Understanding normal and aberrant stem cell biology to improve human health (Stem Cells Biology)

This program brought together Australia's top stem cell researchers from three iconic organisations to work together on two new topics:

i. identification of the major pathways that regulate megakaryocyte commitment from blood stem cells (haemopoietic stem cells; HSC), the maturation of megakaryocytes and the production of platelets and use of this information to optimise platelet production in vitro; and
ii. understanding the mechanism of mobilisation of HSC from the bone marrow to the peripheral blood and, in doing so, develop more effective strategies for mobilisation in a clinical setting. The two new projects combined cutting edge basic research with well-established and highly-committed routes to clinical and commercial translation.

The objective of this initiative were to conduct extensive cellular, molecular and functional analyses of blood stem cells, their progeny and their bone marrow environment. This information was then used to generate research tools, identify new drug targets, which were then used to develop a new strategy and small molecule to mobilise blood stem cells improving the outcomes of bone marrow transplantation, as well as to generate mature blood cells for transfusion.

The project has achieved the outcomes and provided a number of key advances that have/will result in impact in a number of areas. Firstly, in the area of megakaryocytes, together the team has identified a number of new markers associated with megakaryocyte development, defined new roles in megakaryocyte regulation and generated a number of new murine models. The immediate users of these outputs is the research community, who have adopted these findings to "leapfrog" their own specific research. The outcome of this is the better understanding of megakaryocytopoiesis and therefore advancing the field towards the efficient generation of platelets in the laboratory. This is an ultimate goal that will have a significant impact on the lives of many people who require platelet transfusions.

In the second area of blood stem cell mobilisation, a new molecule has been generated and characterised in pre-clinical models that could have significant impact on improving the lives of patients that require bone marrow transplants. Blood stem cells reside in the bone marrow, so for a stem cell transplant, these have to be "coxed" into the peripheral blood for collection. This then negates the need for a significant operation under general anaesthetic for the highly invasive direct harvesting of stem cells from the marrow. This is important, as stem cells for transplant commonly come from a healthy donor, known as an allogeneic transplant, so ease of collection is critical. Bone marrow stem cell transplants are routinely used to treat cancer patients with leukaemia or myeloma who have undergone high dose chemotherapy. Current methods for harvesting stem cells from the peripheral blood require multiple injections of a growth factor over several days in order to boost stem cell numbers in the blood for subsequent collection.

The new method for stem cell harvesting involved the generation of a small molecule "BOP" that enables stem cells to be collected from the blood within an hour of administration and eliminates the need for the current growth factor. The uptake of this is currently with pharmaceutical

companies as well as clinicians, who together with our team are planning a phase I clinical trial. The initial use is planned for healthy stem cell donors in the allogeneic setting and will result in a significantly reduced impact on the donor, with a single dose and collection one hour later.

Furthermore, in addition to stem cells, BOP also boosts the numbers of “regulatory T-cells” in the blood. Regulatory T-cells suppress immune responses and are known to improve transplant outcomes and reduce fatal complications such as graft-versus-host disease (GvHD). The consequence is that the use of this small molecule should provide an enhanced stem cell product for transplant, with the impact being better clinical outcomes for patients.