SEMS: RESEARCH PROJECT DESCRIPTION

1. Project Background and Description

Novel Muscle-on-a-Chip models for the preclinical investigation of therapeutics

Organ-chips are 3-D in-vitro models, designed to recapitulate key architectural, functional and cellular components of a tissue. They are poised to transform biomedical research and therapeutic delivery, by providing much needed model systems in which to successfully explore human health and disease and investigate new drugs and therapeutics, offering improved recapitulation of human physiology and disease, relative to current 2D in-vitro or non-human in-vivo models.

An area of organ-chip models which has received minimal attention to date is muscle models. Skeletal muscle is fundamental to motion and activity in daily life. Wasting can be attributed to ageing, trauma, injury, autoimmune disease or genetic muscular dystrophies and causes progressive weakness, leading to significantly impaired strength and mobility. Smooth muscle lines much of the digestive and cardiovascular systems, enabling them to contract and apply crucial functional pressures. Vascular disorders are generally characterised by increased contractile or hypertrophic response of smooth muscle cells, and constitute one of the most extensive and costly groups of health conditions in the Western world.

Organ-chip muscle models that emulate the structural organization, functional capabilities, and regenerative potential of native muscle could provide powerful new tools for probing disease states.

The current project is in collaboration with our industrial partner Emulate, utilizing their "Human Emulation System", platform technology as a framework in which to build and validate muscle-chips to recapitulate skeletal and smooth muscle.

We will first design and develop appropriate hydrogels to recapitulate muscle, investigating capacity to integrate appropriate cells. We will then validate models using a detailed multi-omic phenotyping approach, before mechanistic validation to explore if the model responds to known drugs like muscle tissue.

The project will join a team developing musculoskeletal models, providing avenues to use muscle-chips within complete joint models, to explore novel regenerative medicine drugs and products.

2. Project Scope

Objective 1: Model Development

We will adopt 3D printing to develop appropriate cell-laden gelatin hydrogels and align fibres with external forces. We will integrate myoblasts, which we will differentiate into myotubes using classic myoblast differentiation media containing horse serum. For our smooth muscle model, we will additionally develop an adjacent endothelial cell layer, to recapitulate the architecture of arterial walls.

Objective 2: Model Phenotypic Validation

We will confirm cell viability within the models using live cell imaging approaches, specifically exploring the impact of different stress environments on cell viability and organisation.

We will continue to carry out phenotypic validation of the cell population, and to explore the cell metabolism, integrating transcriptomics, proteomics, microscopy. Transcriptomics will utilise key genes such as MYOD, MYF5 and MRF4 or MYOCD, ACTA2, MYH11 and aSMA.

Global label-free proteomics will then be completed using an Orbitrap QExactive HF mass spectrometer. Transcriptome and proteome data will be analysed using network interaction maps, comparing against native tissue by ranking prevalence and regression mapping.

Objective 3: Model Mechanistic Validation

Here we will utilised stress-responsive genes (Hsp68, Hsp90, XIN, MARP2) to recapitulate the known molecular pathways in muscle pathology and initiate the inflammatory response seen in early injury, checking for resulting pathology markers (MEF-2) and validating the model in injury. Drugs known to target the MEF-2 pathway (Atorvastatin) will be investigated.

3. Desired Skills from the Student

An interest and some background in the following areas would be of benefit:

cell culture

PCR or proteomics

histology

Knowledge of musculoskeletal tissue extracellular matrix

4. Supervisory Team

Primary: Professor Hazel Screen

Secondary: Professor Martin Knight

Additional: Dr Simon Grossemy