SEMS: RESEARCH PROJECT DESCRIPTION

1. Project Background and Description

Identifying and treating the causes of age-related tendon dysfunction

Tendinopathy is the most common musculoskeletal complaint, with extensive and growing socioeconomic societal burden.

Tendinopathy results from mechanical overload concurrent with cell driven inflammation/degradation. We have extensive data showing that a specific region of tendon - the interfascicular matrix (IFM) niche - drives tendinopathy progression, and can be targeted in management. We have shown how the mechanical environment and cell population of the IFM changes with ageing, and hypothesise this drives inflammation and degradation in the IFM in age tendon subject to loading.

In this project, we hypothesize that tendinopathy can be effectively treated by recovering IFM cellular changes, with drug approaches which target the cell signalling cascade leading to disease.

We will explore this hypothesis using a novel tendon-chip - an in vitro model in which to explore the interplay of cells in the IFM and surrounding tendon.

We will establish tendon-chips with cell populations from aged tendons and explore how aged chip models differs in mechanoresponse. We will investigate mechanoresponse of isolated tenocytes or IFM cells, looking at gene expression, soluble inflammatory mediators and signalling pathways, before establishing co-culture to explore how paracrine signalling between cell populations mediates mechanoresponse, isolating the influence of crosstalk in co-culture and mechanoresponse.

We will adopt conditioned media experiments, to see if crosstalk interactions are one-way or two-way and if synergistic loading is necessary, and augment exploration with use of cytokine stimulation and pharmacological inhibitors to probe pathways, and identify key pathways to target therapeutically.

2. Project Scope

Three research project objectives

1. Establish the tendon-on-a-chip model with young and aged tenocytes, and explore how the mechanoresponse of different tendon cell populations differs with ageing
2. Explore the impact of co-culture and paracrine signalling on cell mechanobiology in young and aged cell populations
3. Identify and test target molecules to treat the signalling pathways driving inflammatory / degradatory mechanoresponse in aged tendons

3. Desired Skills from the Student

Key skills needed for the PhD project

The project involves extensive cell culture

Some understanding of biochemistry / molecular biology techniques would be of benefit

4. Supervisory Team

Primary: Professor Hazel Screen

Secondary: Professor Steve Greenwald (Blizard Institute)

Additional: Professor Martin Knight