SEMS: RESEARCH PROJECT DESCRIPTION

1. Project Background and Description

Understanding the mechanisms of dysfunctional wound repair by multimodal biophysical imaging

Dysfunctional wound healing – e.g. in hypertrophic skin scarring, burns or following surgery – is a very significant biomedical problem (clinical treatment following such injuries costs >$ 4 billion p.a. in the US alone). However, the biophysical origins of hypertrophic and pathological scarring are unclear. The extracellular matrix (ECM) of tissues like skin is a biological composite consisting of fibrils (collagen, elastin), matrix (e.g. proteoglycans) and water at the nanoscale. These components exist in dynamic mechanical equilibrium with each other in healthy tissue. Increasing evidence suggests that **this biomechanical equilibrium is disrupted** in dysfunctional wound healing. Understanding the biophysical origins of how scarring develops will enable development of effective therapeutics against this (presently incurable) condition. An extreme case of pathological scarring is **keloid formation**, resulting in large raised scars on the skin.

Our aim is to explore the biophysics of scarring using keloids as a model system. Using state-of-the-art high-brilliance synchrotron X-ray imaging combined with nanomechanical testing, we will directly measure the nanoscale response of the keloid ECM to biophysical load. Small-angle X-ray scattering (SAXS) on collagenous tissues (like keloids) provides a direct map of the fibril-level strain, orientation and intrafibrillar order. We will use SAXS with a small (micron-sized) X-ray beam to map out the fibrillar-level mechanics inside keloid scars *in situ* when they are subjected to physiological and injurious loads. The fibrillar-level response will be correlated with measurements of matrix protein composition using Raman microscopy and mass spectroscopy and measured at increasing levels of applied load. By linking how these ultrastructural biophysical mechanisms vary within the scar and how the variation is linked to differential-levels of growth factor and ECM protein expression, we will make a pioneering advance in developing an integrative understanding of the mechanobiology in pathological scarring.

2. Project Scope

Objective 1: To utilize scanning microfocus synchrotron SAXS to map out the 3D fibrillar orientation, pre-strain and order in the collagen fibrils of the ECM within the keloid scar, combined with cross-correlative Raman and mass spectroscopy to identify the different noncollageneous molecular components and their spatial distribution within the keloid.

Objective 2: To apply time-resolved microfocus synchrotron SAXS combined with *in situ* micromechanics to measure the fibrillar-level strain-maps in the ECM of keloids at progressively increasing levels of macroscopic stress - shear, compression and tension – which simulate physiological levels of applied biomechanical stress on the scar.

Objective 3: To correlate the spatially resolved *in situ* fibrillar-strain levels and matrix compositional variations across the keloid with elevated growth factor signaling and

expression of specific ECM proteins, in order to develop an integrative understanding of the mechanobiology in pathological scarring.

3. Desired Skills from the Student

Essential: A degree in Biomedical Engineering, Biomaterials, Materials Science and Engineering, Physics or related
Desirable: Experience in materials and tissue characterization techniques (incl. mechanical, micromechanical, microscopy (various types including confocal, fluorescence), spectroscopy, diffraction and scattering)
Desirable: Experience in scientific and visualization software
Desirable: Coding and data analysis in programming languages like Python

4. Supervisory Team

Primary: Dr. Himadri S. Gupta

Secondary: Dr. John Connelly (SMD/Barts)