Mechanisms of mechanosensation and membrane tension modulation in red blood cell development

Supervisory team:
Lead supervisors: Prof Ashley Toye (University of Bristol) and Dr Tim Satchwell (University of the West of England; UWE)
Prof Jan Frayne (University of Bristol), Prof Tony Killard (UWE),

Host institution: University of Bristol / University of the West of England; UWE
Submit applications for this project to University of Bristol

Project description:
Red blood cells (RBCs) are the most abundant cells in the human body. Amongst their defining characteristics, these cells possess a remarkable capacity for deformation, a feature necessary for transit through sub-cellular diameter microcapillaries that arises from a unique membrane-cytoskeletal architecture. Throughout its development, through the process of erythropoiesis, the rapidly remodelling membrane of the developing RBC is subject to a variety of surface receptor-mediated and mechanical stimuli that culminate in the dramatic extrusion of the cell nucleus to form a nascent reticulocyte, followed by its exit from the bone marrow and subsequent passage through splenic sinusoids and microcapillaries as a RBC. Mechano-modulation of the plasma membrane can arise via a variety of routes and proteins, and a common means by which stimulus is transmitted is via the influx of calcium. Notably, orthochromatic erythroblasts display transient calcium bursts prior to enucleation which have also been observed in RBCs transiting capillary mimics. However, the role that mechanosensory proteins play in enabling these processes and the interactions and redundancies that exist between different mediators in erythropoiesis are poorly understood.

This multidisciplinary and collaborative project will investigate mechanisms of membrane mechano-modulation in RBC development and function. It will exploit a tissue culture system that enables the recapitulation of erythropoiesis and its efficient genetic manipulation in vitro using primary haematopoietic stem cells and an immortalised erythroblast cell line BEL-A (PMID: 28290447).

The successful student will employ this system, further building on previous studies of enucleation (PMID: 23565219) and membrane deformation (PMID: 31506283) to explore the requirement and functions of mechanosensory ion channels expressed in erythroid cells (e.g. TRPM7 and Piezo1) with modulation of expression of these and other proteins achieved using CRISPR-based gene editing and lentiviral transduction of cells. Fluorescent reporters of activity such as GenEPi (PMID: 37468521) will be expressed to monitor activation and localisation of activated protein at stages with pronounced membrane perturbation such as enucleation and in response to membrane stimulus. Central to the project, assessment of membrane tension in live cells at different stages and under different conditions employing Fluorescent Lifetime Imaging (FLIM) in concert with Flipper TR probe will be undertaken, dissecting the hypothesis that changes in membrane tension initiate mechanosensory signalling and leveraging world class microscopy facilities at the University of Bristol. In development of the project the student will be able to explore different methods by which to apply mechanical stimulus to in vitro derived cells.

***Please note**: This project is in collaboration with the University of Bristol and the University of the West of England (UWE) and subject to a **joint degree award**. Successful applicants will be registered at both these institutions, and graduates will be awarded a joint degree from these two institutions upon successful completion of the PhD programme.*

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.