Predicting malignant transformation of Bone Marrow Failure Syndromes using longitudinal targeted sequencing of peripheral blood and cell-free DNA (cfDNA)

Dr Piers Blombery

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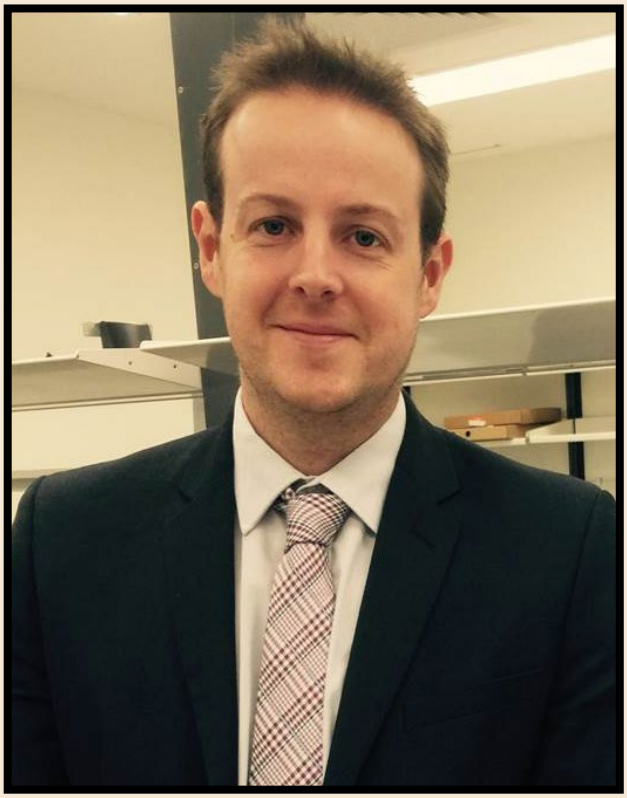
Dr Piers Blombery is the medical lead of the Molecular Haematology Laboratory at Peter MacCallum Cancer Hospital, an accredited diagnostic laboratory that specialises in performing next generation sequencing assays for patients with blood cancer and related conditions. The laboratory prides itself on both performing high quality genomic diagnostics but also in leading the field in development of new technology and new applications of existing technology to improve the outcomes of patients with blood cancers and bone marrow conditions. He explains further, “We are a translational genomics laboratory - we use new

technologies to detect alterations in patients DNA which may provide further insight into their condition. Our research into bone marrow failure with Maddie Riewoldt's Vision involves looking for DNA mutations in patients with Aplastic Anaemia that may predict their transformation to more aggressive haematological malignancy such as acute myeloid leukaemia. We are following a cohort of patients with Aplastic Anaemia and testing their blood and bone marrow for development of these mutations."

Dr Blombery has taken the novel approach of investigating the potential role of cell free DNA (cfDNA) to monitor the bone marrow compartment in patients with BMFS. He elaborates, "Cell free DNA is present in the blood of all people and is derived from cells throughout the blood system and the rest of the body. This sample type is thought to be more representative of what is going on in the body as a whole rather than just the site from which the blood/bone marrow is taken. We are using a range of technologies to perform this analysis on cellular and cfDNA including hybridisation capture based target enrichment, hybrid single-primer extension target enrichment and digital droplet PCR. An important aim of our research is to find out whether the same information can be derived from this liquid biopsy and potentially replace painful invasive procedures such as bone marrow biopsy."

The same technology that Dr Blombery utilised in his initial research of analysing mutations in a cohort of patients with Aplastic Anaemia will now be applied to a national interventional prospective clinical trial, entitled the DIAAMOND study. This important study will look at using a cell stimulating agent, Avatrombopag, to improve outcomes of patients with Aplastic Anaemia. Dr Blombery's team will look for mutations in the blood and cell free DNA in these patients in order to understand how to use these agents safely. "One of the big clinical questions in the treatment of Bone Marrow Failure Syndromes at the moment is the use of bone marrow transplant alternatives, such as immunosuppression and cell stimulating agents like Avatrombopag and Eltrombopag. Specifically the question of what constitutes best clinical practice. There are concerns that using cell stimulating agents may possibly lead to the promotion of unwanted haematological changes in some patients. Our research is focussed on pre-emptively detecting through mutational analysis which patients may be susceptible."

The Bone Marrow Failure Syndromes are a unique entity in which Dr Blombery believes genomics can have a profound effect on diagnosis and management. In addition, the use of genomics in this area in Australia has been historically underdeveloped and not routinely



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available to clinicians and patients treating these rare disorders. He remarks that it has been highly satisfying to be able to use this technology and research to make a meaningful difference to the diagnosis and treatment of patients with Bone Marrow Failure Syndromes through this research project, the Melbourne Genomics Health Alliance Bone Marrow Failure Flagship and diagnostic testing more generally.

The Molecular Haematology Laboratory team consists of over 20 staff members including haematologists, medical scientists, bioinformaticians and laboratory technicians. The team involved in this research project includes Dr Lucy Fox and Dr Georgina Ryland who both also worked on the highly successful Melbourne Genomic Health Alliance Bone Marrow Failure Flagship which used genomics to improve diagnosis in patients with Bone Marrow Failure Syndromes – both acquired and inherited.