DIPARTIMENTO DI FARMACIA E BIOTECNOLOGIE

AVVISO DI SEMINARIO

All'interno degli eventi organizzati dalla CMB PhD school

Il giorno mercoledì **1 Marzo 2023**, alle ore **15:00**

presso:
Aula 1 Bodoniana - Via San Donato 19/2

oppure in streaming:
https://teams.microsoft.com/l/meetup-join/19%3aN09c0NIyEssBnF7ObCyDOQwkgDWm1qdd9f7F2nJV9fw1%40thread.tacv2/1631519544944?context=%7b%22Tid%22%3a%22e99647dc-1b08-454a-bf8c-699181b389ab%22%2c%22Oid%22%3a%225a941351-ef41-4aa4-8771-fa50a6d62ca1%22%7d

Francesco Chemello, PhD

(ospite Prof. Giovanni Perini)

terrà un seminario dal titolo:

PRECISE GENE EDITING IN CARDIAC AND SKELETAL MUSCLE DISEASES

Colleghi e studenti sono cordialmente invitati

Commissione Ricerca e Attività Correlate – FaBiT

ABSTRACT

CRISPR-Cas9 gene editing is emerging as a prospective therapy to treat genetic disorders of heart and skeletal muscle. Our myoediting approach consists in the: i) identification of a genetic mutation or an interesting target involved in cardiac or skeletal muscle diseases; ii) utilization of genome editing technologies to correct the mutation in human induced pluripotent stem cells (hiPSCs) from patients and the validation of functional recovery in hiPSCs-derived muscle cells; iii) delivery in mouse models of the myoediting components to prove their efficacy in vivo. Among the various CRISPR-Cas9 gene editing technologies, adenine base editor (ABE) offers the advantage of the permanent precise conversion of adenine to guanine nucleotides without introducing double-stranded DNA breaks. We showed the application of ABE in various muscle diseases, editing a point mutation causing hypertrophic cardiomyopathy, inducing exon skipping in mutations causing Duchenne muscular dystrophy, and disrupting a pathological signaling pathway involved in cardiac disease. Although more studies regarding the safety of the treatments are needed, our findings demonstrate the effectiveness of base editing for the correction of diverse muscle disorders and pave the way for the development of new ABE-based strategies to treat patients with muscle diseases.

BIOGRAPHICAL SKETCH

Francesco Chemello's major research interest is about the **biology of cardiac and skeletal muscles**.

During his PhD training in the laboratory of Professor Gerolamo Lanfranchi (University of Padova, Padova, Italy) he developed and applied **microgenomic protocols** to analyze at the single cell level the **miRNA-mRNA regulatory networks specific for the different myofiber types**. He validated the effects of selected miRNAs differentially expressed between oxidative and glycolytic myofibers on mitochondrial functionality and cellular metabolism. Later, he focused his research on post-transcriptional regulation of biological pathways of muscle in **disease models**, such as **SMA** (spinal muscular atrophy), **ALS** (amyotrophic lateral sclerosis), and **DMD** (Duchenne muscular dystrophy).

In particular, regarding studies about DMD, during his postdoc training in the laboratory of Professor Eric Olson (UT Southwestern, Dallas, USA) he generated **new mouse models of DMD** lacking specific exons (recapitulating the most frequent mutations in DMD patients) or "humanizing" exons of the Dmd mouse gene (as tools for preclinical gene editing approaches). Analysis of the skeletal muscle of one of these mouse models by **single nucleus RNA sequencing** identified a specific transcriptional regulatory pathway altered in the different types of nuclei (i.e., myonuclei and nuclei of the mononucleated cells) of the dystrophic muscle. Interestingly, he identified a previously unknown population of **regenerative myonuclei** that is exclusively present in the dystrophic muscles. In order to correct the DMD phenotype in mouse and human induced pluripotent stem cells (hiPSCs), he explored different **genome editing** technologies. He demonstrated the restoration of dystrophin expression in different DMD models by "single-cut" approach, and by the precise nucleotide genome editing technologies of **base editing** and **prime editing**.

Recently he used **base editing in heart diseases**. He demonstrated that this genome editing technology can be used not only to correct **point mutations**, but also to **ablate a detrimental signaling pathway** in the adult heart and thereby provide therapeutic benefits for already-established heart disease.

In the future, he will continue to develop **new base editing- and prime editing-based strategies** to treat cardiac and skeletal muscle disorders. He will also explore the utilization of modified RNAs (**modRNAs**) and lipid nanoparticles (**LNPs**) for the delivery of the gene editing components to the target tissues. He will use **mouse models** and hiPSC-derived **cardiac organoids** as preclinical in vivo and in vitro tools to test the **efficacy and safety** of the most recent gene editing technologies with the ultimate goal of proposing **new treatments for patients with muscle diseases**.