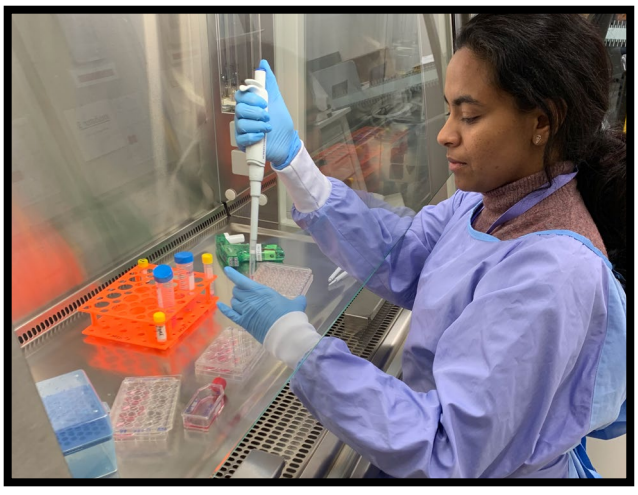
Modelling consequences of cell abundance, heterogeneity and origin for autologous cell therapy in genetic Bone Marrow Failure Syndromes

Dr Parvathy Venugopal

Fellowship 2020 ongoing

Centre for Cancer Biology



Dr Parvathy Venuogopal, Centre for Cancer Biology

Professor Hamish Scott's laboratory team, Centre for Cancer Biology, Adelaide, SA

Dr Parvathy Venugopal is a post-doctoral researcher with a strong interest in the genetics of haematological disorders, particularly in inherited bone marrow failure disorders and predisposition to blood cancers. She completed a Masters degree in stem cell biology at Manipal University (India) before moving to Adelaide to pursue her PhD at the University of Adelaide under the guidance of Professor Hamish Scott and Dr Christopher Hahn. She currently holds a Maddie Riewoldt's Vision early career Fellowship and works within the Genetics and Molecular Pathology Research group led by Professor Scott at the Centre for Cancer Biology, a SA Pathology and University of South Australia alliance. The research group is internationally recognised in the area of inherited predisposition to haematopoietic malignancies, and has been responsible for the discovery of the genetic causes of several bone marrow failure disorders. They have enrolled over 200 families into the Australian Familial Haematological Cancer Study (AFHCS) where they seek to identify the causal genes to end the diagnostic odyssey for families, and offer hope for better patient management.

Multiple studies have shown that bone marrow cells of some bone marrow failure patients have the ability to self-correct - a spontaneous cure by correcting the disease-causing genetic mutation from the genome. A better understanding of this incredible phenomenon, known as revertant somatic mosaicism, may enable us to induce or facilitate this effect in patients with bone marrow failure. The Maddie's Vision Fellowship supports Dr Venugopal's ongoing work which focusses on investigating these naturally occurring correction events in blood from patients. "For patients showing a spontaneous correction in a few cells, my research aims to test conditions that select for the corrected cells such that they replace the defective bone marrow cells."

To better understand the mechanism, Dr Venugopal aims to induce correction in an inherited bone marrow failure mouse model, and to identify conditions to help corrected cells expand to re-populate the bone marrow to cure symptoms of disease, thereby determining conditions required to restore and maintain normal blood formation in bone marrow failure patients. With the growing possibilities of gene corrected autologous cell therapy, whereby a patient's own corrected cells are transfused back, Dr Parvathy's research will provide timely insight into several key questions such as optimal cell dose for transplantation to ensure sustained long-term correction of phenotype, and correlation between cell dose and risk of stem cell exhaustion in the context of immune challenges such as infection. It would also serve as a proof-of-principle that assisted correction of a small subset of the patient's own stem cells may be a viable therapeutic approach with the potential of modifying treatment to be more patient-friendly than the current alternatives.

Identification of strategies to select for revertant cells and better understanding of the effects of haematopoietic stress can be informative in patients where reversion has occurred spontaneously. Experimental manipulations to give competitive growth advantages to clones that improve clinical phenotype have substantive implications for the requirements of efficiencies of gene manipulations, manufacture and quality control of autologous cellular therapies. It could potentially bridge the gaps in therapy for bone marrow failure and open up new avenues to effective personalised therapy, aligning perfectly with the mission of Maddie's Vision to find a cure.