Project Details	
Project Code	MRC21IIREx Richards
Title	Phagocytosis and red blood cells: sorting new cells from old
Research Theme	Infection, Immunity & Repair
Summary	This PhD will investigate, using a unique combination of experiments and simulations, how old red blood cells are cleared by our immune systems via phagocytosis. This has implications for a variety of conditions such as sickle-cell anaemia and thrombosis. Unlike most PhDs, this is an excellent opportunity to learn both the experimental and modelling sides of modern research. Full training in both these areas will form an important part of this project.
Description	Background: Clearance of old red blood cells (RBCs) is essential for correct physiological maintenance of the blood. However, detailed mechanisms of this process remain a mystery, and it is unclear how RBCs "know" how old they are, and how this affects phagocytosis. Understanding this process is critical as premature RBC ageing and abnormal clearance is relevant to a range of common medical conditions such as sickle-cell anaemia, hemoglobinopathies, Gaucher's disease, chronic kidney disease, diabetes and parasite infections. The approach: Often the quickest way to make progress with this type of problem is to intimately combine experiments and modelling. Here, this will involve imaging phagocytosis of RBCs in the lab (with time-lapse microscopy of both real and artificial RBCs) and designing mathematical models (based on the immune cell shape and RBC stiffness). This combination means that the experiments can directly inform the model and that the modelling can suggest novel experimental directions. This approach will allow the student to learn a highly-desirable combination of modelling and experimental skills, leading to excellent future career prospects. Project plan: This cross-disciplinary studentship will be based at Exeter University but will also involve spending time at both Bristol University and Bath University, meaning the student will spend time in three separate labs at three separate institutes. The student will also join the growing GW4 NanoMedicine network that the PIs have recently set-up using a GW4 Initiator Award (see https://www.gw4nanomedicine.com/). The project itself will include: 1. Phagocytic assays. The engulfment of plastic beads will be examined to determine the role of target stiffness and coating on the efficiency and rate of phagocytic uptake. This will involve using a dual-micropipette system and an environmental-controlled Leica microscope. The student will also use our brand new state-of-the-art NanoSight microscope. 2. Modelling. A mathematical/computational model that involves membrane shape, receptor dynamics and intracellular signalling will be designed. This will be based on a published phagocytosis model recently developed by the Richards group. For the first time, this model will involve the role of target stiffness, which is critical for understanding RBC clearance. 3. Design and culture of RBCs. Erythrocyte lines that overexpress CD47 (a "don't eat me" signal) will be developed in Dr Toye's lab in Bristol, before moving on to isolate primary white cells and utilise macrophage and neutrophil culture models. Cells with a range of deformabilities will be designed by altering membrane and cytoskeleton composition. 4. Image analysis. Building on existing custom-built software within the Richards

	group, image analysis software will be developed that automatically interprets the time-lapse images of phagocytosis, focusing on the rate of engulfment and the phagocytic cup shape. This part will also be based on a novel imaging-analysis system recently developed in Bristol by the Toye lab. 5. Properties of RBCs. Cultured RBCs under- or overexpressing CD47 will be characterised (e.g. for turgidity, stiffness and membrane tension) with a variety of biophysical measures in Prof Edler's and Dr Toye's labs (e.g. using an automated rheoscope). Outreach: Public involvement will also play an important part of this studentship. The student will work directly with Dr Silvia Bortoli (the Communities Engagement Manager within the Centre for Biomedical Modelling and Analysis at Exeter University) and the MAGPIEs (a group of lay people involved in medical research) in order to disseminate results and guide research. Drs Jeynes and Richards are already heavily involved with this programme.
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