SEMS: RESEARCH PROJECT DESCRIPTION

1. Project Background and Description

Organ-on-a-chip technology to test effects of primary cilia manipulation on arthritis

Osteoarthritis (OA) is typically characterised by loss of articular cartilage, but is very much a disease of the entire synovial joint. The cross talk between the different tissues within the joint, as well as the mechanical environment to which the joint is exposed is therefore critical to the development of this debilitating disease. This PhD studentship project will examine, the effect of synoviocytes on cartilage pro-inflammatory signalling and degradation and how this is influenced by physiological mechanical loading.

Furthermore, we aim to identify the role of synoviocyte primary cilia. In chondrocytes we have shown that this poorly understood organelle and the associated process of intraflagellar transport are involved in pro-inflammatory NF-κB signalling. However, the function of synoviocyte cilia and their role in cell-cell communication has never been examined. We will test their involvement using isolated cells treated with siRNA and a combination of biochemical assays, western blot, qRT-PCR and confocal/super resolution microscopy. We will investigate the potential of FDA-approved small molecules that regulate primary cilia expression in order to discover potential new therapeutics which can be used to regulate pro-inflammatory signalling and cross-talk as a means of controlling arthritis.

Currently there is a lack of suitable, commercially scalable, synovial joint *in vitro* model systems for studying arthritis and testing new therapeutics. Therefore, to facilitate our ambitious research programme we will work with one of the leading organ-on-a-chip companies, Emulate Inc., to develop a novel model incorporating 1) the essential interaction between different cell types; 2) the physiological biomechanical forces; 3) the response of human as opposed to animal cells; and 4) the presence of pro-inflammatory cytokines.

This multidisciplinary project aims to deliver novel therapeutic strategies for treating arthritis based on fundamental new understanding of disease aetiology and the importance of cell-cell communication and primary cilia.

2. Project Scope

This studentship will test the following fundamental and translational hypotheses:

- Synoviocytes regulate chondrocyte response to pro-inflammatory cytokines in a mechanically sensitive manner dependent on primary cilia.

- Small molecule regulation of primary cilia expression disrupts pro-inflammatory signalling and synoviocyte-chondrocyte cross talk, providing potential new treatments for inflammatory joint disease.

The overall purpose is therefore to provide academia and the pharmaceutical industry with validated, commercially scalable organ-on-a-chip models for arthritis research and drug discovery. We will use these models to examine fundamental synoviocyte-chondrocyte interactions and to test the efficacy of potential new ciliotherapies for inflammatory joint disease.

3. Desired Skills from the Student

Experience of practical cell culture

Experience of conducting a research project, writing reports and performing experiments

Enthusiasm to learn new multidisciplinary skills within a bioengineering environment

4. Supervisory Team

Primary: Prof Martin Knight

Secondary: Prof Hazel Screen

Additional: QM-Emulate Organs-on-chips Centre