High resolution imaging of extracellular matrix formation.

Supervisory team:
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Project description:

Understanding the biology of the extracellular matrix is fundamental to the development and health of all multicellular animals. Collagen is the most abundant protein in the human body, forming a vital protein scaffold to support cells and maintain tissue integrity. It is a critical component of cartilage and bone. As we age, loss of skin elasticity, poor wound healing, and an increased susceptibility to osteoarthritis and bone fractures become prevalent and the underlying cause is usually a reduction in the quality of collagen in the affected tissues. There are no effective treatments for many of these diseases. Conversely, abnormal accumulation of collagen causes fibrosis, a type of scarring, which is associated with 45% of all deaths (including those from cancer and cardiovascular disease). Recent data have defined a key role for the circadian rhythm in regulating the synthesis and secretion of procollagen. This has been shown to impact directly on the early secretory pathway machinery. This has profound implications for our understanding of how this pathway works, the impacts of circadian rhythm on matrix formation, and the consequences for long term health, for example where we know the circadian clock becomes dampened as we age.

Here, we have developed a project to define how the synthesis and secretion of key extracellular matrix proteins is linked to the formation of a functional extracellular matrix. We study this both from the perspective of the matrix proteins themselves as well as the machinery that directs its synthesis and assembly. Recent data have defined new regulators of these processes including the circadian rhythm. In this project we propose to use genome engineering to knockout key pathway components to then define the outcomes on ECM formation. We will target proteins of the early secretory pathway as well as key drivers and regulators of the circadian clock. The matrix formed by these cells will then be analyzed using high resolution imaging technologies including super-resolution light microscopy, transmission and canning electron microscopy, and high-speed atomic force microscopy. The integration of these approaches presents a fantastic opportunity for training in diverse imaging methods, from technical implementation through to data analysis. The project will be based primarily in Bristol in the lab of David Stephens. The Wolfson Bioimaging Facility provides the core technology platform for much of the imaging. This will be augmented by use of the high-speed atomic force microscopy at Plymouth Marine Laboratory under the direction of Professor Mike Allen.