Role of neutrophils in bone marrow fibrosis

Professor Simon Mendez-Ferrer https://www.stemcells.cam.ac.uk/people/pi/mendez-ferrer
Dr Ryan Collinson, Department of Hematology

Bone marrow (BM) scarring or fibrosis can occur in malignant or non-malignant haematological diseases, like myeloproliferative neoplasms and grey platelet syndrome, respectively. BM fibrosis compromises normal blood cell production and facilitates leukaemia development. Yet, the cellular and molecular underpinnings are poorly unknown; consequently, BM fibrosis remains to be difficult to treat. Megakaryocytes are suspected drivers of fibrosis through the release of profibrotic cytokines, such as TGF. However, the role of neutrophils in BM fibrosis remains poorly defined. Abnormal invasion of megakaryocytes by neutrophils (emperipolesis) correlates with BM fibrosis in myeloproliferative neoplasms and grey platelet syndrome. Yet, the mechanisms underlying neutrophil-megakaryocyte interactions and fibrosis development have remained elusive, whilst elucidating them could pave the way for novel therapeutic strategies to prevent or treat BM fibrosis in the future.

A stepwise research programme has been designed to investigate the molecular mechanisms (prospectively built on candidate pathways) leading to 1) Neutrophil-megakaryocyte adhesion; 2) invasion of the demarcation membrane system of the megakaryocyte; 3) inflammatory pathways and 4) activation of profibrotic cytokines.

The student will be co-supervised and trained on a daily basis by Dr Ryan Collinson, who is an expert in emperipolesis. They leverage on primary cells from genetically-modified mice, cutting-edge *ex vivo* models, time-lapse microscopy (Etaluma) of optimized co-culture systems, flow cytometry, transcriptomics and proteomics analyses to investigate the role of neutrophils and their interaction with megakaryocytes in BM fibrosis. Candidate targets will be first tested *ex vivo* and ultimately validated *in vivo*.

The rotation will use established *ex vivo* models of myeloproliferative neoplasms to investigate the dynamics of emperipolesis and the non-mutually exclusive pathways through which neutrophils might prime megakaryocytes for fibrotic cytokine secretion. The rotation will characterize key aspects of emperipolesis and its impact on megakaryocytes. The rotation could lead to a PhD project to test candidate targets identified through the transcriptomic and proteomic analyses. Both will be needed, as critical steps might involve the activation of profibrotic cytokines through proteolytic cleavage. For PhD, the proof of principle obtained in myelofibrosis will be independently tested in the context of fibrosis associated with grey platelet syndrome. This could elucidate unknown potentially shared mechanisms of BM fibrosis in haematological diseases. The project scope will be extended to investigate the impact of neutrophils in megakaryocyte functions, including platelet production, immune and HSC niche functions. The PhD project will be co-supervised by Professor Cedric Ghevaert at the Department of Haematology, who will provide key input, training and models to investigate megakaryocyte functions and validate findings in a humanised setting using a cutting-edge human iPSC-derived megakaryocytes and a functionalised bioscaffold. This project will characterize the dynamics and molecular underpinnings of neutrophil-megakaryocytes interaction and its potential pathogenic effects spanning fibrosis, thrombocytosis and BM niche deregulation.