iim
Interuniversity Institute of Myology

15th IIM Meeting
Assisi 11-14 October 2018

Pathogenesis and Therapies of Neuromuscular Diseases

TOPICS

- Biophysics and E-C coupling
- Genetics and epigenetic
- Muscle stem cells and regenerative medicine
- Muscle wasting and cachexia
- Circadian rhythm
- Signaling and metabolism
- Therapeutic approaches

Confirmed Keynote Lectures

Nenad Bursac (Duke University-USA)
Giorgio Fanò (Libera Università di Alcatraz-Italy)
Paolo Sassone-Corsi (University of California Irvine-USA)
Carmine Settembre (TIGEM-Italy)
Shahragim Tajbakhsh (Institut Pasteur-France)

Venue

Hotel Il Cenacolo (Assisi-Italy)
http://www.hotelcenacolo.com/

Scientific Committee

Barbieri E, Blaauw B, Fulle S, Gabellini D, Gargioli C, Grassi F, Musarò A, Mammucari C, Moresi V, Puri PL, Sampaolesi M, Sandri M, Sorci G.

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CITTÀ DI ASSISI
SERAPHICA CIVITAS

COMUNE DI SPELLO

UNIVERSITÀ DEGLI STUDI G. D'ANNUNZIO CHIETI PESCARA
Facoltà di Medicina e Chirurgia

UNIVERSITÀ DEGLI STUDI DI PERUGIA

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Association Française contre les Myopathies

INVITED SPEAKERS

SPECIAL TALK **Giorgio Fanò** (Libera Università di Alcatraz-Italy)

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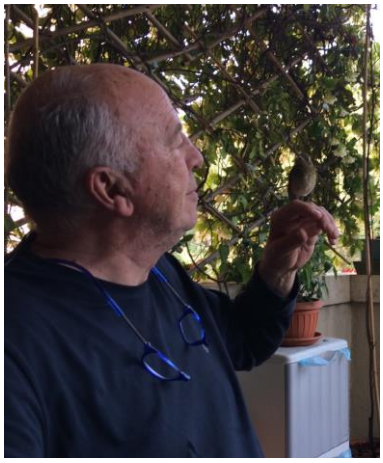


AFFILIATIONS:

- Libera Università di Alcatraz, Santa Cristina of Gubbio (ITALY)
- Laboratorio di Valutazione Funzionale, Department of Neuroscience, Imaging and Clinical Sciences, University "G. d'Annunzio ", Chieti-Pescara
- A&C M-C Foundation for Translational Myology, Padova

LATEST ACADEMIC POSITIONS:

1. Full Professor of Physiology, Faculty of Medicine and Surgery - University "G. d'Annunzio ", Chieti- Pescara.
2. Coordinator of the Ph.D. Course "Basic and Applied Medical Sciences"- University "G. d'Annunzio ", Chieti-Pescara.
3. Deputy Director of the Department of Neurosciences & Imaging - University "G. d'Annunzio ", Chieti-Pescara.

Other scientific responsibilities:

1. 1997- 2017 Head of the School of Physiology and Biophysics of the Italian Society of Physiology
2. 2001-2008 Founder and Head of the Center for Physical Exercise in Nature of the National Park of Abruzzo, Lazio and Molise (Valfondillo, AQ)
3. 2002-2010 Head of the U.O. of Clinical Physiology of the Center of Excellence for the Study of Aging of the "G. d'Annunzio " University of Chieti-Pescara
4. 2004-2010 Member of the Scientific Council of the Inter-University Research Center in Bioengineering and Motor Sciences (CeBISM) University of Trento, Verona, Udine, Brescia
5. 2004-2013. President of the CoRAM, Consortium (Universities-Private companies) for environmental research
6. 2004-2007 Founder and first Director of the Interuniversity Institute of Myology (IIM): Consortium of Italian Universities of Chieti, Florence, Messina, Milan, Perugia, Siena, Brescia, Padua, Rome "La Sapienza"
7. 2005-2011 Director of the Department of Basic and Applied Medical Sciences (BAMS)
8. 2008-2012 Secretary-Treasurer of the Italian Society of Physiology
9. 2010-2013 Head of the Functional Laboratory of the Department of Neuroscience & Imaging of the University "G. D'Annunzio. "
10. 2011-2014 Scientific Advisor for the Biomedicine of the Italian Space Agency (ASI).

SCIENTIFIC EXPEDITIONS

1. 2008 Interuniversity Project Coordinator: INTERAMNIA 8000- MANASLU EXPEDITION (NEPAL-HIMALAYA).
2. 2012 Interuniversity Project Coordinator: TREK GOKIO CUMBU / AMADABLAM (NEPAL-HIMALAYA): GENDER DIFFERENCES IN PHYSIOLOGICAL RESPONSES TO HYPOBARIC HYPOXIA.
3. 2014 Head of Unity: MEDICAL RESEARCH ON HYPOXIA (MERHY): MAN AT ALTITUDE from molecular level to man, in healthy and pathological conditions. General Coordinator: Paolo Cerretelli

LECTURE 1 **Shahragim Tajbakhsh (Institut Pasteur-France)**

Extrinsic and intrinsic regulation of muscle stem cells

The regulation of skeletal muscle stem cells during homeostasis and regeneration involves the interplay of multiple mechanisms. The mechanisms by which niche molecules and intrinsic factors regulate muscle stem cell quiescence and properties remain largely unknown. In a series of studies, we investigated Notch as a key mediator of muscle satellite cell stability and fate. Specifically, Notch mediates extrinsic (extracellular matrix) and intrinsic (microRNA) mechanisms to stabilise satellite cells within their niche. Interestingly, Notch/RBPJ-bound regulatory elements are located adjacent to specific collagen genes in adult muscle satellite cells. These molecules are linked to the ECM and constitute putative niche components. Notably, satellite cell-produced collagen V (COLV) is a critical component of the quiescent niche, as conditional deletion of Col5a1 leads to anomalous cell cycle entry and differentiation of satellite cells. Strikingly, COLV specifically regulates quiescence through Calcitonin receptor mediated activity. In other studies, we have identified a microRNA pathway that is modulated by Notch, and it is required for stabilising muscle stem cells in their niche by regulating the migration status of the muscle stem cell. These observations lead us to propose a two-step mechanism for niche occupancy.

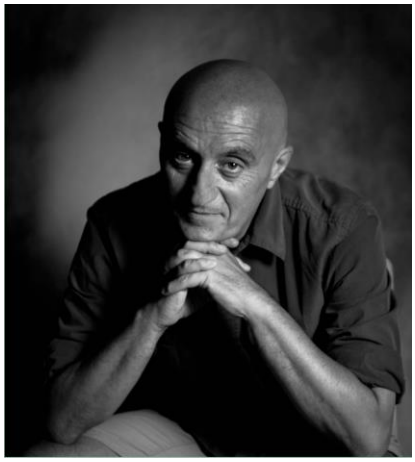
Prof. Shahragim Tajbakhsh obtained a Doctor of Philosophy degree in Biology from Carleton University, Canada (1988) working on the molecular biology of viruses. Following postdoctoral research at the Pasteur Institute he established an independent group in 2001 called "Stem Cells & Development" where he has been interested in how stem cells establish and regenerate organs and tissues, with a particular focus on skeletal muscle. The aim of the laboratory is to investigate stem cell properties during development and postnatally to understand how skeletal muscle is established, and how it regenerates during disease, and after injury. Areas of focus include quiescence, niche, self-renewal, symmetric and asymmetric cell divisions, ageing.
Prof. Tajbakhsh is an EMBO member, former Head of the Dept. of Developmental & Stem Cell Biology and co-Director of the "Laboratory of Excellence" Consortium, REVIVE, regrouping leading labs working on stem cells (2011-2022). He is member of 2 scientific councils for associations, several SABs and presides on editorial boards of 4 scientific journals. He has participated in a number of EU consortia (FP6, EuroStemCell; FP7, EuroSyStem, Optistem, NotchIT) and received several awards including the Chair of Excellence Louis Pasteur (Institut Pasteur, 2017) and the French Academy of Sciences/Fondation Generale de Santé, for achievements in stem cell research.

LECTURE 2 **Paolo Sassone-Corsi (University of California Irvine-USA)**

Common Threads: Metabolism, Epigenetics and the Circadian Clock

The circadian clock is responsible for biological timekeeping on a systemic level. The mammalian central pacemaker is localized in the hypothalamus, in a paired neuronal structure called the suprachiasmatic nucleus (SCN). The discovery that all tissues and virtually all cells contain an intrinsic circadian clock revolutionized the field, providing a conceptual framework towards the understanding of organismal homeostasis and physiological tissue-to-tissue communications (1). The circadian clock controls a remarkable array of physiological and metabolic functions through governing a significant portion of the genome. Furthermore, the clock drives cyclic chromatin remodeling associated to circadian transcription, including spatial nuclear organization (2). The circadian epigenome shares intimate links with cellular metabolic processes and has remarkable plasticity showing reprogramming during aging and in response to nutritional challenges (3, 4). We will present findings that reveal specific molecular connections between chromatin remodelers, metabolic pathways and the circadian clock.

1. Schibler, U. and Sassone-Corsi, P. (2002) A Web of Circadian Pacemakers. *Cell* 111, 919-922.
2. Aguilar-Arnal, L., Hakim, O., Patel, V. R., Baldi, P., Hager, G. L. and Sassone-Corsi, P. (2013) Cycles in spatial and temporal chromosomal organization driven by the circadian clock. *Nature Struct. Mol. Biol.* 20: 1206-13.
3. Asher G and Sassone-Corsi P. (2015) Time for Food: the intimate interplay between nutrition, metabolism and the circadian clock. *Cell* 161: 84-92.
4. Sato S, Solanas G, Peixoto FO, Bee L, Symeonidi A, Schmidt MS, Brenner C, Masri S, Benitah SA, Sassone-Corsi P. (2017) Circadian Reprogramming in the Liver Identifies Metabolic Pathways of Aging. *Cell* 170: 664-677



During the past three decades my research has focused on the molecular mechanisms of transcriptional regulation and chromatin remodeling, specifically in response to changes in signaling transduction and cellular metabolism. In the past twenty years we uncovered the specific role of transcriptional and epigenetic regulators in circadian clock function and deciphered how metabolic circuits intimately connect to the circadian system. Our studies have significantly impacted the fields of transcription, epigenetics, metabolism and endocrinology. Our expertise covers molecular, cellular, physiological and behavioral analysis of circadian rhythms in mammals, including genomics, metabolomics high-throughput profiling and Biocomputing. The high impact of our research is witnessed by the numerous high-profile publications, numerous invitations as plenary speaker at high-profile conferences and by an h-index of 123.

Positions: After PhD in Italy and post-doctoral studies in France and USA (1980-1988), PSC established his research group in Strasbourg, France, with the position of Directeur de Recherche (1989-2006). Moved to University of California, Irvine as Distinguished Professor and Chair of the Department of Pharmacology (2006-2011) and then as Director of the Center for Epigenetics and Metabolism (2011-present) and Donald Bren Professor (2011-present). PSC is also External Professor of the Max-Planck Institute (Germany).

Honors (partial list): EMBO Gold Medal (1994); Grand Prix Liliane Bettencourt, France (1997); Grand Prix Charles-Léopold Mayer of the Académie des Sciences, Paris (2003); Edwin B. Astwood Award, Endocrine Society, USA (2004); Ipsen Award in Endocrinology (2011); Transatlantic Medal of The Society of Endocrinology, UK (2012); Fellow of AAAS (2014). August and Marie Krogh Medal, Denmark (2015); Leonardo da Vinci Gold Medal, FMSI Federation, Italy (2016); Albert Hogan Memorial Award Lecture, University of Missouri (2017); UC Distinguished Faculty Award for Research (2018).

LECTURE 3 **Carmine Settembre (TIGEM-Italy)**

Developmental regulation of lysosome biogenesis shapes cellular identity and function

Lysosomes are catabolic organelles devoted to the degradation of intracellular proteins and organelles that are delivered to the lysosomes via autophagy. Lysosome biogenesis and autophagy are very dynamic processes, which are modulated in response to cues. My laboratory has recently identified the fibroblast growth factor (FGF) signalling as main regulator of post-natal activation of autophagy and lysosome biogenesis in chondrocytes of the cartilage during bone growth. This process is mediated by the FGFR3 and FGFR4 receptors through both transcriptional and post-translational mechanisms. The FGF-mediated induction of lysosomal catabolism is required to remodel the endoplasmic reticulum (ER) of chondrocytes through a process known as ER-phagy. Preliminary data indicate that ER-phagy promotes chondrocyte hypertrophic differentiation and collagen production. Our findings unveil an unexpected role of the lysosome/autophagy pathway in organismal development and growth.

My research has focused on the lysosome, autophagy and lysosomal storage disorders for the last 15 years. During my PhD (2004-2007) at the Telethon Institute of Genetics and Medicine I studied the role of autophagy in the pathogenesis of Lysosomal Storage Disorders (LSDs) and demonstrated that an impairment of autophagy accounts for part of the phenotypic manifestation LSDs, defining these disorders as “autophagic disorders’ (Settembre et al. 2008). Subsequently (in 2007) I moved to United States as visiting student and subsequently as post-doctoral fellow in the laboratory of Dr. Karsenty (Columbia University, NY) where I was involved in the study of the role of proteoglycans during skeletal development and growth (Settembre et al. 2008). In 2009, I moved to Houston at Baylor College of Medicine where I focused on the basic biological mechanisms regulating lysosome and autophagosome biogenesis and found that the formation of these organelles is co-regulated at the transcriptional level through the activity of a master transcription factor, TFEB (Settembre et al 2011). These studies also led me to identify a lysosome to nucleus signaling mechanism, through which the lysosome can control its biogenesis and function in response to environmental cues (Settembre et al. 2012). In 2013 I returned to Italy as assistant investigator at the Telethon Institute of Genetic and Medicine (TIGEM) and assistant professor at the Federico II University of Naples. IN 2016 I was selected as EMBO Young Investigator and my laboratory received the ERC starting grant. The main research interest of my lab is to study the role of lysosomal and autophagy pathways during bone growth and maintenance and develop novel therapeutic approaches for the treatment of skeletal abnormalities in genetic disorders (Cinque et al.2015, Bartolomeo et al. 2017, Forrester et al. submitted).

LECTURE 4 **Nenad Bursac (Duke University-USA)**

Muscle Mimicry in a Dish

Engineering of three-dimensional human skeletal muscle tissues is motivated by the need for improved physiological systems that would serve for modelling and studying of muscle diseases, pre-clinical drug development, and potential muscle regenerative therapies. In this talk, I will describe first-time engineering of contractile human engineered muscle tissues made of primary myogenic cells derived from muscle biopsies and myogenic progenitors derived from induced pluripotent stem cells by transient overexpression of satellite cell marker Pax7. Resulting bioengineered muscle microtissues ("myobundles") exhibit aligned architecture, multinucleated and striated myofibers, and a $Pax7^+$ cell pool. They contract spontaneously and respond to electrical stimuli with robust calcium transients, twitch and tetanic contractions. During culture, myobundles maintain functional acetylcholine receptors and structurally and functionally mature, as evidenced by increased myofiber diameter, improved calcium handling and contractile strength, formation of triads, localization of dystrophin in sarcolemma, and enhanced expression of various maturation genes. In response to diversely acting drugs, myobundles undergo dose-dependent hypertrophy or toxic myopathy similar to clinical outcomes. In response to exercise-mimetic electrical stimulation, myobundles undergo significant hyperplastic and hypertrophic growth, enhanced force-generating capacity, and increased metabolic flux. When derived using cells from patients with congenital skeletal muscle diseases, myobundles exhibit expected pathological phenotypes. Upon implantation into immunocompromised mice for 3 weeks, the myobundles progressively vascularize and maintain functionality. Overall, biomimetic human myobundles provide an enabling platform for predictive drug and toxicology screening and development of novel therapeutics for degenerative muscle disorders.

Dr. Nenad Bursac is a Professor of Biomedical Engineering, Cell Biology, and Medicine at Duke University and one of the pioneers and leaders of the cardiac and skeletal muscle tissue engineering fields. In 1999, as a member of Dr. Robert Langer' group at MIT, he demonstrated the first engineering of functional heart tissues using mammalian cardiomyocytes. His postdoctoral research with Dr. Leslie Tung at Johns Hopkins University resulted in new methods to control architecture and function of 2- and 3-dimensional heart cell cultures. Currently, Dr. Bursac's research involves use of cell, tissue, and genetic engineering techniques and electrophysiological and biomechanical studies to advance fields of somatic and stem cell based therapies for heart and skeletal muscle disease.

For the last 20 years, Dr. Bursac's work has pushed the boundaries of the field by demonstrating a number of "firsts", including: the first use of bioreactors for functional cardiac tissue engineering; the first studies of electrophysiology and arrhythmias in engineered heart tissues; the first engineering of anisotropic cardiac tissue patch and methods to control patch anisotropy; the most functionally advanced mouse cardiac tissue patch; the first engineering of highly functional, large (40mmx40mm) heart tissues from human pluripotent stem cells; first engineering of functional human skeletal muscle tissues from primary and pluripotent stem cells; and first engineering of biosynthetic excitable cells and tissues for studies and treatment of cardiac arrhythmias and heart failure.

Dr. Bursac has authored more than 100 scientific manuscripts, presented over 120 invited talks, and has mentored more than 30 PhD students and postdoctoral and medical fellows. He co-directs Regeneration Next Initiative at Duke University. He is a recipient of the Stansell Family Distinguished Research Award, Mendel Center Award, and Stem Cell Innovation Award. In 2014, Dr. Bursac was the president of the North Carolina Tissue Engineering and Regenerative Medicine Society. Since 2015, Dr. Bursac has been a Fellow of American Institute for Medical and Biological Engineering and since 2018 a Fellow of Biomedical Engineering Society. Dr. Bursac has served on various NIH grant review panels and is a member of editorial boards of *Nature Scientific Reports* and *NPJ Regenerative Medicine.*

PROGRAM SCHEDULE

Thursday, October 11th

11:30-14:30 Registration

14:45 Welcome and opening of the meeting

15:00-15:20 Special Talk
Giorgio Fanò (Libera Università di Alcatraz-Italy)
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15:20-16:50 Session 1: Signaling in muscle growth, homeostasis and diseases. Chair: Emilie Venereau

15:20-15:35 **Role of muscle interstitial cells in neurogenic muscular atrophy**
Luca Madaro

15:35-15:50 **Are Toll like receptor and type I interferon key factors in autoimmune inflammatory myopathies: studies in an experimental murine model**
Clara Sciorati

15:50-16:05 **Myo-REG: a new web portal for exploring cell and signaling interactions in muscle regeneration**
Alessandro Palma

16:05-16:20 **Dissecting the role of AMBRA1 in skeletal muscle**
Lisa Gambarotto

16:20-16-35 **Characterization of a novel embryonal rhabdomyosarcoma murine model**
Enrico Pozzo

16:35-16:50 **Musclin: a myokine induced by aerobic exercise useful to contrast muscle wasting during cancer**
Andrea David Re Cecconi

16:50-17:10 Coffee break

17:10-17:30 Welcome from Authorities

17:30-18:10 Lecture 1
Shahragim Tajbakhsh (Institut Pasteur-France)
Embryonic and adult skeletal muscle stem/progenitor cells. Chair: Antonio Musarò

18:10-19:30 Session 2: Satellite cells and muscle regeneration in healthy muscle and in diseases. Chair: Martina Baraldo; Alessandra Renzini

18:10-18:25 **Pax3 modulates AhR-mediated resistance to Dioxin in muscle stem cells**
Frédéric Relaix

18:25-18:40 **Cripto modulates angiogenesis and EndMT by controlling the shaping of pro-healing macrophages in skeletal muscle regeneration**
Francescopaolo Iavarone

18:40-18:55 **High mobility group box 1 orchestrates regeneration in skeletal muscle**
Emilie Venereau

18:55-19:10 **Nfix drives the phenotypical switch of macrophages for successful muscle regeneration**
Marielle Saclier

19:10-19:25 **Decrypting the cell language: the secretome network during muscle regeneration**
Simone Vumbaca

20:00-21:30 *Aperitivo Umbro* and YOUNG SCIENTISTS ROUNDTABLES

Friday, October 12th

9:00-9:40 Lecture 2
Paolo Sassone-Corsi (University of California Irvine-USA)
Molecular control of circadian rhythms. Chair: Davide Gabellini

9:40-10:40 Session 3: Synaptic transmission and E-C coupling in healthy and diseased muscle. Chair: Valeria Bianconi

9:40-9:55 **Canonical Wnt and Hippo regulators ensure proper synaptic gene transcription and aggregation of acetylcholine receptors at the neuromuscular junction**
Jasna Friscic

9:55-10:10 **Binding of JPH1, a protein of the triadic membrane contact site of skeletal muscle cells, to CLIMP63, a microtubule-binding protein**
Caterina Amato

10:10-10:25 **Polyglutamine-expanded androgen receptor causes primary toxicity to skeletal muscle in vivo**
Caterina Marchioretti

10:25-10:40 **CaVβ1: The missing link from voltage sensing to muscle mass homeostasis**
Traoré Massiré

10:40-11:10 Coffee break

11:10-12:40 Session 4: Genetic and epigenetic alterations in muscle dystrophies and myopathies. Chair: Ester Di Filippo

11:10-11:25 **HDAC4 regulates skeletal muscle regeneration via soluble factors**
Alessandra Renzini

11:25-11:40 **Myoexosomes cargo triggers muscle regeneration and provides molecular cues for next-generation therapy in muscular dystrophy**
Andrea Brambilla

11:40-11:55 **H3K9 methylation controls Fibro-Adipogenic Progenitors identity and skeletal muscle repair**
Chiara Mozzetta

11:55-12:10 **Therapeutic activity of modified U1 core spliceosomal particles in Spinal Muscular Atrophy**
Franco Pagani

12:10-12:25 **Genetic deletion and pharmacologic targeting of GLUD1 breaks glutamine competition between macrophage and satellite cells improving muscle regeneration**
Emanuele Berardi

12:25-12:40 **The voice of patients and their families**: **Parent Project Onlus**

Gloria Antonini

13:00 lunch

14:30-16:00 POSTER DISCUSSION (odd numbers)

16:00-16:30 Coffee break

16:40 Bus departure: Guided Tour of Spello and Ancient Roman Dinner

Saturday, October 13th

09:00-09:40 IIM young committee invited lecture 3
Carmine Settembre (TIGEM-Italy)
Lysosomal and autophagy pathways. Chair: Andrea Armani

09:40-11:10 Session 5: Metabolic alterations and muscle diseases. Chair: Anaïs Franco, Giorgia Careccia

9:40-9-55 **Mitochondrial adaptation in parvalbumin knockout muscle fibres**
Gaia Butera

9:55-10:10 **Loss of Mitochondrial Calcium Uniporter rewires skeletal muscle metabolism and substrate preference**
Gaia Gherardi

10:10-10:25 **Diet-based metabolic reprograming impacts on the differentiation potential of muscle progenitor cells and ameliorates the *mdx* dystrophic phenotype**
Alessio Reggio

10:25-10:40 **Metabolic changes associated with muscle expression of SOD1G93A**
Elisa Lepore

10:40-10:55 **Muscle-specific Plin2 downregulation affects ectopic lipid metabolism and myofiber size**
Maria Conte

10:55-11:10 **Defective glycosylation of IGF-1Ea prohormone and IGF-1 secretion in fibroblasts from congenital disorders of glycosylation**
Giosuè Annibalini

11:10-11:40 Coffee break

11:40-13:00 Session 6: Muscle fibrosis, sarcopenia and cachexia. Chair: Gaia Gherardi

11:40-11:55 **Nature and role of interstitial non myogenic cells in human fibrotic muscles**
Elisa Negroni

11:55-12:10 **The effect of muscle activity on tumor cell growth and survival**

Hassani Medhi

12:10-12:25 **Altered iron metabolism promotes cancer cachexia**
Myriam Hsu

12:25-12:40 **Targeting mitochondria with SS-31 in experimental cancer and chemotherapy-induced cachexia**
Riccardo Ballarò

12:40-12:55 **Role of ghrelin peptides in aging**
Simone Reano

13:30 lunch

15:00-16:30 POSTER DISCUSSION (even numbers)

16:30-17:10 Lecture 4
Nenad Bursac (Duke University-USA)
Pluripotent stem cell therapies for heart and muscle disease. Chair: Cesare Gargioli

17:10 - 17:40 Coffee break

17:40-19:00 Session 7: Therapeutic approaches for muscle diseases. Chair: Claudia Fuoco, Sara Chiappalupi

17:40-17:55 **Engineering skeletal muscle tissue with innovative 3D bioprinting approaches**
Marco Costantini

17:55-18:10 **A human neuromuscular junction model system: an organ-on-a-chip approach.**
Ersilia Fornetti

18:10-18:25 **New biomimetic scaffolds for the expansion of functional adult satellite cells and the generation of mature myofibers *ex vivo***
Francesca Gattazzo

18:25-18:40 **Fibrosis rescue improves cardiac function in dystrophin-deficient mice and Duchenne patient-specific cardiomyocytes by immunoproteasome modulation**
Pamela Bella

19:15-20:00 IIM General meeting

20:30 Social Dinner - Awards and prizes

22:00 Dance and Karaoke Party

Sunday, October 14th

Departure

POSTERS

ALWAYS ON DISPLAY
DISCUSSION:
ODD numbers: Friday, October 12th (14:30-16:00)
EVEN numbers: Saturday, October 13th (15:00-16:30)

P.01 The role of vitamin D binding protein (VDBP) in cancer cachexia
M. Alves Teixeira

P.02 Silencing Nfix rescues Muscular Dystrophy by delaying muscle regeneration
Giuseppe Angelini

P.03 Identification of a novel TFEB-exercise dependent gene
Andrea Armani

P.04 Over-expression of mIGF-1 in skeletal muscle attenuates the effects of sarcopenic obesity
Francesca Ascenzi

P.05 The role of raptor in adult skeletal muscle
Martina Baraldo

P.06 Identification of novel molecular targets to manipulate satellite cell function
Anna Benedetti

P.07 Histone 3 Lysine 9 methyltransferases G9a and GLP as potential pharmacological targets in skeletal muscle regeneration and Duchenne Muscular Dystrophy
Valeria Bianconi

P.08 Tyrosol delays dexamethasone-induced skeletal muscle wasting
Debora Burini

P.09 HMGB1 as a novel target in Duchenne Muscular Dystrophy
Giorgia Careccia

P.10 Group I Paks support muscle regeneration and counteract cancer-associated muscle atrophy
Michela Chiappa

P.11 Involvement of a RAGE/p38 MAPK/myogenin axis in cancer cachexia
Aleksandra Vukasinovic

P. 12 Characterization of biomechanical signals on the functional remodeling of X-MET
Marianna Cosentino

P.13 CD26/DPP4 Expression in Muscle Biopsies of Patients Affected by Idiopathic Inflammatory Myopathies

Rebecca De Lorenzo

P.14 Opposing effects of 25-hydroxy- and 1α,25-dihydroxy-vitamin D_3 on pro-cachectic cytokine- and cancer conditioned medium-induced atrophy in C2C12 myotubes
Marilisa De Feudis

P.15 The effects of microgravity on human skeletal muscle regeneration
Ester Sara Di Filippo

P.16 2-Deoxyglucose interferes with IGF-1Ea prohormone glycosylation and IGF-1 secretion
Laura Di Patria

P.17 The HDAC inhibitor givinostat dampens the atrophy program induced by TNF-related cytokines in human skeletal myotubes *in vitro*
Monica Forino

P.18 Identification of a novel FoxO-dependent regulator of muscle mass
Anaïs Franco-Romero

P.19 The mass cytometry application to unravel the skeletal muscle physiological and pathological state
Claudia Fuoco

P.20 mTOR is required for maintaining myofiber integrity and muscle force
Alessia Geremia

P.21 FAP heterogeneity: important functional feature or experimental noise?
Giulio Giuliani

P.22 Pericyte derived-IGF-1 is required during muscle recovery after acute injury.
Peggy Lafuste

P.23 Ly6c-hi inflammatory monocytes accumulate in mdx mouse spleen and contribute to dystrophic muscle pathology
Biliana Lozanoska-Ochser

P.24 Immune cells of *mdx* mice fed with a high fat diet secrete high levels of IGF-1 that promote satellite cells differentiation
Giorgia Massacci

P.25 Approaches to delay the progression of Muscular Dystrophy
Graziella Messina

P.26 The interference with IL-6 trans-signaling modulates secondary mechanisms of dystrophic muscle
Carmen Miano

P.27 Intracellular calcium dyshomeostasis in GAP-43-knockout cardiomyocytes
Sara Nobilio

P.28 A molecular toolbox to modulate muscle progenitor cell differentiation
Marco Rosina

P.29 Could PIN1 be a target to delay the ageing process in skeletal muscle?
Camilla Pezzini

P.30 Sphingosine kinase 1 and 2: their role in skeletal muscle cell phenotype
Federica Pierucci

P.31 Steroid myopathy: understanding the pathogenesis
Deborah Recchia

P.32 Ghrelin peptides and stem cells to counteract sarcopenia
Flavio Lorenzo Ronzoni

P.33 Novel data support the use of microencapsulated Sertoli cells as a potential treatment of DMD patients
Laura Salvadori

P.34 New evidences about the involvement of muscle stem cells in the pathogenesis of Amyotrophic Lateral Sclerosis
Illari Salvatori

P.35 "Noisy" field electrical stimulations promote muscle cell differentiation
Marina Sciancalepore

P.36 Evo-Devo approach to study Pax3/7 functions
Valentina Taglietti

P.37 Drug repurposing for Duchenne muscular dystrophy: the monoamine oxidase B inhibitor Safinamide ameliorates the pathological phenotype in mdx mice and in myogenic cultures from DMD Patients
Marcella Canton

SELECTED TALK ABSTRACTS

October 13th
SESSION 6
MUSCLE FIBROSIS, SARCOPENIA AND CACHEXIA

6.1 Nature and role of interstitial non myogenic cells in human fibrotic muscles

Elisa Negroni[a], Mona Bensalah[a], Laura Muraine[a], Fanny Roth[a], Victorine Albert[a], Alison Oliver[a], Teresa Gidaro[a], Sophie Perié[a,b], Jean Lacau St-Guily[a,b], Gillian Butler-Browne[a], Anne Bigot[a], Vincent Mouly[a] and Capucine Trollet[a]

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Fibrosis is one of the common pathological outcomes of many chronic diseases, and the main complication in many muscular dystrophies (MD). MD represent an heterogeneous group of disorders characterized by weakness and/or progressive degeneration process of skeletal muscle with a wide clinical presentation and severity. Among MD, Duchenne muscular dystrophy (DMD) is a fatal genetic disorder with an early onset, caused by mutations in the dystrophin gene. Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant inherited, slow progressing, late onset degenerative muscle disorder caused by a short triplet expansion in the PABPN1 gene. MD, whether they involve repeated cycles of degeneration and regeneration such as in DMD or not such as OPMD, result inexorably in skeletal muscle atrophy inevitably associated with fibrosis. Fibrosis represents the final consequence of the muscle degeneration process, as a result of reactive and/or reparative processes. These processes involve mechanical, humoral and cellular factors. Fibrotic muscular substitution is attributed to excess deposition of extracellular matrix components (ECM).
Fibroblasts are known to be involved in several biological processes such as wound healing, inflammation, and angiogenesis. However, their causal implication in dystrophic muscle progression and fibrosis remain still poorly characterized. Here, we characterized interstitial non myogenic cells (CD56-) isolated from control and affected fibrotic muscles of OPMD and DMD patients. Proliferation capacity, adipogenic/osteogenic differentiation, lifespan studies, co-culture experiments, FACS analysis and high-dimensional single-cell analysis have been performed. Xenotransplantation experiments to decipher the influence of CD56- cells during muscle regeneration in vivo were also performed. We demonstrate that human CD56- cells from fibrotic muscles are different compared with those from control muscles, showing a strikingly high proliferative capacity, an effect on fusion index in vitro and an exacerbated secretion in vivo.

6.2 The effect of muscle activity on tumor cell growth and survival

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Exercise is now recommended in multimodal therapies for cancer patients. The beneficial effects of exercise span from the rescue of muscle homeostasis to the control of inflammation, ultimately resulting in increased survival of tumor bearing animals and patients. A modern vision of the skeletal muscle includes the idea that this highly vascularized organ posses an important paracrine and endocrine activity, which is exercise-dependent. Secreted muscle factors (myokines) affect multiple target tissues. Only recently, a pioneer study showed that the tumor itself can be targeted by myokine-directed NK cells and its growth blunted following muscle stimulation by exercise. Whilst suggested by other studies, it is not clear if muscle cells per se possess a antitumoral activity, nor its dependence by mechanical stimulation. This project aims to demonstrate in vitro that (a) muscle cells secrete factors with anti-tumor activity (by either stopping cell proliferation of inducing cell death) and (b) mechanical stimulation of muscle cells affects their secretome, possibly enriching it in antitumoral factors; in addition, an initial characterization of the products released by muscle cells is proposed, with the aim to start identifying the biochemical nature of these antitumoral factors.

6.3 Altered iron metabolism promotes cancer cachexia

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Cachexia is a multi-organ wasting syndrome characterized by irreversible skeletal muscle atrophy that dramatically increases both the morbidity and mortality in various diseases. Despite its high prevalence in cancer patients, knowledge regarding the mechanism of cancer-induced cachexia remains very scarce.
In this study, we first show that iron deprivation by several means (knockdown of transferrin receptor-TfR, responsible for the cellular uptake of iron, and selective iron chelators) induces myotube atrophy *in vitro*. Moreover, cachectic mice bearing C26-colon cancer feature striking alterations in key regulators of iron metabolism, notably an overexpression of ferroportin (iron exporter), a downregulation of TfR and an altered ferritin (main storage site of iron) recycling. Consistently, we found a decreased iron loading in skeletal muscle and in spleen along with a strong increase in serum levels, indicating that iron homeostasis is altered at a systemic level in cachectic mice. Intriguingly, normalizing iron levels *in vitro* counteracted cancer-induced