The Megakaryocyte-Platelet Defect in Myeloproliferative Neoplasms

The BCR/ABL1-negative myeloproliferative neoplasms (MPN) are a heterogeneous but related group of clonal stem cell disorders characterised by proliferation of one or more of the myeloid lineages in the bone marrow (BM). The MPN entities include polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (PMF). They result from one or more acquired genetic mutations in a haemopoietic stem cell (HSC). Megakaryocytes are morphologically atypical and subtle differences in the appearance of the MK between each MPN entity is critical in their classification according to World Health Organisation (WHO) criteria. This implies that megakaryocytes and their platelet progeny may play a critical role in the clinical manifestations and progression of these diseases, including thromboses, haemorrhage, fibrotic progression and transformation to acute leukaemia.

In this project the candidate will use help to develop highly innovative scientific methods to interrogate the MK-platelet axis. Identification of changes in MK proteome and/or platelet function will be correlated with clinico-pathological features. This will set the foundation to develop clinically useful MK and platelet biomarkers in the future. The outcome will be enhanced diagnostic precision, leading to more clinically predictive therapeutic decision-making and improved disease monitoring in MPN.

Proteomic analysis will be performed on MK isolated from the aspirated BM of MPN patients and controls. MK will be isolated using CD61 magnetic microbeads and the autoMACS Proseparator instrument and fractionated using generic subcellular localisation techniques. The relative abundance of platelet proteins in the MPN subtypes will be defined using Isobaric Tags for Relative and Absolute Quantitation (8-plex iTRAQ; ABSCIEX) combined with mass spectrometry. This will be to determine expression of molecules associated with MK proliferation, apoptosis, signalling and function. Whole blood mass cytometry methods will be used to assess canonical parameters of platelet function, kinomic and surfaceome expression in the MPN and control samples.

We aim to translate the changes identified in MK and platelets to develop biomarker testing for disease classification, stratification and the identification of patients at risk for complications and progression. MK biomarkers will enable the assessment of inappropriately expressed proteins in MK *in situ* at the time of BM examination (for diagnosis or monitoring). Platelet biomarkers will provide a less invasive, more objective and quantitative method for disease monitoring on serial blood samples.

Other details: The supervisors for this project are Dr Matthew Linden and Dr Katie Meehan. If you would like additional information regarding this project, please email matthew.linden@uwa.edu.au or call (+61 8) 9346 1050.

If you have questions about how to apply to become a PhD student at UWA, please email pghelp@postgraduate.uwa.edu.au or call (+61 8) 6488 2807.