**BBSRC MIBTP Studentship Project**

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| **Project Title** | Understanding mechanical induced signalling in the healthy tendon |
| **Project Summary**  |
| Tendon problems are a common medical complaint, our current understanding highlights that mechanical stimulus (running and walking) triggers adaptations at the cellular level1. We know very little about these adaptations and the signalling processes behind them which lead to the adaptive response. This cross-disciplinary project focuses on healthy tendon cells (tenocytes) to model the human tendon to allow for the investigation of how they respond to mechanical stimulation. The tissue environment is much more than just the cellular component however, and we need to consider the how cells interact with their surrounding matrix2. This project will work from the ground up to develop tissue engineering-based models which incorporate both the cellular and matrix components of the human tendon. This will then be utilised to investigate the biological effect of mechanical triggers in the healthy tendon, in a representative model from which findings can be translated to the human tendon. We also understand that various readily used pharmaceuticals induce unwanted tendon symptoms. Many of these medications are used in patients with cardiovascular disease and diabetes, whom are often prescribed lifestyle interventions that involve physical activity. This results in tendon pain and reductions in quality of life preventing these individuals from completing an important intervention and all the benefits this would bring. As such the second phase of this project will seek to understand the relationship between mechanical load and pharmaceutical agents in the context of the healthy tendon, to uncover the biological manifestation of this undesirable interaction. This studentship is crucial to understanding how tendon problems might occur and will offer valuable insight into healthy tendon cells and the way in which they interact with their environment, which will be directly transferable into further work with diseased tendon cells with the end goal of improving clinical care. We anticipate the tissue-engineering based model developed as a part of this project will provide a sound basis for ongoing biological investigations. If this excites you, please reach out to the supervisory team to discuss this project further prior to submitting your application. Aims and objectives: * To characterise in-vitro human tenocytes and the effect of matrix manipulation on cellular phenotype
* Establish the effect of mechanical loading and/or inflammatory stimuli on tenocyte phenotype
* Investigate the interplay between cellular stress and pharmaceutical agents (eg. Statins, NSAIDs & Antibiotics) in the context of the healthy tendon

This project will be broken down into 3 distinct lab-based work packages with the findings of one informing the next, without the findings of one dictating the success or delivery of another. These are detailed below and aligned to the aims: 1. To develop mono-layer based methodologies to study the tenocyte: matrix interaction in a controlled in-vitro environment using human tenocytes. 2. To expand mono-layer based methodologies into bespoke tissue-engineered human tendons through a combination of cellular and matrix biology, and develop methodologies to investigate mechanical loading. 3.To investigate the effect of mechanical load and pharmaceutical intervention (and the combination of the two) on tendon phenotype and matrix organisation. To achieve the above work packages a variety of cross-disciplinary research methods will be utilised and implemented within the context of cell-culture methodologies. Expertise will be brought together around this topic area including those in the molecular and cell signalling response to interventions, biochemical analysis, materials science, genomic manipulation, tissue-engineering, clinical tendinopathy, and human physiology.Techniques that will be undertaken during the project:* 2D & 3D cell culture
* Molecular Biology Techniques (eg. RT-PCR, Western Blotting)
* Immunocytochemistry
* Microscopy (eg. Light, confocal and electron)
* Scaffold production – lyophilisation and collagen processing

BBSRC Strategic Research Priority: Integrated Understanding of Health – Ageing, Diet and Health, Pharmaceuticals, Regenerative Biology |
| **References** |
| Magnusson, S.P., Langberg, H. & Kjaer, M.(2010). <https://doi.org/10.1038/nrrheum.2010.43>  Millar, N.L., et al. (2021). <https://doi.org/10.1038/s41572-020-00234-1>   |