IBEC-VHIR INTERNATIONAL PhD PROGRAMME

Position

1. Project Title/ Job Position title:
   Development of 3D skeletal muscle models mimicking muscular glycogenesis disorders as alternative to animal experimentation

2. Research project / Research Group description

In vivo mouse models are valuable tools to physiopathologically characterize human diseases and evaluate potential therapeutic strategies, however the technical challenges and the ethical concerns limit their extended issues. *In vitro* models are usually selected as alternative to *in vivo* models, but their inability to recapitulate the structural and biochemical complexity of organic tissues due to their two-dimensional character limit the reliability of the obtained results. As solution to this problem, this project will explore the use of different biofabrication techniques, including 3D bioprinting, to recreate 3D skeletal muscular disorders.

This project will specifically focus in the recreation of Glycogen Storage Disorders (GSD), a family of rare diseases with an approximate incidence of 1:100.000 individuals, and the evaluation of potential therapeutic strategies including small molecules and gene therapy. In order to achieve this aim we will develop 3D muscular tissues derived from the Pompe (GSD type II) and McArdle disease (GSD type V) mouse models to perform the following objectives:

a) Characterization of the biochemical, proteomic and metabolic profile of these 3D *in vitro* models compared to the samples obtained from in vivo models.

b) Analysis of the subcellular and sarcomere architecture analysis using Airyscan super-resolution microscopy

c) Evaluation of the efficacy of different potential therapeutic strategies for GSD, including small molecules, such as inhibitors of muscle glycogen synthesis such as MZ-101, and personalized gene therapy strategies for Pompe and McArdle disease

3. Job position description

The PhD student will be involved in the development of 3D skeletal muscle tissues derived from the McArdle and Pompe disease mouse models (in IBEC), as well as in their biochemical, metabolic and proteomic characterization (in IBEC and VHIR) using qPCR gene expression and western blot analyses of the main proteins involved in glycogen metabolism, glycolysis, fatty acid oxidation, Krebs cycle and mitochondrial Oxphos, along with the enzymatic determination of different Oxphos complex activities. Additionally, the PhD student will participate in the ultrastructural subcellular and sarcomere architecture analysis of the 3D muscle models using Airyscan super-resolution microscopy (in VHIR). After the muscle model validation, the PhD student will take part in the preclinical evaluation of potential therapeutic strategies, including inhibitors of muscle glycogen synthesis and gene therapy strategies specific for McArdle and Pompe diseases.

Group Leader at IBEC

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Group Leader at VHIR

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