and the social activities, this session seamlessly led into a cultural experience designed to strengthen connections among participants. Attendees had the opportunity to explore renowned sites in the area, including a guided tour of the Basilica of Saint Francis or the "Rocca Maggiore" fortress, followed by free time in Assisi before dinner. These moments, enriched by the beauty of the surroundings, provided a unique setting for networking and fostering new collaborations among researchers.

The third day of the XXI IIM meeting began with the lecture held by Prof. Julia von Maltzahn (Brandenburg Uni-

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versity of Technology, Cottbus-Senftenberg, Germany), who focused her talk on muscle stem cells in aging and disease, and on the key role of microenvironment and innervation in muscle stem cell behavior and regeneration potential of the skeletal muscle. This intervention opened the fourth session of the congress related to "Muscle aging", where three selected oral presentations presented unpublished data on Kennedy disease, anti-inflammatory strategies to counteract age-related muscle wasting, and cellular and molecular mechanisms involved in sarcopenic obesity. After enjoying a refreshing coffee break featuring local specialties, participants engaged in the session on "Genetic and Epigenetic Regulation in Muscle Pathologies." During this session, four selected speakers from the United Kingdom, Italy, France, and Belgium presented their research on genetic and epigenetic molecular regulators involved in muscle inflammatory responses, muscular dystrophy, and rhabdomyosarcoma cancer progression. During the break, round tables held outside the cloister provided an informal yet stimulating environment, fostering scientific exchange and networking among participants.

The final afternoon of the meeting began with the second poster session, leading into the last keynote lecture delivered by Prof. Denis C. Guttridge (Medical University of South Carolina, Charleston, SC, USA). His insightful talk focused on cancer cachexia, highlighting the crucial role of inflammation and its regulation within the muscle microenvironment, and opened the last session on "Muscle wasting and cachexia". Six selected speakers from Italy and USA exposed their results in the field, focusing on molecular mediators of muscle wasting induced by cancer and novel therapeutic approaches. The congress talks closed with the "IIM General meeting", where all the participants were invited to take part to give feedback on the congress and to an open discussion regarding the activities organized for the young researchers and to foster their support. To strengthen social interactions and scientific connections, the XXI IIM Meeting concluded with a lively social dinner. During this celebratory evening, several awards and prizes were assigned to young attendees, the winners being selected by dedicated committees of experts who actively participated in the congress. The best poster blitz prize went to Alessandro Arcari, 3 prizes were assigned for poster presentations (1st Frida Karakashi, 2nd Marco Simula, 3rd equal merit Francesco Millozzi and Beatrice Biferali) and further 3 to best talks (1st Giacomo Bincoletto, 2nd Ashley Wang, 3rd Nikki Wanders). To conclude the event on a high note, all participants were invited to join the traditional and lively dance party, fostering new interactions and strengthening scientific collaborations in a relaxed and enjoyable atmosphere.

The "Advanced Myology Update 2024" high-training course took place the next morning, for the 11 enrolled students and the 4 invited speakers, that was based on discussion of real experimental problems to be solved with the support of the experienced lecturer, allowing the student to fully engage in the activity.

We are actively working for the 22nd meeting that will be hosted again in the beautiful Assisi, from September 11-14, 2025. We already secured 4 international invited speakers: Giulio Cossu (Manchester University, UK), Karin Esser (University of Florida, USA), Marika Pane (Università Cattolica del Sacro Cuore, Italy) and Markus Ruegg (University of Basel, Switzerland). Don't miss the chance to join us for a relaxed scientific discussion, spending 4 days in the heart of a UNESCO World Heritage site, learning from the latest myology research and building new connections. Last but not least, we confirm our strong commitment to promote the scientific growth of the new generation of myologists. This is certified first by keeping the meeting highly cost-effective and by the dedicated activities such as the round tables to meet mentors, the prizes (best talk, best poster, best poster blitz) and the unforgettable night social events. You have no excuses for missing this opportunity! You can follow us on our web pages (https://iim-myology.it; https://iim2025.azuleon.org) or on your social media of choice: https://twitter.com/IIM_myology; https://www.instagram.com/iim_myology/; https://www.linkedin.com/company/iim-interuniversity-institute-of-myology/.

Conflict of interest

The authors declare no potential conflict of interest, andall authors confirm accuracy.

Ethics approval and informed consent

Not applicable.

Patient consent for publication

Not applicable.

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Disclaimer

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IIM Interuniversity Institute of Myology

21st IIM Meeting

Assisi, Italy • 4-7 September 2024

From Muscle Physiology to Pathogenesis and Therapies of Neuromuscular Diseases

Programme & Abstracts

https://IIM2024.azuleon.org

Topics

Muscle function and E-C coupling
Genetic, epigenetic, and metabolic regulation of muscle
Muscle plasticity and physical exercise
Muscle stem cells and regenerative medicine
Muscle aging
Muscle wasting and cachexia
Modeling and treating muscle diseases
Cardiac muscle and cardiomyopathy

Keynote Lectures

Leonardo
Ferreira

Denis C.
Guttridge

Michael
Rudnicki

Julia
von Maltzahn

IIM Scientific Committee

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Falcone

Stefania
Fulle

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Anna
Urciuolo

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ACQUA AI FIORI DI SPELLO
Umbria, Italia

Programme

Convegno *(Assisi, Hotel Cenacolo)*

L'ESERCIZIO FISICO COME PREVENZIONE

Dalla contrazione muscolare alla nutrizione

Moderatori: Guglielmo Sorci (Università di Perugia; Direttore IIM)
Anna Villarini (Università di Perugia)

9:30 **Saluti delle Autorità**

9:50 **Francesca Riuzzi** *(Università di Perugia; IIM)*
Evoluzione e proprietà del muscolo scheletrico

10:10 **Antonio Musarò** *(Università Sapienza Roma; IIM)*
Il muscolo come organo endocrino. Le miochine

10:30 **Massimo Raffaele Mannarino** *(Università di Perugia)*
Effetti benefici dell'esercizio fisico. Esercizio fisico come poli-pillola

10:50 **Raffaella Spada** *(Istituto di Medicina e Scienza dello Sport - CONI)*
Aspetti nutrizionali legati all'esercizio fisico

11:10 **Roberto Cammarelle** *(ex pugile, campione olimpico e campione del mondo)*
La mia esperienza da campione

11:40 **Discussione generale**

12:00 **Conclusioni**

Diretta streaming sul sito https://IIM2024.azuleon.org.

15:00-15:10 **Welcome and opening of the IIM meeting**

15:10-15:50 **Lecture 1**
Chair: Giacomo Rubini (Young IIM Committee)

Leonardo F. Ferreira *(Duke University, Durham, NC, USA)*
Molecular and biophysical basis of skeletal muscle dysfunction in heart failure

15:50-17:00 **Session 1: Muscle function and weakness**
Chairs: Dario Coletti, Sara Roccabianca

Stefano Perni *(Siena, Italy)*

Charlotte Gineste *(SFM; Illkirch-Graffenstaden, France)*

Federica Fiore* *(Siena, Italy)*

Jacqueline Ji* *(Illkirch-Graffenstaden, France)*

17:00-17:30 ***Coffee break***

17:30-18:55 **Session 2/a: Muscle diseases and regenerative medicine**

Chairs: France Pietri-Rouxel, Beatrice Biferali

Lorenzo Giordani *(Paris, France)*

Multimodal Single Cell spatial profiling of Duchenne Muscular Dystrophy

Caterina Boccia* *(Rome, Italy)*

Targeting IL-6 signalling to attenuate dystrophic muscle degeneration

Sonia Albini *(Evry, France)*

Disease exacerbation in MYOrganoids derived from Duchenne Muscular Dystrophy iPSC reveals limitations of microdystrophin therapeutic efficacy

Laura Lociuro* *(Milan, Italy)*

Enhancing micro-dystrophin gene therapy: the role of SRT2104, a new Sirtuin1-activating compound, for the treatment of Duchenne Muscular Dystrophy

Ilaria Zito *(Parent Project; Rome, Italy)*

The role of patients' associations in IHI European multi-partner projects

19:30 ***Dinner - Aperitivo Umbro***

and (only for participants registered for the Advanced Myology Update course)

Roundtable 1: "How to choose a lab for a Post-Doc experience" with **M. Rudnicki** and **J. von Maltzahn**

Roundtable 2 "Approaches to optimize the Post-Doc experience" with **L. Ferreira** and **D. Guttridge**

***Young Investigator. Eligible for Best Talk awards.**

9:00-10:10 **Session 2/b: Muscle diseases and regenerative medicine**

Chairs: Cesare Gargioli, Mariam Zouhair

Riccardo Gamberale* *(Monza, Italy)*

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

Cassandra Margotta* *(Milan, Italy)*

Rodrigo D'Amico* *(Rome, Italy)*

Consequences of CNBP reduced expression in DM2 pathogenesis

Alexis Boulinguiez *(SFM; Egham, United Kingdom)*

10:10-10:35 ***Coffee break***

10:35-11:15 **Lecture 2**

Chair: Pier Lorenzo Puri

Michael Rudnicki *(Ottawa Hospital Research Institute, Ottawa, Canada)*

Molecular regulation of muscle stem cell function

11:15-12:25 **Session 3: Muscle stem cells and stem cell niche**

Chairs: Chiara Sassoli, Federica Esposito

Andrea Münsterberg *(Norwich, United Kingdom)*

Muscle stem cell function is impaired in absence of Talpid3 - a gene required for primary cilia formation

Cristina Parisi* *(Rome, Italy)*

Stefano Cagnin *(Padua, Italy)*

Non-coding RNAs to Treat Skeletal Muscle Atrophy

Nikki Wanders* *(Maastricht, The Netherlands)*

12:25-12:40 **Technical talk *(by Prodotti Gianni/Abcam)***

Danilo Lemos

Tackling reproducibility crisis with recombinant technology

12:40-12:50 **Poster blitz 1** (ODD numbers; selection)

13:00	***Lunch***
14:30-16:00	**Poster Session 1** (ODD numbers)
16:00	***Bus departure to Assisi: guided tour of the Basilica of Saint Francis or the "Rocca Maggiore" Fortress (free time after the visits)***
19:00	***Bus departure to the "Cantico di San Francesco" restaurant***

***Young Investigator. Eligible for Best Talk awards.**

9:00-9:40 **Lecture 3**

Chair: Maurilio Sampaolesi

Julia von Maltzahn *(Brandenburg University of Technology, Cottbus-Senftenberg, Germany)*

Muscle stem cells in age and disease

9:40-10:40 **Session 4: Muscle aging**

Chairs: Libero Vitiello, Katja Hönzke

Giacomo Bincoletto* *(Padua, Italy)*

Susanna Molinari *(Modena, Italy)*

Nanoparticle-mediated delivery to skeletal muscle cells of N-palmitoylethanolamide (PEA), an endocannabinoid-like molecule with anti-inflammatory properties

Clara Sciorati *(Milan, Italy)*

Sarcopenic obesity in the elderly: a dysfunctional crosstalk between tissues?

10:40-11:10 ***Coffee break***

11:10-12:20 **Session 5: Genetic and epigenetic regulation in muscle pathologies**

Chairs: Vanina Romanello, Alex Pezzotta

Paul Kemp *(London, United Kingdom)*

Emanuele Mocciaro *(Milan, Italy)*

Pre-clinical development of a drug inhibiting the chromatin remodeling protein WDR5 in FSHD muscular dystrophy

Alexis Osseni *(SFM; Lyon, France)*

Ashley (Ju-Wei) Wang* *(Leuven, Belgium)*

Investigating the potential of MICAL2 modulation for impeding rhabdomyosarcoma cancer progression

12:20-12:30 **Poster blitz 2** (EVEN numbers; selection)

13:00 ***Lunch***

14:30-16:00 **Poster Session 2** (EVEN numbers)

16:00-16:40 **Lecture 4**

Chair: Fabio Penna

Denis C. Guttridge *(Medical University of South Carolina, Charleston, SC, USA)*

Regulation of the inflammatory muscle microenvironment in cancer cachexia

16:40-17:00 ***Coffee break***

17:00-18:45 **Session 6: Muscle wasting and cachexia**

Chairs: Andy Judge, Sara Chiappalupi

Gabriele Guarnaccia* *(San Diego, CA, USA)*

Serum amyloid protein A1 (SAA1) impairs myogenesis and myotube size in pancreatic cancer cachexia

Martina Biglietto* *(Rome, Italy)*

Engineered exosomes as a therapeutic tool to counteract muscle degeneration

Giacomo Rubini* *(Turin, Italy)*

Immunomodulation via interleukin-4 improves energy metabolism in C26 tumor-bearing mice

Martina Paiella* *(Novara, Italy)*

Andy Judge *(Gainesville, FL, USA)*

Andrea Ghiroldi *(Cinisello Balsamo, Italy)*

Unraveling the therapeutic potential of givinostat in muscle atrophy induction

18:45-19:30 **IIM General meeting**

20:00 ***Social Dinner - Awards and prizes***

22:00 ***Dance party***

***Young Investigator. Eligible for Best Talk awards.**

Reserved to participants registered to the
High Training Course in AADVANCED MYOLOGY UPDATE 2024

10:00 ***Bus departure to Palazzo Bernabei***

10:30 **J. von Maltzahn**
Driving rhabdomyosarcoma into myogenic differentiation

11:00 **L. Ferreira**
Assessment of muscle function in rodents: old approaches, modern applications

11:30 **M. Rudnicki**
Developing innovative regenerative therapies for neuromuscular diseases

12:00 **D. Guttridge**
Identifying limitations in mouse models of cancer cachexia

12:30 ***Light lunch***

Posters always on display during the meeting

Discussion

ODD numbers: Thursday, 5 September (14:30-16:00)

EVEN numbers: Friday, 6 September (14:30-16:00)

P.1 **Valentina Guardascione**** *(Siena, Italy)*

P.2 **Sara Roccabianca**** *(Siena, Italy)*
Changes in CLIMP63 expression alter the organization of the microtubule network of mouse skeletal muscle fibers

P.3 **Lucrezia Puccini**** *(Siena, Italy)*
Gene expression analysis in skeletal muscles of mice carrying a deletion in a muscle-specific stretch/super enhancer region inside the ANK1 locus

P.4 **Paul Kemp** *(London, United Kingdom)*
Regulation of individual sensitivity to inflammation by myc contributes to muscle loss in COPD

P.5 **Marco Simula**** *(Rome, Italy)*
Long noncoding RNAs at the interface between muscles and nerves

P.6 **Maxime Gelin**** *(Paris, France)*

P.7 **Margaux Van Puyvelde**** *(Leuven, Belgium)*

P.8 **Muhammad Dawood Amjad**** *(Chieti, Italy)*
Complex Magnetic Fields (CMFs): harnessing electromagnetic symphony for muscle regeneration

P.9 **Alessandro Arcari**** *(Milan, Italy)*

P.10 **Pietro Chiolerio**** *(Padua, Italy)*

P.11 **Aly Bourguiba Villeneuve**** *(Paris, France)*
GDF5 therapeutic potential on neuromuscular junction defects

P.12 **Sabrina D'Amore**** *(Chieti, Italy)*

P.13 **Beatrice Biferali**** *(Milan, Italy)*

P.14 **Francesca De Paolis**** *(Rome, Italy)*
Human mytendineous junction 3D *in vitro* modeling

P.15 **Giorgia Cavioli**** *(Rome, Italy)*

P.16 **Rebecca Deodati**** *(Rome, Italy)*

P.18 **Federica Esposito**** *(Milan, Italy)*

P.19 **Fabiana Fanelli**** *(Urbino, Italy)*

P.20 **Rachele Garella** *(Florence, Italy)*

P.21 **Serena Germani**** *(Milan, Italy)*
CHOP/ERO1A pathway of unfolded protein response (UPR) in RYR1 and SEPN1-related myopathies

P.22 **Martina Parigi**** *(Florence, Italy)*

P.23 **Alex Pezzotta**** *(Milan, Italy)*

P.24 **Elena Ruggieri**** *(Milan, Italy)*

P.26 **Cristina Purcaro**** *(Chieti, Italy)*

P.27 **Ilaria Versari**** *(Bologna, Italy)*
Nuclear Phospholipase C delta 4 is a crucial player in modulation of rhabdomyosarcoma cells proliferation

P.28 **Fabio Ferrini** *(Urbino, Italy)*
Hyaluronan improves the C2C12 murine myoblast proliferation and myogenic differentiation under oxidative and inflammatory conditions

P.29 **Francesco Millozzi**** *(Rome, Italy)*

P.30 **Alessandro Antonioli**** *(Novara, Italy)*

P.31 **Paul Kemp** *(London, United Kingdom)*
AntagomiR inhibition of miR-424(322) increases muscle fibre diameter in old mice and in response to respiratory viral infection

P.32 **Bianca Bartoloni**** *(Florence, Italy)*
An autocrine loop of lactate sustains cancer cachexia in skeletal muscle

P.33 **Frida Karakashi**** *(Milan, Italy)*

P.34 **Lorenza Bodo**** *(Turin, Italy)*

P.35 **Martina Lupoli**** *(Rome, Italy)*

P.36 **Karolina Majchrzak**** *(Senftenberg, Germany)*
Role of Sbno2 in myogenic differentiation under cachectic conditions

P.37 Mariam Zouhair** *(Rome, Italy)*

P.38 Michele Mannelli** *(Florence, Italy)*

P.39 Giovanni Delli Carpini** *(Rome, Italy)*

P.40 Mark Griffiths *(London, United Kingdom)*

P.41 Katja Hönzke *(Senftenberg, Germany)*

P.42 Tommaso Raiteri** *(Perugia, Italy)*

P.43 Libero Vitiello *(Padua, Italy)*
Targeting monoamine oxidase B (MAOB) in dystrophic mdx hearts dampens inflammation and fibrosis

P.44 Laura Salvadori *(Novara, Italy)*
Vaccinium macrocarpon extract restrains muscle wasting induced by Western diet-derived AGEs

P.45 Giorgia Maria Renna** *(Milan, Italy)*
Molecular characterization of ER stress mediators in the pathogenesis of SEPN1 and RYR1-related myopathies

P.46 Sara Chiappalupi *(Perugia, Italy)*
Proteomic analysis suggests novel mechanisms involved in the protection against cancer-induced muscle wasting in mice lacking RAGE at myofiber level

****Young Investigator. Eligible for Best Poster Blitz and Best Poster awards.**

Selected Talks Abstracts

Multimodal single cell spatial profiling of Duchenne Muscular Dystrophy

L. Virtanen[1], C. D'Ercole[2], L. Saillaird[1], F. Grandi[1], C. Peccate[1], V. Karunanuthy[3], C. Bertholle[3], B. Izac[4], B. Saintpierre[4], M. Andrieu[3], F. Letourner[4], L. Madaro[2], Lorenzo Giordani[1]
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[2]Department of Anatomy, Histology, Forensic Medicine and Orthopedics, University of Rome "la Sapienza", Rome, Italy
[3]Cybio Platform, Institut Cochin, INSERM U1016, CNRS UMR8014, Paris, France
[4]GenomIC Platform, Institut Cochin, INSERM U1016, CNRS UMR8014, Paris, France

Duchenne muscular dystrophy (DMD) is one of the most severe pediatric degenerative myopathies. In the initial phase of the disease, muscle is exposed to continuous cycles of degeneration and regeneration; over time, regenerative potential is exhausted, and necrosis prevails. As of today, the cellular and molecular determinants responsible for this functional exhaustion remain largely uncharacterized.
Adult tissue repair requires the activation of resident stem cells that can both self-renew and generate differentiated progeny. To establish and maintain their properties, stem cells require constant interactions with their microenvironment and their neighboring cells that altogether constitute the niche. The stem cell and its niche form as a whole the minimum functional unit of adult tissue repair. Any given perturbation affecting either the stem cell or the molecular/cellular components of the niche will invariantly impact repair potential. Therefore, in DMD the changes hindering the correct execution of the repair process must therefore occur either in the stem cell or in its niche.
Here we present a multi-omic Spatial strategy to elucidate the determinants interfering with regeneration in the dystrophic muscle and study the niche-stem cell interactions. By leveraging multi-modal data integration (Spatial transcriptomics, snRNAseq and snATACseq), we assessed changes in cell-type compositions, their spatial relationships and dependencies on other cell types, and the evolution of their respective crosstalk. Through our approach, we highlight the changes that occur in the transcriptome and muscle epigenome during disease progression in those regions associated with injury, regeneration, and degeneration. In conclusion, our study delivers an integrative molecular map of dystrophic muscle and lays the groundwork for future studies aimed at the identification of novel biomarkers and potential therapeutic approaches to promote muscle regeneration.

Targeting IL-6 signalling to attenuate dystrophic muscle degeneration

Caterina Boccia[1], L. Forcina[1], S. Sideri[1], C. Nicoletti[1], F. Forconi[1], E. Rizzuto[2], A. Musarò[1,3]
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Duchenne Muscular Dystrophy (DMD) is a muscle wasting genetic disease caused by mutations in the dystrophin gene. The absence of dystrophin protein triggers degenerative events in muscle, including necrosis, inflammation and fibrosis. A curative treatment for the disease is not currently available, despite the development of different therapeutical approaches aimed to restore dystrophin expression. Since dystrophic muscle is dominated by pro-oxidant and pro-inflammatory conditions, our hypothesis is that this hostile environment might interfere with the efficacy of therapeutic strategies. Mounting evidence support the role of IL-6 in fostering degenerative events in DMD muscle, triggering chronic inflammation. Thus, we propose to selectively interfere with the pro-inflammatory functions of the cytokine without compromising its homeostatic activity in order to slow down disease progression. The data collected suggest that the modulation of IL-6 activity during the necrotic phase of the disease could be a good strategy to stabilize dystrophic muscle, attenuating muscle inflammation, necrosis and preserving muscle functionality. Furthermore, the attenuation of later-stage muscle degeneration by IL-6 signalling modulation highlights the protective action of our approach against the grave loss of functional muscle tissue over time.

Disease exacerbation in MYOrganoids derived from Duchenne Muscular Dystrophy iPSC reveals limitations of microdystrophin therapeutic efficacy

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Duchenne muscular dystrophy (DMD) is a lethal muscle-wasting disease caused by the absence of Dystrophin, a protein essential to preserve muscle integrity continuously challenged by contractions. Gene therapy utilizing adeno-associated virus (AAV) to deliver truncated forms of dystrophin (µDys) is currently the most promising therapeutic approach. However, the therapeutic outcome in treated patients has not been as successful as anticipated by animal studies, underscoring the need for improved and high-throughput models for fast and accurate prediction of human response. Here, we describe the generation of MYOrganoids, an in vitro 3D muscle platform based on direct myogenic conversion of human induced pluripotent stem (iPSC) cells including fibroblasts to ensure proper muscle structure and function. We also exploited the secretory activity of fibroblasts to provide microenvironmental cues, essential for pathophysiological studies. Remarkably, MYOrganoids derived from DMD-iPSC including DMD fibroblasts, show exacerbated pathogenic hallmarks such as extracellular matrix remodeling, muscle force loss and fatiguability, across the different DMD iPSC cell lines employed. As proof of the suitability of our system for gene therapy screening, we employed AAV9-mediated µDys gene transfer in DMD-MYOrganoids. We showed that µDys delivery, partially improved muscle resistance and environmental stress but failed to significantly restore dystroglycan components at the membrane. Transcriptomic analysis confirmed an amelioration of mechano-stability and inflammatory hallmarks but, more importantly, revealed that only a partial correction of the DMD signature is achieved after microDys restoration. This evidence highlights the necessity to identify additional therapeutic targets and places our bioengineering approach at the forefront of exploring complementary strategies beyond gene therapy with the potential to accelerate the discovery of more effective therapeutics.

Enhancing micro-dystrophin gene therapy: the role of SRT2104, a new Sirtuin1-activating compound, for the treatment of Duchenne Muscular Dystrophy

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Duchenne Muscular Dystrophy(DMD) is an X-linked recessive disorder caused by mutations in the *dystrophin* gene. The lack of dystrophin protein disrupts the dystrophin-glycoprotein complex eliciting structural degeneration and functional impairments of myofibers. Currently, there's no cure for DMD. However, progress has been made in gene therapies to restore dystrophin and among the different trialed strategies, the approach based on AAV-delivered micro-dystrophin (MD) is the last to be approved. Nevertheless, it still presents some limits. Indeed, the dystrophic muscle milieu exhibits chronic inflammation and early sarcolemmal fragility that do not support MD engraftment and its preservation over time. Therefore, to enhance gene therapy efficacy, it is crucial to develop conservative therapies that preserve dystrophic muscles.
For this purpose, the NADH-dependent deacetylase Sirtuin1 (SIRT1) might be the suitable target. In *mdx* mice, SIRT1 overexpression tends to counteract the dystrophic muscular and cardiac phenotype.
Among the new SIRT1-activating compounds, SRT2104 has never been tested in DMD. We assessed its efficacy on *mdx* mice demonstrating that, after 12 weeks of administration, treated mice show functional, metabolic and histological improvements compared to the controls.
Overall, given its effects on crucial hallmarks of DMD, SRT2104 could be the proper candidate to sustain MD-based gene therapy in a combined treatment. Noteworthy, this dual approach could also allow to reduce the required AAV dose and, consequently, reduce the dangerous adverse effects related to viral vector immunogenicity.
In a dose-response study, we selected the minimum sub-optimal doses of AAV-MD able to restore at least 20% of dystrophin expression in *mdx* mice and two of these doses have been injected into mice previously treated with SRT2104 to assess whether this can promote a recovery superimposable to the optimal dose of MD, thus demonstrating the advantages of a combined therapy.

The role of patients' associations in IHI European multi-partner projects

Ilaria Zito
Parent Project aps, Rome, Italy

Parent Project (PP) is an association of patients with Duchenne and Becker Muscular Dystrophy. With the main goals of improving quality of life, prolonging life expectancy and finding a cure, we accompany patients and their families throughout their journey with a multidisciplinary approach.
The scientific office is involved in many activities that work in this direction, including funding research and organizing our annual International Conference. Other less direct yet extremely powerful ways by which we aim to speed up the development of new therapies and supporting research are being generated thanks to the growing number of partnerships with different stakeholders. In fact, as our association expanded, the same happened with connections with various partners and we are now well established in an international network rotating around the pathology that sees us also involved in different, important IHI European Projects, among which the MAGIC and the PaLaDIn Project.
The MAGIC project is a multi-partner ambitious scientific project aiming at developing advanced models of human skeletal muscle and innovative gene therapy approaches. In addition to several scientists, different patients' associations (PAs) are involved in this project, to highlight the importance of the partnership among scientists and PAs, which becomes evident in our role of disseminating the scientific findings in a family-friendly language and in bringing the patients' voice to scientists to guide them in the best direction.
PaLaDIn is a multi-stakeholder project, coordinated by PP, that aims to align registry-reported data with Patient Reported Outcome Measures and other data, e.g. wearable devices, to be collected in an omni-interoperable-platform (the Interactium) to improve outcomes and decision-making, and accelerate innovation for a range of stakeholders. Once again the role of PAs is crucial to the outcome of such a project due to our high-level of experience with patient data collection.

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

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Fibrodysplasia Ossificans Progressiva (FOP) is a rare congenital disease that results in heterotopic ossification (HO) of skeletal muscles. It arises from a mutation (R206H) in the Acvr1 gene encoding for the activin type I receptor, leading to an aberrant activation of the bone morphogenetic proteins and activin A signalling pathways.
FOP patients develop HO in response to flare-ups in skeletal muscles. In this context, macrophages still have an unclear role and require a better characterization.
To model FOP, we used the Acvr1(R206H)loxP;Gt(ROSA26)SorCreERT2 conditional transgenic FOP mouse strain. Tamoxifen induced FOP mice received muscle injury in the gastrocnemius to trigger local inflammation. Computerized tomography (CT) showed that FOP mice formed HO at 14 and 21 days post injury.
To investigate the role of macrophages during HO, we depleted circulating monocytes by injecting clodronate liposomes intravenously. CT revealed that macrophage-depleted FOP mice had lower HO at 14 and 21 days after injury.
To explore the early signalling leading to HO, we performed single-cell RNA sequencing on the gastrocnemii of control and FOP mice at 5 and 7 days after injury. We analysed the differentially expressed genes in macrophages and fibroadipogenic precursors (FAPs), the cells mainly responsible for HO in FOP.
We observed an upregulation of ossification genes in FOP FAPs and an upregulation of glycolysis/OXPHOS in FOP macrophages. Moreover, both clusters were enriched in hypoxia and extracellular matrix remodelling pathways.
Next, we studied the interactions between FAPs and macrophages in vitro. We tested whether FAPs and macrophages interaction could affect HO formation by culturing FAPs with the conditioned medium (CM) derived from polarized macrophages. Both control and FOP FAPs treated with CM from FOP macrophages showed increased mineralization.
Overall, our data indicate that macrophages and FAPs interaction promotes bone formation since early timepoints in FOP mice.

Consequences of CNBP reduced expression in DM2 pathogenesis

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Myotonic dystrophy type 2 (DM2) is a dominant autosomal disease that primarily affects skeletal muscle, causing degeneration and dysfunction of muscle fibers. DM2 is due to a CCTG repeat expansion mutation in intron one of CNBP (Cellular Nucleic acid Binding Protein) gene. The pathogenic mechanism involved in DM2 development is still uncertain.
Our studies demonstrated that a decrease of CNBP expression in muscles can affect locomotor activity by causing a reduction in polyamine levels, linked to a decrease of the key polyamine biosynthesis enzyme ODC (Ornithine Decarboxylase) translation in Drosophila. We demonstrated that the locomotor defects caused by CNBP depletion can be rescued by polyamine supplementation or restoring dOdc expression.
CNBP deficiency correlates with a reduction of polyamine levels in muscle cells from DM2 patients, which are both downregulated compared to healthy individuals.
We investigated the effect of CNBP depletion in the constitutive KO CNBP mouse model. We have observed that mice with heterozygous deletion of CNBP show a late onset phenotype of impaired locomotor activity reminiscent of DM2, associated with morphological alterations of muscle tissues.
The exact mechanism linking the impairment of CNBP/ODC/polyamine axis to the observed muscle dysfunction is currently unknown and it is not clear if polyamine supplementation might provide therapeutic benefit to other animal models and, most relevantly, to DM2 patients. Emerging observations are pointing at the translation factor eIF5A, whose activity is strictly dependent on the polyamine levels. We analyzed eIF5A hypusination, in dCNBP-depleted larvae, that resulted reduced compared to controls, suggesting that dCNBP may regulate eIF5A activity, through its translational control of ODC.
Our results revealed a new role of CNBP in muscle diseases, linked to polyamine metabolism. Further studies may provide innovative approaches to treat DM2 patients.

Muscle stem cell function is impaired in absence of Talpid3 - a gene required for primary cilia formation

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Skeletal muscle stem cells (MuSC) are crucial for tissue homeostasis and repair after injury. Following activation, they proliferate to generate differentiating myoblasts. A proportion of cells self-renew, re-enter the MuSC niche under the basal lamina outside the myofiber and become quiescent. Quiescent MuSC have a primary cilium, which is disassembled upon cell cycle entry. Ex vivo experiments suggest cilia are important for MuSC self-renewal, however, their requirement for muscle regeneration in vivo remains poorly understood. Talpid3 (TA3) is essential for primary cilia formation and Hedgehog (Hh) signalling. We used tamoxifen-inducible conditional deletion of TA3 in MuSC (iSC-KO) and showed that regeneration is impaired in response to cytotoxic injury. Depletion of MuSC after regeneration suggested impaired self-renewal. This was consistent with an exacerbated phenotype in TA3iSC-KO mice after repeat injury. Single cell transcriptomics of MuSC progeny isolated from myofibers identified components of several signalling pathways, which were deregulated in absence of TA3, including Hh and Wnt pathways. Pharmacological activation of Wnt restored muscle regeneration in vivo, while purmorphamine, an activator of the Smoothened (Smo) co-receptor in the Hh pathway, had no effect. Together, our data show that TA3 and primary cilia are important for MuSC self-renewal and that pharmacological treatment can efficiently restore muscle regeneration in the absence of cilia.

Non-coding RNAs to Treat Skeletal Muscle Atrophy

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Skeletal muscle atrophy occurs due to malnutrition, age, genetics, lack of physical activity, or certain medical conditions. The most harmful effect of muscle atrophy is decreased quality of life due to functional disability, increased risk of fractures, decreased basal metabolic rate, and reduced bone mineral density. Increasing evidence suggests the central role of non-coding RNAs in genetic and epigenetic modulation of muscle function. We analyzed coding and non-coding RNAs in different conditions of muscle atrophy to identify signatures based on non-coding RNAs involved in the maintenance of muscle mass. We focused on a specific process associated with muscle aging and loss of nerve function to identify short and long non-coding RNAs capable of inducing myotube formation and enhancing muscle mass. Conclusions. We have shown that satellite cells overexpressing a specific miRNA (patent process) produce thicker myotubes and secrete the same miRNA to affect other non-engineered muscle cells. These cells are also able to reverse muscle atrophy induced by a pathological condition such as ALS. In addition, overexpression of a specific long non-coding RNA, which counteracts miRNA activity and is overexpressed in pathological conditions in muscle, is able to limit the beneficial effect of miRNA.

Nanoparticle-mediated delivery to skeletal muscle cells of N-palmitoylethanolamide (PEA), an endocannabinoid-like molecule with anti-inflammatory properties

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Much evidence supports the idea that chronic low-grade inflammation contributes to sarcopenia, that is the loss of muscle function and mass observed during aging, suggesting the potentiality of daily anti-inflammatory strategies to counteract age-related muscle wasting. In this work we assessed whether N-palmitoylethanolamide (PEA), a natural endocannabinoid like molecule, might represent an anti-inflammatory compound of putative relevance to treat sarcopenia as its use is not linked to serious side effects. The use of PEA as a drug is highly limited due to its extremely low solubility in biological fluids and consequent poor bioavailability. We developed nanotechnology-based formulations (nanoparticles, NPs) to deliver PEA to muscle cells in culture. We found that PEA loaded NPs are efficiently internalized in muscle cells and they do not interfere with cell viability or muscle cell terminal differentiation. Furthermore, our preliminary results indicate that PEA-loaded NPs reduced lipopolysaccharides (LPS)-mediated increase of the level of transcripts encoding interleukin (IL)-6 and Tumor Necrosis Factor (TNF)-alpha. Our results will contribute to clarify clinical potential of PEA-loaded NPs to evaluate further *in vivo* development of this preclinical study.
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Sarcopenic obesity in the elderly: a dysfunctional crosstalk between tissues?

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Sarcopenic obesity (SO) is a growing health problem, especially in the elderly. The mechanisms linking obesity, sarcopenia, and inflammation are largely unknown. To unravel their interplay at cellular and molecular levels, we developed a mouse model of SO in aging using 12-month old female mice fed for 7 months with high fat diet (HFD, 60% of kCal derived from fat) or standard diet (SD). We monitored the onset of obesity and sarcopenia measuring weight, fat/lean mass ratio and muscle strength. At selected time points, we performed histological and molecular analyses of blood, skeletal muscle, and subcutaneous and visceral adipose tissue.
HFD induced a rapid increase of body weight and fat, and a loss of muscle strength. Muscle mass was reduced after 7 months of HFD when appeared a significant inflammatory infiltrate in muscle tissue. Adipose tissues showed an increase in adipocyte size after 1 month of HFD. The metabolic profiles of skeletal muscle, adipose tissue, and plasma revealed significant alterations starting from 1 month of diet (e.g. reduced capacity to metabolize fatty acids and decreased oxidative stress buffering). Accordingly, skeletal muscle mitochondrial respiratory capacity was reduced in HFD.
To dissect mechanisms underlying the cross-talk between adipose tissue, skeletal muscle, and blood, we also characterized circulating extracellular vesicles (EVs). Preliminary results demonstrate that EVs of leukocyte, macrophage, endothelial, platelet or adipocyte origin were present in both mouse groups. EVs of adipocyte and endothelial origin decreased in mice receiving HFD indicating a possible uptake by the tissues.

Pre-clinical development of a drug inhibiting the chromatin remodeling protein WDR5 in FSHD muscular dystrophy

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Facioscapulohumeral muscular dystrophy (FSHD) is one of the most prevalent neuromuscular disorders. Weakness is slowly progressive with high variability among patients. The disease is caused by the aberrant expression of the transcription factor DUX4, which is normally confined to early embryonic development. In FSHD, DUX4 mis-expression activates a pro-apoptotic transcriptional program leading to block of differentiation and muscle wasting. Given its pivotal role in FSHD, blocking DUX4 expression with small molecule drugs is an attractive solution.
Previously, by combining proteomics with genetic and pharmacological targeting, we identified the chromatin remodeling protein WDR5 as a key activator of DUX4 expression in FSHD. By testing various compounds, we identified a novel WDR5 inhibitor (WDR5i) showing higher potency and better pharmacological properties, which are important for pre-clinical testing. To this aim, we evaluated WDR5i safety and efficacy in preclinical models of FSHD. We confirmed WDR5i ability to inhibit DUX4 expression using muscle cells isolated from multiple FSHD patients. We also found that an intermittent WDR5i treatment if sufficient to obtain long-term DUX4 repression. Importantly, long-term WDR5i treatment does not significantly affects muscle cells proliferation or differentiation. To perform in vivo tests, we set up a humanized animal model of FSHD that will allow us to evaluate WDR5i safety and efficacy in a relevant setting.
Results from our work could provide a novel therapeutic opportunity for FSHD patients that, up to now, have no cure.

Investigating the potential of MICAL2 modulation for impeding rhabdomyosarcoma cancer progression

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MICAL2 is a member of the Microtubule Associated Monooxygenase, Calponin And LIM domain containing protein family that is involved in regulating F-actin depolymerization and actin cytoskeleton rearrangement, which underlie cell motility and division, via oxidation-reduction reactions. The overexpression of MICAL2 in rhabdomyosarcoma (RMS), among many other cancers, prompted us to examine the role this gene may play in RMS as it represents the most common soft tissue sarcoma afflicting children and young adults and is characterized by dysregulated myogenesis. Initial *in vitro* investigations involving MICAL2 knockdown (KD) using plasmid constructs containing short hairpin RNAs (shRNAs) designed to target *mus musculus* (*Mm*) MICAL2 mRNA demonstrated significant reductions in migratory and invasive properties of murine fusion negative RMS (FN-RMS) cell lines. Upon transitioning to *in vivo* experiments by loading these shRNAs into inducible TET ON lentiviral constructs to assess the impact of stable MICAL2 KD, our results corroborated the *in vitro* observations, wherein MICAL2 silencing gave rise to positive outcomes including reduced primary tumor size, absence of metastatic sites, and improved functional performance. Subsequent analyses of the muscle tissues from the *in vivo* experiments using bulk RNA-sequencing also confirmed the beneficial effects of MICAL2 KD, and proteomic analyses are now in progress in order to further enhance our understanding of the molecular alterations that contribute to RMS pathophysiology. The results obtained thus far motivate more in-depth examinations into the role of MICAL2 in FN-RMS and highlight targeting MICAL2 as a potential therapeutic strategy for RMS treatment.

Serum amyloid protein A1 (SAA1) impairs myogenesis and myotube size in pancreatic cancer cachexia

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Cancer cachexia is a multifactorial syndrome characterized by a progressive loss of skeletal muscle mass, leading to increased mortality in cancer patients. The complexity of cachexia makes diagnosis challenging, with major clinical manifestations including systemic inflammation and muscle wasting. This syndrome can reduce body weight by up to 30%, negatively impacting patient response to treatments and decreasing life expectancy. Cachexia occurs in individuals with various types of cancer, with the highest incidence reported in pancreatic cancer. Understanding the systemic factors influencing muscle in cachexia may lead to novel therapeutic targets. A currently debated issue is whether cachexia also negative affects the ability of skeletal muscle to regenerate. To assess if circulating factors negatively affect muscle stem cells (MuSC), I treated human MuSCs (hMuSCs) with serum from cachectic patients. The results show reduced self-renewal potential and upregulated levels of Serum Amyloid A1 protein (SAA1), a protein released during acute phase response. Treatment of hMuSC with SAA1 protein alone produces effects comparable to those of the cachectic serum. In an *in vivo* model of pancreatic cancer, we found that mice exhibites muscle loss (~10%) and a reduced MuSC self-renewal. Proteomic analysis of plasma from these cachectic mice show increased SAA1 levels. Further, RNAscope and ELISA tests demonstrate high production of SAA1 by skeletal muscles in cancer cachexia, suggesting SAA1 as a potential target for treatment. I am investigating the molecular mechanisms by which SAA1 affects the myogenic process and causes muscle loss. An increased understanding of the processes underlying cancer cachexia will accelerate the discovery of novel treatments, ultimately improving the survival and quality of life for cancer patients.

Keywords: cancer cachexia, SAA1, muscle stem cells, muscle wasting.

Engineered exosomes as a therapeutic tool to counteract muscle degeneration

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Duchenne muscular dystrophy (DMD), caused by mutations in the dystrophin gene, is the most prevalent form of muscular dystrophies (MDs). Other MDs involve mutations in components of the dystrophin-associated protein complex (DAPC), such as the sarcoglycan complex, where mutations in the SCGB gene result in autosomal recessive limb-girdle muscular dystrophy type 2 (LGMD2E). Furthermore, muscle degeneration is also associated with aging and various chronic pathologies such as diabetes and cancer. Recent studies highlight the importance of paracrine factors in sustaining muscle homeostasis. Extracellular vesicles (EVs), carrying specific host factors such as microRNAs (miRNAs), can play a role in muscle physiological growth, development, and regeneration (1). We have identified miRNAs that can boost myogenic differentiation of mesodermal progenitors derived from human induced pluripotent stem cells (hiPSCs) (2). Our research focuses on developing custom-engineered EVs as therapeutic tools to counteract muscle degeneration. To this end, we are developing in vitro 2D and 3D models to mimic different types of muscle degeneration, using patient-derived DMD hiPSCs (3), bSGC null hiPSCs, and human immortalized myoblasts. EVs from DROSHA knockout HEK-293T cells have been enriched with selected miRNAs or combinations thereof. These EVs will be tested on our cell models to evaluate their efficacy in improving myogenic differentiation. The generation and delivery of EVs with custom-engineered cargos, either alone or in combination with other therapies, may offer innovative approaches for treating muscle wasting, providing new hope for patients with various muscle degeneration conditions.

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Immunomodulation via interleukin-4 improves energy metabolism in C26 tumor-bearing mice

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Introduction. Cancer cachexia is a complex syndrome featuring loss of body weight and skeletal muscle mass, systemic inflammation, mitochondrial alterations and altered energy metabolism. Pro-inflammatory cytokines are central in the pathogenesis of cancer cachexia, suggesting the use of antagonistic cytokines as a potential therapeutic strategy. Indeed, previous studies proved that treating tumor-bearing (TB) mice with interleukin-4 (IL4) improves muscle function, myogenesis and survival. Whether IL4 administration improves energy metabolism in the skeletal muscle is unknown.
Methods. Eight-week-old Balb/c male mice were inoculated with 5 x 10^5 C26 colon carcinoma cells. Daily IL4 treatment (66.5 µg/kg) was performed by intraperitoneal injection. The gastrocnemius muscle was used to assess mitochondrial proteins (western blot) and respiration (high-resolution respirometry, Oroboros Instruments). Liver and gastrocnemius muscle were used to perform mass spectrometry based metabolomic analyses (University of Colorado, Aurora, USA).
Results. Treatment with IL4 counteracted the loss of body weight, muscle mass and muscle strength in TB mice. Spleen enlargement was found in treated TB mice. The protein levels of the oxidative phosphorylation (OXPHOS) complexes II and III, cytochrome c and PGC-1α in the skeletal muscle were significantly increased in treated vs untreated TB mice, while trends to decrease were found for BNIP3 and TFAM. The activity of OXPHOS complex II was significantly increased in treated vs untreated TB mice. Tumor and IL4 dependent modulations in liver and skeletal muscle metabolomic profiles were observed.
Conclusion. Treatment with IL4 improves energy metabolism in the skeletal muscle of TB mice, possibly exerting an exercise-mimetic role. Spleen enlargement suggests that IL4 modulates the immune response. Whether IL4 effectiveness also results from modulation of the immunological milieu in the tumor microenvironment remains to be investigated.

Unraveling the therapeutic potential of givinostat in muscle atrophy induction

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Muscle atrophy is a debilitating condition characterized by muscle degradation and subsequent weakness. It arises from several conditions ranging from temporal muscle disuse to genetic pathologies, including Duchenne Muscular Dystrophy (DMD). In healthy muscles, homeostasis alteration by atrophic stimuli is transient, and satellite cells contribute to muscle repair. In pathological conditions such as DMD, persistent inflammation and fibrotic tissue accumulation is coupled with reduced satellite cell function and to irreversible muscle loss. While corticosteroids represent the standard for the treatment of DMD, their efficacy is often hindered by undesirable side effects, and many alternative therapeutic strategies have been explored. Recently, our proprietary small molecule HDACs inhibitor givinostat has been approved by FDA as the first nonsteroidal drug to treat DMD patients with all genetic variants. This study aimed at elucidating the effect of givinostat on muscle atrophy using an *in vitro* model based on differentiated human primary skeletal myotubes (HSkM). Cells were treated with TNF-α, both in the presence and absence of Deflazacort (DZ) and/or givinostat, followed by transcriptomic analysis to unravel the molecular mechanisms. Givinostat alone reduced the activation of inflammatory and cell cycle pathways and upregulated metabolic and intracellular vesicles trafficking pathways. These modulations were confirmed by a proteomic analysis on murine myotubes that showed a mRNA-protein correlation of 80.3%. Moreover, givinostat reversed the TNF-α deleterious effects, in contrast to DZ, downregulating key pathways associated with muscle degradation, as inflammation, proteasome core complex and necroptosis. Furthermore, givinostat increased protein deubiquitination, both independently and in combination with DZ. Remarkably, DZ induced ferroptosis that was restored by givinostat. These findings further support the role of givinostat in reducing muscle damage in DMD.

Poster Abstracts

Changes in CLIMP63 expression alter the organization of the microtubule network of mouse skeletal muscle fibers

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The endoplasmic reticulum (ER) is a highly specialized organelle, responsible for protein synthesis and Ca^{2+} handling. It establishes contacts with several other organelles and is closely associated with microtubules (MTs). MTs act as a scaffold for ER positioning and remodeling, playing a central role in ER morphogenesis. Recent data revealed of a role of ER dynamics in regulating MT network distribution and stability, providing novel insights on the extent of interconnection between ER and MTs. In skeletal muscle, the sarcoplasmic reticulum (SR) is a specialization of the ER, dedicated to Ca^{2+} storage and release necessary for muscle contraction. Recent data suggested that the SR protein triadin is involved in MT-dependent organization of SR membranes by interacting with the cytoskeleton-linking membrane protein 63 (CLIMP63), an ER/SR-shaping protein able to directly bind MTs. Research conducted in our laboratories identified CLIMP63 as an interactor of two additional SR proteins, junctophilin 1 and 2. To further evaluate the role of CLIMP63 on the SR and MT organization, we performed experiments of either overexpression or downregulation of CLIMP63 in skeletal muscles from newborn and adult mice. Analysis of expression of SR proteins and MT organization suggest that, in newborn mice, changes in CLIMP63 expression alter the architecture of the MT network, confirming the role of this protein as a structural tether between the ER and MT.

P.3

Gene expression analysis in skeletal muscles of mice carrying a deletion in a muscle-specific stretch/super enhancer region inside the ANK1 locus

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The *ANK1* gene, encoding for ankyrin-1, is characterized by the presence of a first promoter (P1), driving the ubiquitary expression of the full length ANK1 protein, and a second muscle-specific internal promoter (P2), located in the 3' region, driving the expression of a small muscle specific isoform, sAnk1.5. Analysis of tissue-specific transcriptome data and chromatin accessibility indicated that the 3' region of the *ANK1* gene, including P2 promoter, has the features of a stretch/super enhancer (SSE), characterised by a strong enrichment of transcriptional coactivators binding regions that can regulate long distance genes by 3D chromatin remodelling. To elucidate the role of this regulatory region we took advantage of sAnk1.5 (P2) KO mouse model, carrying a 941 bp deletion in the P2 region, that we found to have altered glucose homeostasis. Thus, we hypothesized that the deleted region could exert a role in transcriptional control on genes related to metabolism. Therefore, we performed a microarray analysis of gene expression in soleus and EDL muscles of sAnk1.5 (P2) KO mice. Genes involved in glucose or lipid metabolism or genes with higher differential expression levels between WT and sAnk1.5 (P2) KO muscles were prioritized for the analysis. sAnk1.5 (P2) KO mice showed a reduced expression of several genes participating in glucose metabolic pathways and an overexpression of fatty acids transporters type 4 and 5. This different expression suggests that sAnk1.5 (P2) KO mice could have a shift in the energy source towards fatty acids utilization. Additionally, genes involved both in myogenic differentiation and muscle regeneration were found altered in sAnk1.5 (P2) KO mice. Further investigations are ongoing to better unravel the molecular mechanisms altered in the sAnk1.5 (P2) KO mice and the correlation with altered glucose homeostasis.

P.4

Regulation of individual sensitivity to inflammation by myc contributes to muscle loss in COPD

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Inflammation is a likely contributor to muscle loss. However, studies comparing inflammatory cytokines with muscle loss in patients have mixed results. The picture is further complicated by the inter-relationship of inflammation and inactivity. We compared Fat free mass index (FFMI), physical activity and inflammatory cytokines in controls, patients with mild (n=28) or severe COPD (n=51). FFMI was similar in mild COPD vs controls but lower in severe patients vs both other groups. Neither activity nor circulating inflammatory cytokines differed between patient groups, but activity was lower, and inflammatory cytokines higher, in both patient groups vs controls. Consequently, neither activity nor inflammatory cytokines alone explain the difference in FFMI.
Comparison of quadriceps gene expression quantified by microarray with lung function (Transfer capacity of the lung for CO) showed genes associated with the epithelial mesenchymal transition, inflammatory pathways and myc targets increased with disease severity. Further analysis showed the expression of multiple cytokine receptors (e.g. OSMR and IL31RA) and signalling intermediates increased with disease severity. Comparison of circulating cytokines with the array data in mild and severe disease groups separately showed that proinflammatory cytokines associated positively with inflammatory gene sets strongly in severe COPD but weakly in mild COPD. Anti-inflammatory cytokines were negatively associated with inflammatory gene-sets in mild disease but positively associated in severe disease. Comparison of myc expression with the microarray showed positive association for inflammatory genes including OSMR, IL31RA, CCL2 and IL6. Together our data suggest that the muscle of patients with severe COPD is more sensitive to inflammatory signals than those with mild COPD leading to greater muscle loss with myc as a potential regulator.

P.5

Long noncoding RNAs at the interface between muscles and nerves

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Extensive high-throughput analyses and innovative biochemical approaches have unveiled, beyond protein factors, the additional and essential contribution of RNA-mediated molecular mechanisms in the regulation of myogenic gene expression. In particular, tissue-specific long noncoding RNAs (lncRNAs) were shown to play pivotal roles in muscle physiology and development, although the knowledge concerning their mechanisms of action is still far from being complete. Our aim is to study the contribution of lncRNAs to muscular and neuromuscular physiology through the integration of gene editing, induced pluripotent stem (iPS) cell technology and interactome analyses. Our investigations include Charme (Taliani V. et al., Elife 2023), previously identified in mice as a myogenic lncRNA, and currently under investigation in human skeletal muscle differentiation. Emphasis is also placed on the impact of lncRNA on muscle-nerve communication, specifically focusing on the spinal cord and skeletal muscle functional interactions at the neuromuscular junction (NMJ). By applying CRISPR-cas9 genome editing we generated human iPSCs lines knocked out for either Charme or the motoneuronal lncRNA nHotairM1 (Tollis P. et al., Cell Death & Dis 2023). We exploit co-cultures of iPSC-derived spinal motoneurons and myotubes and 3D model systems (neuromuscular organoids) to untangle the contributions of neural and muscular lncRNAs to the structural and functional properties of the NMJ.

Complex Magnetic Fields (CMFs): harnessing electromagnetic symphony for muscle regeneration

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Sarcopenia is a physiological condition in which loss of muscle mass and function, presents a significant challenge in aging populations, due to the decline in ability of satellite cells to proliferate and differentiate into new muscle fiber. This study highlights Complex Magnetic Fields (CMFs) as a non-invasive approach to enhance muscle regeneration utilizing human myogenic precursor cells (hMPC). We applied varying intensities and configurations of CMFs to assess their impact on cellular proliferation, differentiation, myotube formation and wound healing. The results demonstrated that exposure to CMFs enhances cell viability and proliferation as evidenced by MTT assay. Moreover, the characterization showed increase in the fusion index, indicated improved myotube formation. The wound healing assay demonstrated accelerated wound closure, suggesting enhanced regenerative properties of the CMFs. In conclusion, CMFs being a non-invasive approach enhances muscle regeneration and exhibit the potential for regenerative medicine.
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P.11

GDF5 therapeutic potential on neuromuscular junction defects

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Neuromuscular junction (NMJ) is a tripartite structure essential for neuromuscular communication and supports motor function of the muscle. Communication between the nervous system and the muscle will be impacted if one of the NMJ components is damaged. In this context, Growth Differentiation Factor 5 (GDF5) appears to be a potential candidate for the treatment of NMJ defects. Indeed, GDF5 has been described to support neuronal survival and neurite growth *in vitro.* In addition, GDF5 has been demonstrated as required in promoting skeletal muscle re-innervation after nerve crush and limiting denervation-related atrophy. Notably, our previous study described that its overexpression is important to limit age-related muscle mass loss and NMJ defects. Here, we hypothesize that GDF5-based treatment could preserve innervation, muscle mass and function in neuromuscular diseases. We used, for pre-synaptic damage indication the $SOD1^{G93A}$ mice one of the best characterized amyotrophic lateral sclerosis mouse model, and for post-synaptic damage, the mdx mice well described Duchenne muscular dystrophy mouse model. We first characterized muscle mass evolution and NMJ alterations in these two models.Then, we overexpressed GDF5 in $SOD1^{G93A}$ mice by systemic adeno-associated virus (AAV) injection and revealed a therapeutic benefit of this treatment on the maintenance of skeletal muscle mass, reinnervation markers NMJ integrity. To further understand the role of GDF5 at NMJ, we investigated the potential interaction between GDF5 and muscle-specific kinase MuSK and we showed, with *ab initio* molecular docking, a strong affinity between GDF5 and MuSK. We will confirm this interaction by biochemical experiments. In addition, we will study the impact of GDF5 treatment on post-synaptic damage in the mdx mice. These studies will generate important insights on the beneficial effect of GDF5 on neuromuscular system and paving the way for the possibility of a GDF5-based treatment for NMJ defects.

P.14

Human mytendineous junction 3D *in vitro* modeling

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Tendons are specialized connective tissues that transfer force from muscles to bones, promoting overall body motility and stability. The interface between muscle and tendon is called Myotendinous Junction (MTJ), that represents the crucial tethering point between theese two tissue. Given its junctional nature, it is often difficult to obtain MTJ-containing biopsies and to prepare comparable samples for imaging studies, due to technical difficulties in proper orientation and sectioning. In this context, 3D constructs represent a reliable tool for mimicking MTJs, based on the use of myogenic (muscle-derived pericytes) and tendon progenitors in combination with biomimetic matrix scaffold. By relying on 3D biocompatible printing technologies, we will generate 3D bioengineered functional constructs by depositing in one step cells and a supporting material, with the highest biomimetic and architectural spatial arrangement.
This novel approach enables the creation of compact and precisely organized three-dimensional constructs, which can aid the scientific community in studying junction-related diseases in a patient-specific manner and serve as an experimental platform for drug testing.

P.21

CHOP/ERO1A pathway of unfolded protein response (UPR) in RYR1 and SEPN1-related myopathies

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The most common mutations in core myopathies are those of the gene encoding for RYR1 calcium channel, although more rarely, also mutations in the gene encoding for SEPN1 lead to the disease. Due to their low incidence in the population, both are classified as rare diseases. RYR1-RM and SEPN1-RM overlap the clinical signs of infancy onset, delayed motor development, and muscle weakness. They also overlap for histological features on muscle biopsies. In the mice models of these two congenital myopathies it has been observed the presence of ER stress at the muscular level, but how it is involved needs more studies. All of these suggest a potential common underlying pathological mechanism, which is worth investigating, given the potentiality of setting a target therapy for these untreatable diseases. Using a genomic approach, we crossed the RYR1^{I4898T} mice with the CHOP KO mice, to evaluate the recovery rate of the pathological phenotype and we crossed SEPN1-KO mice with the ERO1 KO mice. On their collected diaphragms we performed histological analysis, ran RNA-Seq analysis and RT-PCR. To pharmacologically mimic the effect of ERO1 deletion, we tested a chemical chaperone (TUDCA) a pan ER stress inhibitor. We observed a reduction of UPR markers levels in the skeletal muscles of the double mutant pups, but CHOP deletion neither restored RYR1 function nor protected the pups from perinatal lethality. The SEPN1 KO/ERO1 KO mice showed improved muscle function. RNA-Sequencing analysis identified a downregulation of UPR in DKO diaphragms compared to SEPN1 KO diaphragms, suggesting UPR as a disease pathway rescued by the ERO1 deletion. TUDCA treatment reflected the beneficial effects of ERO1 genetic deletion in SEPN1 KO mouse muscles, paving the way for a novel pharmacological treatment. This study suggests ER stress/UPR and specifically the branch CHOP/ERO1 as a disease mechanism of RYR1-RM and SEPN1-RM and opens the possibility of treatment with chemical chaperones.

P.27

Nuclear Phospholipase C delta 4 is a crucial player in modulation of rhabdomyosarcoma cells proliferation

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Human rhabdomyosarcoma (RMS) is a common pediatric soft tissue sarcoma and, due to its aggressivity, current treatments are often unsuccessful. RMS originates from mesenchymal precursors of skeletal muscle cells which have impaired differentiation ability due to the presence of chromosomal translocations and driver mutations, leading to uncontrolled cell growth. A crucial player in RMS aberrant proliferation could be the nuclear protein Phospholipase C delta 4 (PLCδ4), whose role in driving proliferative processes in mesenchymal stromal stem cells has already been described. Our molecular and morpho-functional analyses reveal that PLCδ4 is mainly expressed in A204 embryonal RMS cells, whereas it is only slightly detected in RD rhabdomyosarcoma cells. To better characterize the role of PLCδ4, rhabdomyosarcoma RD cell line was stably transfected with wild-type PLCδ4. When PLCδ4 is overexpressed in RD cell line, its localization is purely nuclear. Proteome profiler array analysis demonstrates that enhanced expression of PLCδ4 in RD cells positively influences the phosphorylation of PRAS40 (T246), Chk2(T68), WNK1(T60) and Akt 1/273 (S473). Overexpression of PLCδ4 in RD cells results in G2/M phase cell cycle arrest, enhancing cyclin B1 expression. Overall, our study identifies a novel role for nuclear PLCδ4 to block proliferative functions via inducing cyclin B1 phosphorylation by Akt. Therefore, the modulation of PLCδ4 expression and of its downstream targets could represent a crucial strategy to block embryonal RMS cells proliferation.

P.28

Hyaluronan improves the C2C12 murine myoblast proliferation and myogenic differentiation under oxidative and inflammatory conditions

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Hyaluronan (HA) is a non-sulfated glycosaminoglycan widely used for medical and pharmaceutical applications, including tissue muscle repair. A recent study demonstrates that HA activates muscle stem cells to repair damaged muscle: when muscle damage occurs, stem cells start producing and coating themselves with hyaluronic acid and demethylase JMJD3-driven hyaluronic acid synthesis that allows muscle stem cell adaptation to inflammation and the initiation of muscle repair [(1)]. In this study, we analyzed HA's effect on myoblast rescue under stress and inflammatory conditions using C2C12 murine muscle cell proliferation and differentiation. First, we evaluated the wound healing of myoblast cell monolayer at (t0) and after 24 hours (t1) in the presence/absence of an HA blend of 2 to 1000 KDa (0.3 mg/ml, Regenflex T&M Regenyal Laboratories SRL) and with/without pro-inflammatory agents (IL-1β, TNF-α, LPS); with/without pro-oxidants (H_2O_2) that slow their proliferation. The wound healing assay revealed an improvement in reparative mechanisms even under oxidative and inflammatory stimuli. Secondly, the C2C12 myogenic properties treated with HA were characterized based on MyoD Mrf4, myogenin, and IGF-1 expression under the previously described stress and inflammatory conditions. From the preliminary results obtained, it appears that HA possesses significant pro-proliferative activity, improving wound healing 24 hours after injury in both stress and inflammatory conditions and inducing an upregulation of the myogenic biomarker as a beneficial effect on the differentiation program, indicating that this HA formulation could be used as a promising treatment for muscle tissue regeneration.

1.Nakka K, et al., Science. 2022 Aug 5.

P.31

AntagomiR inhibition of miR-424(322) increases muscle fibre diameter in old mice and in response to respiratory viral infection

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Muscle loss is a common complication of many diseases that can lead to frailty. We have shown that miR-424 is elevated in the muscle of patients with COPD, ICUAW and in those about to undergo aortic surgery. Furthermore, pre-surgical miR-424 was directly proportional to muscle loss 7 days later in those undergoing surgery. Mechanistically we have also shown that miR-424 inhibits protein synthesis by reducing ribosomal RNA synthesis thereby suppressing the capacity to make new protein. Finally, over-expression of miR-424 (known as miR-322 in mice but referred to here as miR-424) in mouse muscle promoted rapid muscle loss. Together these data suggest that inhibiting miR-424 in muscle would inhibit muscle loss. We developed an antagomiR to miR-424. Transfection of this antagomiR into mouse C2C12 cells inhibited the effects of miR-424, preventing the suppression of UBTF a key component of ribosomal RNA synthesis and relieving the suppression of protein synthesis compared to transfection with a control oligonucleotide. Indeed, in the absence of exogenous miR-424 the antagomiR increased basal protein synthesis. We have recently found that infection of old (>24 month) mice with respiratory syncytial virus provides a useful model of muscle wasting. To determine whether inhibition of miR-424 could increase muscle mass in vivo we electroporated the antagomiR into the left tibialis anterior (TA) of mice a control into the right TA of female old mice with and without infection with RSV and male mice infected with RSV. Quantification of UBTF mRNA showed increased expression in the left TA compared to the right. Quantification of fibre diameter by histological analysis showed increased fibre diameter in the left TA compared to the right TA in all groups. This difference was largest in the female mice infected with RSV.
Together these data show that inhibition of miR-424 promotes muscle fibre maintenance/growth under atrophic conditions.

P.32

An autocrine loop of lactate sustains cancer cachexia in skeletal muscle

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Our previous studies demonstrated that muscle wasting is associated with high production of lactate that, behind the metabolic role, acts as signalling molecule through the binding to the GPR81 receptor. Our aim is to dissect the role of the secreted lactate in the onset and maintenance of the cachectic condition in skeletal muscle. Our results show that lactate in the extracellular environment is involved in myotube wasting, since the inhibition of the lactate transporter MCT1 impedes the formation of the cachectic conditions. Interestingly, the inhibition of MCT1 transporter blocks the decrease of pyruvate dehydrogenase activity which is greatly inhibited in cachectic muscles. Moreover, increased amount of lactate and enhanced level of lactate dehydrogenase has been observed in mitochondria of cachectic myotubes. Interestingly, the abdominal muscle of cachectic patients contains increased level of lactate associated with an upregulation of lactate dehydrogenase in comparison to the noncachectic counterpart. Increased amount of lactate and upregulated lactate dehydrogenase and GPR81 receptor have been detected in human fibroblasts isolated from the abdominal muscle of cachectic patients in comparison to the fibroblasts from non-cachectic individuals. Although preliminary, these findings suggest that in skeletal muscle an autocrine loop of lactate could drive the onset and maintenance of the cachectic condition.

P.36

Role of Sbno2 in myogenic differentiation under cachectic conditions

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Cancer-related cachexia, a condition characterized by progressive skeletal muscle wasting, is one of the common complications in cancer patients, leading to increased mortality. It has been reported that cancer cachexia is responsible for about 20-30% of all cancer related deaths worldwide. This metabolic wasting syndrome leads to atrophy of skeletal muscle as well as impaired muscle stem (MuSC) functionality and so far cannot be reversed by nutritional or medical support.
We compared the changes in gene expression in MuSCs from EDL, soleus and extraocular muscles from cachectic and healthy control mice and thereby identified Sbno2 (strawberry notch homologue 2) as one of the genes being specifically upregulated in cachectic mice. We hypothesized that the aberrant expression of Sbno2 in MuSCs from cachectic mice causes impaired differentiation. To model cancer cachexia in a cell culture system, we used conditioned medium from different cachexia inducing cancer cell lines and verified the aberrant expression of Sbno2 in myoblasts. Of note, when we reduced the aberrant expression of Sbno2 which is caused by the different cancer cell supernatants, we could restore myogenic differentiation under cachectic conditions. To unravel the mechanism by which Sbno2 is impairing myogenic differentiation under cachectic conditions, we are searching for interactions partner of Sbno2 followed by functional analyses.

P.43

Targeting monoamine oxidase B (MAOB) in dystrophic mdx hearts dampens inflammation and fibrosis

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Background Cardiomyopathy is a major cause of death for Duchenne muscular dystrophy (DMD) patients. We previously showed that targeting mitochondrial MAOB with specific inhibitors (iMAOB) improves skeletal muscle function in dystrophic mice by lowering oxidative stress, inflammatory infiltrate and fibrosis.
Aim Explore the therapeutic potential of iMAOB to alleviate DMD cardiomyopathy using dystrophin-deficient *mdx* mice treated at an age when cardiac disfunction is not yet clinically evident.
Methods Three-month-old *mdx* mice were orally treated with iMAOB or vehicle for one month (n≥6). Heart ventricular mononucleated cells were obtained by enzymatic digestion. Myeloid, endothelial and fibroblast cells were then isolated by FACS and analysed by RT-PCR. Oxidative stress, inflammation and fibrosis were measured in tissue cryosections by fluorescent probes, immunofluorescence and immunochemistry, respectively.
Results The expression of proinflammatory and profibrotic genes was increased in myeloid (Il-1b, Il-6, Tgf-b and Spp1), endothelial (Il-1b, Il-6, mmp2 and nos3) and cardiac fibroblast cells (Tgf-b, Spp1, Timp1 and Col1) isolated from *mdx* hearts, as compared to wild type mice. Expression of all these genes was significantly dampened by iMAOB treatment. Noticeably, the differences were not linked to changes in the percentage of the various cell types, as they were unmodified amongst wild type, mdx and iMAOB-treated mdx hearts. In parallel, iMAOB treatment decreased the levels of oxidative stress, inflammation and fibrosis observed in *mdx* myocardium sections. Similar results were also seen in skeletal muscles, considering both mononucleated cells and single fibers.
Conclusions We show that iMAOB can positively affect the phenotype of cells that are important in cardiac tissue remodeling. Our data suggest that iMAOB could be a viable therapeutic tool in DMD cardiomyopathy. As iMAOB are already in clinical use, such approach could be easily translated to patients.

P.44

Vaccinium macrocarpon extract restrains muscle wasting induced by Western diet-derived AGEs

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Western diet (WD) is a modern and diffuse dietary style characterized by high intake of fatty, sugary, ultra-processed and pre-packaged foods containing elevated advanced glycation end-products (dietary AGEs; dAGEs). WD increases the development of insulin resistance and metabolic inflexibility predisposing to muscle wasting (MW), i.e., loss of muscle mass and strength. AGEs are non-enzymatic products that can be endogenously formed in hyperglycemia conditions or exogenously sourced from diet. AGEs induce tissue damage by altering protein function or binding their receptor, RAGE, thus sustaining systemic/local inflammation and oxidative stress, as typically observed in subjects consuming WD. dAGE accumulation in skeletal muscle, blood, and skin has been reported in sarcopenia conditions in the elderly, and in diabetic subjects, and RAGE signaling sustains MW in several conditions. The mechanisms underlying WD-dependent MW and the potential role of dAGEs/RAGE axis have not been investigated so far. Here, we demonstrate that male adult mice fed for 20 weeks with WD containing high dAGEs *vs* standard diet (SD), despite eating the same amount of food, showed increased body, adipose tissue, and liver weights, and signs of steatosis in liver. Moreover, in concomitance with AGE accumulation in muscles and plasma, WD-fed mice showed increased numbers of thin myofibers, reduced amounts of myosin heavy chain (MyHC)-II, increased expression of RAGE, and activation of the ubiquitin-proteasome system in muscles, together with reduced muscle performance. The administration of a *Vaccinium macrocarpon* (*VM*) standardized extract (250 or 500 mg/kg/die) to WD-fed mice reduced the AGE content in muscles and improved muscle parameters. Thus, dAGE accumulation/activity as a consequence of WD consumption induces multi-organ detrimental effects, including MW, which might be restrained by the administration of *VM* extract.

P.45

Molecular characterization of ER stress mediators in the pathogenesis of SEPN1 and RYR1-related myopathies

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SEPN1 and RyR1-related myopathies belong to the common class of multi-mini core diseases and are caused by mutations in *SELENON* and *RYANODINE RECEPTOR type1* genes, encoding SEPN1 and RyR1 proteins, respectively. SEPN1 is a type II protein of the endoplasmic reticulum (ER) which regulates the activity of calcium pump SERCA. RYR1 is a calcium channel of the ER involved in calcium efflux from the ER. These myopathies are characterized by impaired redox and calcium homeostasis accompanied by endoplasmic reticulum stress (ER) at molecular levels. Here, we analyze the pathogenic role of the ER stress mediator ER oxidoreductase-1 (ERO1A) and the ER stress-mediated defect in protein synthesis in these two diseases.
ERO1A is upregulated in SEPN1-devoid preclinical models, suggesting that ERO1 might be a biomarker of SEPN1-RM. Combined immunoprecipitation and mass spectrometric analysis identify a disulfide-bonded mediated physical interaction between SEPN1 and ERO1A. Moreover, ERO1A promotes the formation of redox inactive oligomeric SEPN1, suggesting cross-regulation of their respective activities.
The activity of the ER calcium channel RYR1 is critical for muscle contraction and I4895T mutated form leads to excitation-contraction uncoupling, thus enfeebling muscle contraction. $RYR1^{I4895T}$ models exhibit ER stress with augmented expression of ER stress markers. SUrface SEnsing of Translation (SUnSET) on $RYR1^{I4895T}$ models shows a defect in protein translation, suggesting attenuation of protein translation associated with ER stress. Moreover, treatment with ISRIB, a small molecule that restarts protein synthesis in conditions of ER stress, rescues such a defect. This study sheds light on the pathogenic role of specific ER stress/ ER stress response mediators in SEPN1 and RyR1-related myopathies and it is pivotal for implementing a targeted therapy for such diseases.

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Proteomic analysis suggests novel mechanisms involved in the protection against cancer-induced muscle wasting in mice lacking RAGE at myofiber level

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Cancer cachexia (CC) is a debilitating syndrome characterized by progressive muscle wasting and responsible for about half of cancer patients' deaths. The receptor RAGE (receptor for advanced glycation end-products) is re-expressed in myofibers of tumor-bearing mice undergoing cachexia, where it is stimulated by high amounts of cachexigenic RAGE ligands amplifying catabolic pathways. Tumor-bearing RAGE-null (*Ager*$^{-/-}$) mice showed reduced hallmarks of CC, delayed muscle atrophy, and increased survival. To understand the specific role of RAGE expressed at myofiber level in CC, we generated a conditional tamoxifen-inducible mouse model in which the RAGE gene is selectively deleted in skeletal muscles (*Ager*^{mKO} mice). Following subcutaneous injection of Lewis lung carcinoma (LLC) cells, *Ager*^{mKO} mice showed almost complete maintenance of muscle mass and performance at 25 dpi, similar to *Ager*$^{-/-}$ mice, the opposite being observed in *Ager*^{flox} mice. Moreover, the absence of RAGE in muscles of tumor-bearing mice (LLC/*Ager*^{mKO} mice) slowed down body weight loss and increased survival, although to a lesser extent than in the complete absence of the receptor (*Ager*$^{-/-}$ mice). Restrained degradation of fast myosin heavy chain (MyHC)-II, which is typically degraded in cancer conditions, and increased expression of slow isoform MyHC-I, which confers resistance to cancer-induced atrophy, characterized muscles of LLC-*Ager*^{mKO} and LLC-*Ager*$^{-/-}$ mice. Proteomic analysis revealed the absence of terms related to cell death and apoptosis, and several proteins modulated in common in muscles of *Ager*^{mKO} and *Ager*$^{-/-}$ mice compared with the *Ager*^{flox} mice, in the presence of cancer. In particular, SUMO-conjugating enzyme UBC9, whose expression is associated with slow-twitch myofibers, emerged among the upregulated proteins in muscles of LLC/*Ager*$^{-/-}$ and LLC/*Ager*^{mKO} *vs* LLC/*Ager*^{flox} mice, suggesting a novel RAGE-dependent mechanism involved in the resistance against CC.

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