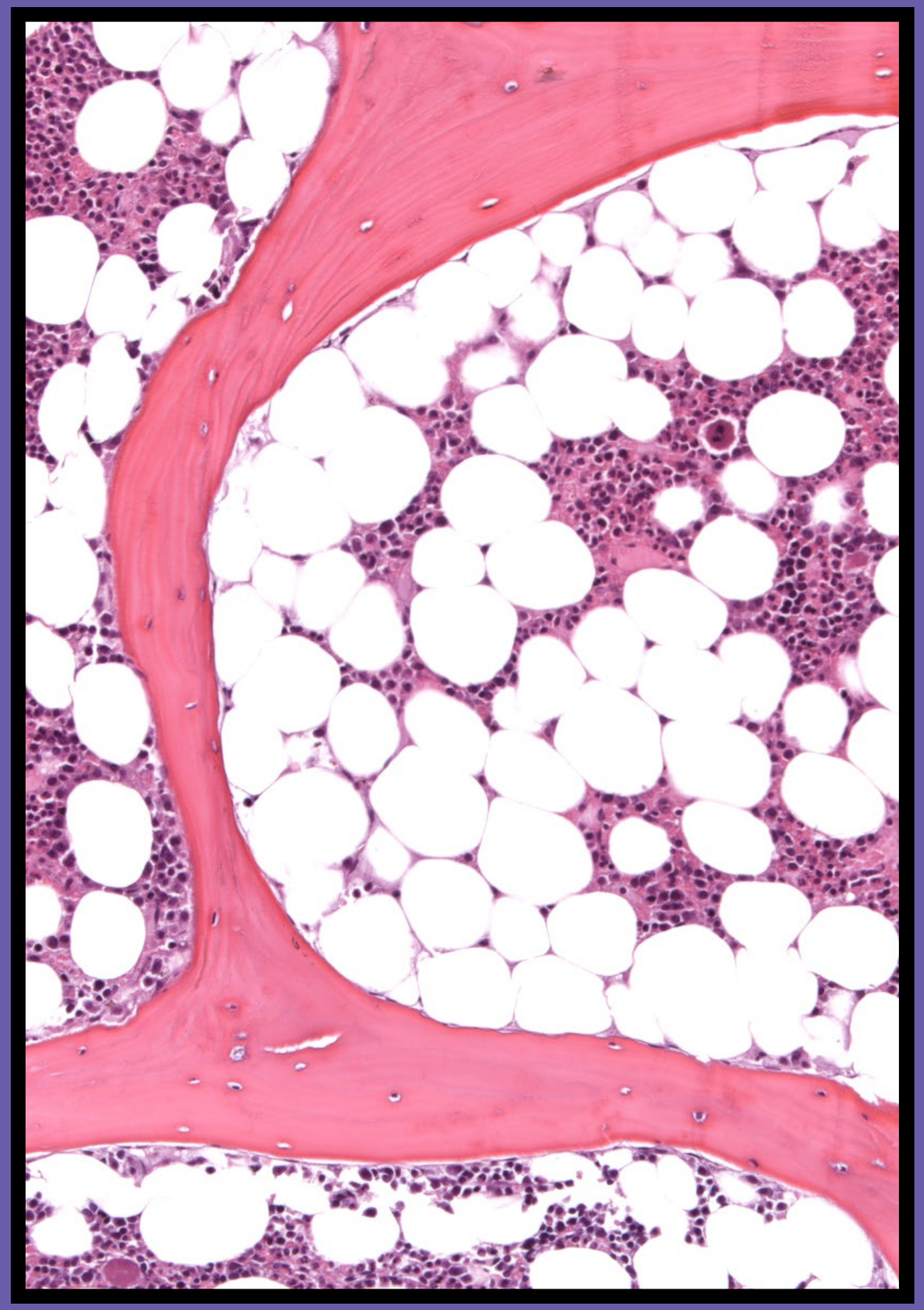
Bone Marrow Biology Centre of Research Excellence.

Maddie Riewoldt's Vision.

# Maddie Riewoldt's Vision Centre of Research Excellence in Bone Marrow Biology

Report to June 2020

# Contents



# Introduction

# 1.

# CRE Director's Message

The Maddie Riewoldt's Vision Centre of Research Excellence (CRE) in Bone Marrow Biology has been a remarkable initiative to both be part of and to see flourish over its first two years. It is a testament to what can be achieved when smart and individually dedicated researchers can be brought together around a common purpose and provided with the logistic and peer support necessary to see their collective vision come to life. The support from the Victorian State government for the CRE and the subsequent support from the Federal government for large projects within the CRE is a quintessential demonstration of smart investment into high quality medical research in an area of startling unmet need. It is my most heartfelt view that the precise, strategic and highly accountable practices of Maddie's Vision that have been in place since its inception have laid the foundation and organisational culture that results in a high rate of research output per dollar spent. That success can only breed further success. That culture of intellectual clarity and striving for better outcomes for patients with Bone Marrow Failure Syndromes (BMFS) has attracted the trust and attention of patients, families, donors and government.

As is outlined in the pages that follow, any reader will draw the same conclusion as me. The trust shown by the community to Maddie Riewoldt's Vision and its CRE has been well placed. The individual projects and fellowships have continued to grow exponentially. The research presentations and publications are remarkable for their quality. The role of the CRE in organising and bringing scientific and family-oriented symposia to life has been truly commendable in the highest of terms. All of these things would be individually sufficient to mark the second year of the CRE as an undiluted success.

But, as the Director of the CRE, what I have seen that fills my heart with the greatest pride is observing the conversations that would not have been possible without the existence of the Maddie Riewoldt's Vision CRE. The conversation between two Maddie Riewoldt's Vision grant holders, one young, one less so, who would have not met without the help of Maddie Riewoldt's Vision, but who have now struck up a collaboration for a new grant application. The conversation between clinicians and laboratory scientists who have, sometimes for years, worked on different aspects of the same problem, but who now can work together. The conversations between international experts in their field and the young researchers who have read of their research, but who can now meet, and be inspired, in the Maddie Riewoldt's Vision symposia and discuss their ideas one on one. The conversations between a grieving family and CRE researchers who are given the precious opportunity to understand what difference their research can really make. These conversations are critical both because they are good in their own right and because of where they can take us. Those conversations have taken us to new ways of approaching the very idea of BMFS. They have taken us to a greater community understanding of the diagnoses and hope in the possibilities for cure. They have taken us to the ability to develop and offer new treatments incorporating genomics, immunology, clinical trials, novel drugs and better data. Those conversations have brought us closer to where we need to be, closer to Maddie's Vision.

**Professor David Ritchie**
**Director**
**CRE in Bone Marrow Biology**



# CRE Director of Operation's Message

The generous awarding of funds by the Victorian State Government in 2018 to establish the Centre of Research Excellence in Bone Marrow Biology provided salaried support for critical positions to underpin the operations and administration of the CRE. My appointment in September 2018, and the subsequent recruitment of Lou Johns, Project's Administrator, in April 2019, has ensured sufficient workforce to increase momentum towards the CRE's goals, to provide a synchronisation of all current and future research opportunities, and to accelerate and amplify research outcomes.

Over the last two years, I have been privileged to acquaint myself with the incredible principal researchers and co-researchers of the projects we support. Their expertise, innovation, optimism and visionary thinking are remarkable to witness, and a harnessing of their collective energy via the CRE Executive and specific sub-committees propels the CRE forward to solve the unanswered questions of Bone Marrow Failure Syndromes. The pandemic era has forced adaptations to both clinical and scientific endeavours, and I am in awe of the flexibility and determination our CRE Executive continue to demonstrate.

Major milestones have occurred in the CRE's existence since inception – Australia's first National Symposium on Bone Marrow Failure Syndromes in May 2019, the appointment of Biobanking Victoria as our homebase laboratory facility for the Australian Marrow Failure Biobank in June 2020, and our inaugural Patient and Family Forum in August 2020. Each of these events signifies a monumental step required on the path to solve the mysteries of these rare diseases, to promote the facilitation of new projects, to provide the valuable samples researchers require, to inform our patients and families of registry, biobank and clinical trial opportunities, and to build a BMFS community with both national and international reach.

I am enormously appreciative of all members of our exceptional Scientific Advisory Committee, who provide wisdom, counsel and instruction to all facets of our Grant Program. Similarly, I extend gratitude to our Collaborative Research Institutes, who provide the infrastructure and support to our CRE Executive to bring their research projects to fruition.

I am truly honoured to be a part of Maddie's legacy, co-ordinating an environment that places Australian researchers at the forefront of BMFS research in our mission to develop new treatments and ultimately cures for patients and families.

**Dr Simonne Neil**
**Director of Operations**
**CRE in Bone Marrow Biology**

# CRE

# 2.

# A trajectory of exceptional progress

## The Maddie Riewoldt's Vision Centre of Research Excellence in Bone Marrow Biology

On 19th April 2018, the Victorian State Government announced a generous $2.1M would be provided to Maddie Riewoldt's Vision (Maddie's Vision), to establish the Centre of Research Excellence in Bone Marrow Biology.

Centres of Research Excellence (CRE) are universally recognised as the best model for managing rare, complex and multifactorial diseases, functioning as a hub of expertise, promoting the collaboration of high quality, highly focussed researchers towards a common goal. The Maddie's Vision CRE in Bone Marrow Biology is a first in Australia; a virtual centre that constitutes the 'front of house' for the research consortium, providing a centralised contact point for existing researchers, future researchers, commercial entities and community groups. The CRE's goals are to provide a critical synchronisation of current and future research opportunities, and to amplify and accelerate research outcomes. Significantly, the CRE's reach is not only nationwide, supporting projects in six different Australian states and territories, but expanding internationally, with three current projects possessing an international collaboration and connection. Ideally, creation of this networked consortium aims to attract ongoing opportunities for discovery and treatment development for commercial enterprise too.

The CRE structure (see page 16) includes Director, Professor David Ritchie, Head Bone Marrow Transplantation and Deputy Director Clinical Haematology The Royal Melbourne Hospital / Peter MacCallum Cancer Centre, the Director of Operations, Dr Simonne Neil, and Projects Administrator Lou Johns, alongside the CRE Executive, comprised of the principal researchers of the 24 projects Maddie's Vision has committed to, or has previously funded. All projects sit within the CRE research portfolio and include Grants-in-Aid, Fellowships, a clinical registry, a tissue sample repository and clinical trials. The hive of activity occurring within the CRE is generating significant momentum, forging collaborations and developing infrastructure.

The CRE Executive meets every six months to formalise planning. The members discuss future opportunities for investment by strengthening the strategic direction within the 5 Pillars of Research focus, potential collaborative projects, talent identification and both national and international clinical trials. Importantly, assembling Australia's bone marrow failure scientific and clinical knowledge around a single table promotes ideas and possibilities. Subcommittees have been formed within the CRE Executive to pursue and progress prioritised areas of unmet need; the Australian Bone Marrow Failure Biobank Subcommittee was formed in May 2019 and the Gene and Cellular Therapy Subcommittee in May 2020.



# Our commitment to funding innovative scientific research

The Centre of Research Excellence research portfolio currently includes commitment to funding 24 research projects. A period of increased growth and expansion has occurred during the 2019-2020 financial year, with a total of eight new projects added. These include

**1.**

**The Australian Marrow Failure Biobank**
After an extensive and exhaustive selection process undertaken by our Scientific Advisory Committee, Biobanking Victoria, a Monash University initiative supported by the Victorian State Government, has been appointed as our homebase laboratory and storage facility for the Australian Marrow Failure Biobank.

The facility operates at international commercial standards and manages more than four million biological specimens linked across the globe to clinical trials and registries. Biobanking Victoria has provided more than 200,000 samples to world class international research activities in the last 12 months, and more than 300 peer-reviewed publications have arisen from the use of biological material and data provided by the biobank to end-users in basic and translational research settings in the last five years.

Importantly, via the shared Monash University affiliation of both the Biobank and our Aplastic Anaemia and other Bone Marrow Failure Syndromes Registry, the registry clinical team and biobanking laboratory team will be able to work in unison, leveraging existing and established connections to over 40 hospitals nationwide.

**2.**

Dr Piers Blombery, for his project entitled **Using whole genome sequence analysis to find answers for unsolved cases of inherited Bone Marrow Failure Syndromes.** Dr Blombery, a molecular haematopathology expert from Peter MacCallum Cancer Centre, is determined to solve 'missing heritability' in inherited BMFS, a term that describes an inability to find the genetic variations that cause a disease.

Dr Blombery's work will involve unravelling the entire genetic information stored in the DNA of not only a patient, but in the patient's parents too. This 'trio analysis' will provide enormous insight into the contribution of all the proteins in DNA - both the coding proteins and the non-coding proteins, and likely discover new genes that are responsible for inherited BMFS.

# 3.

Associate Professor Stephen Ting is a Principal Investigator of the DIAAMOND Trial, a Federal Government MRFF supported clinical trial investigating the treatment of Avatrombopag, a new therapy for Aplastic Anaemia that stimulates a receptor to produce more blood cells.

Associate Professor Ting's GIA grant will be utilised for the **Curation of the DIAAMOND-based Aplastic Anaemia Biobank**, and with consent of patients, will allow for samples of both peripheral blood and bone marrow to be biobanked for future research purposes. New treatment discovery and ultimately cures are contingent on ideas and discovery, and this requires access to research samples for both national and international co-ordinated effort.

# 4.

Furthermore, the awarding of Federal Government MRFF funds from the Emerging Priorities and Consumer Driven Research Initiative to Maddie's Vision has provided resources for increased clinical trial capacity building, and commitment to the opening of an interventional trial entitled The **RESELECT** Trial – **REscuing bone marrow function in patients with relapsed acquired aplaStic anaEmia and/or bone marrow failure post aLlogeneic stEm Cell Transplantation.**

The RESELECT trial will provide patients with the high risk BMFS of relapsed Aplastic Anaemia and bone marrow failure after transplantation, known as Poor Graft Function (PGF) immediate access to novel therapies, whilst simultaneously developing a platform for the delivery of a pipeline of innovative treatments, including cutting edge cellular and gene therapies, for subsequent patient cohorts. The trial will be open for recruitment in mid 2020 at three quaternary bone marrow transplant hospitals across Australia – the combined Clinical Haematology of Peter MacCallum Cancer Centre / The Royal Melbourne Hospital, the Fiona Stanley Hospital in Perth, and St Vincent's Hospital in Sydney. This is the FIRST clinical trial in Australia for patients with PGF, and is an opportunity to make significant impact on the lives of Australian patients and families affected with high risk BMFS.



# Achievements and outputs

The CRE has attained significant achievements and outputs since inception, including hosting Australia's first ever National Symposium on Bone Marrow Failure Syndromes in May, 2019.

## Outputs to end of June 2020 have encompassed:

**The delivery of a total of 62 scientific presentations** 49 oral presentations and 13 poster/abstracts. Presentations have occurred both domestically and internationally, including at Australia's most prestigious haematological conference Blood, and the pre-eminent international conferences of the American Society of Haematology (ASH) and the European Haematology Association (EHA).

**A total of 17 significant scientific manuscripts have been published** in peer reviewed journals by the CRE's principal researchers. 6 publications have occurred in journals with an Impact Factor > 10, including Nature, Nature Medicine, Cancer Cell, Molecular Cell, Trends in Genetics and Nature Communications

**Funding has been leveraged by both Maddie's Vision and principle grantees to a total of $5,821,969.57** from philanthropic and governmental sources, including in the last financial year the exceptional awarding of an NHMRC 2019 Ideas Grant to Dr Yih-Chih Chan, and an NHMRC Investigator Grant MRFF Priority Round 2020 to Dr Paul Yeh.

Maddie's Vision is extraordinarily grateful to the Victorian State Government for its ongoing support and looks forward to continuing to build on the wonderful momentum created within the Centre of Research Excellence, propelling efforts towards the goal of new treatments and ultimately cures.

# Research at a glance

**8.**

Commitment to funding 8 new projects in 2019/20 FY

**17.**

17 significant scientific manuscripts – 7 with an impact factor > 10

**62.**

62 scientific presentations (49 oral and 13 poster/abstracts)

**$5,821,969.57**

Leveraged funding to a total of $5,821,969.57



# Five pillars of research

1. Comprehensive clinical data and sample collection on current and newly diagnosed patients with Bone Marrow Failure.

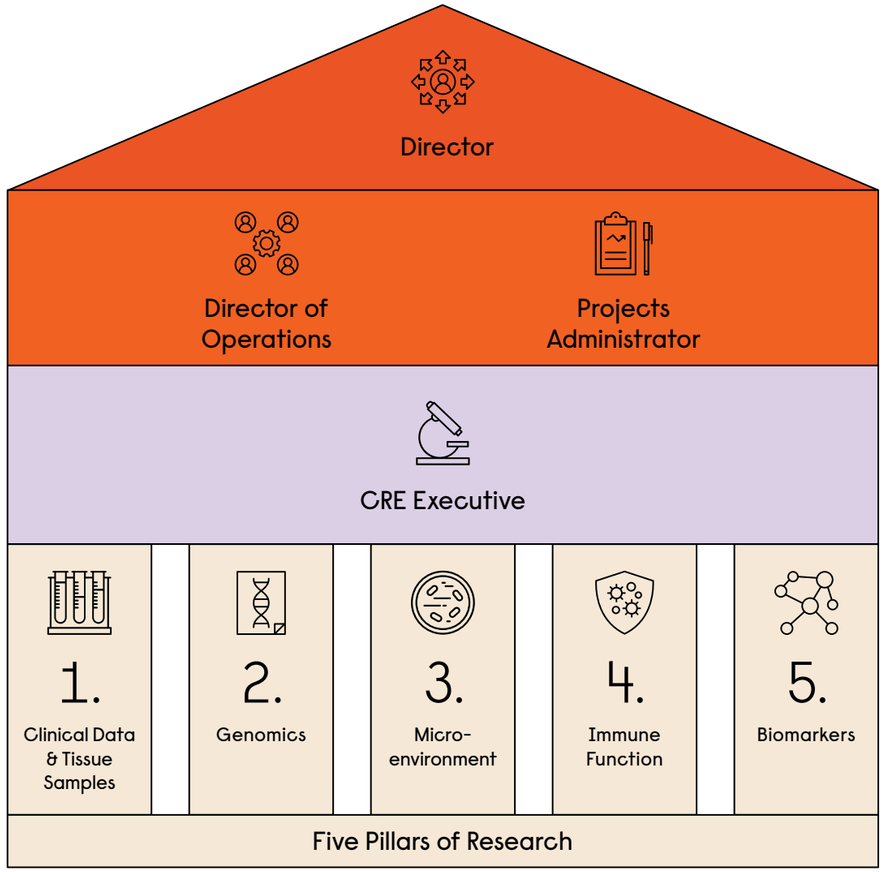
2. Genomic, epigenomic and proteomic control of the Haematopoietic Stem Cell (HSC) survival, growth and differentiation.

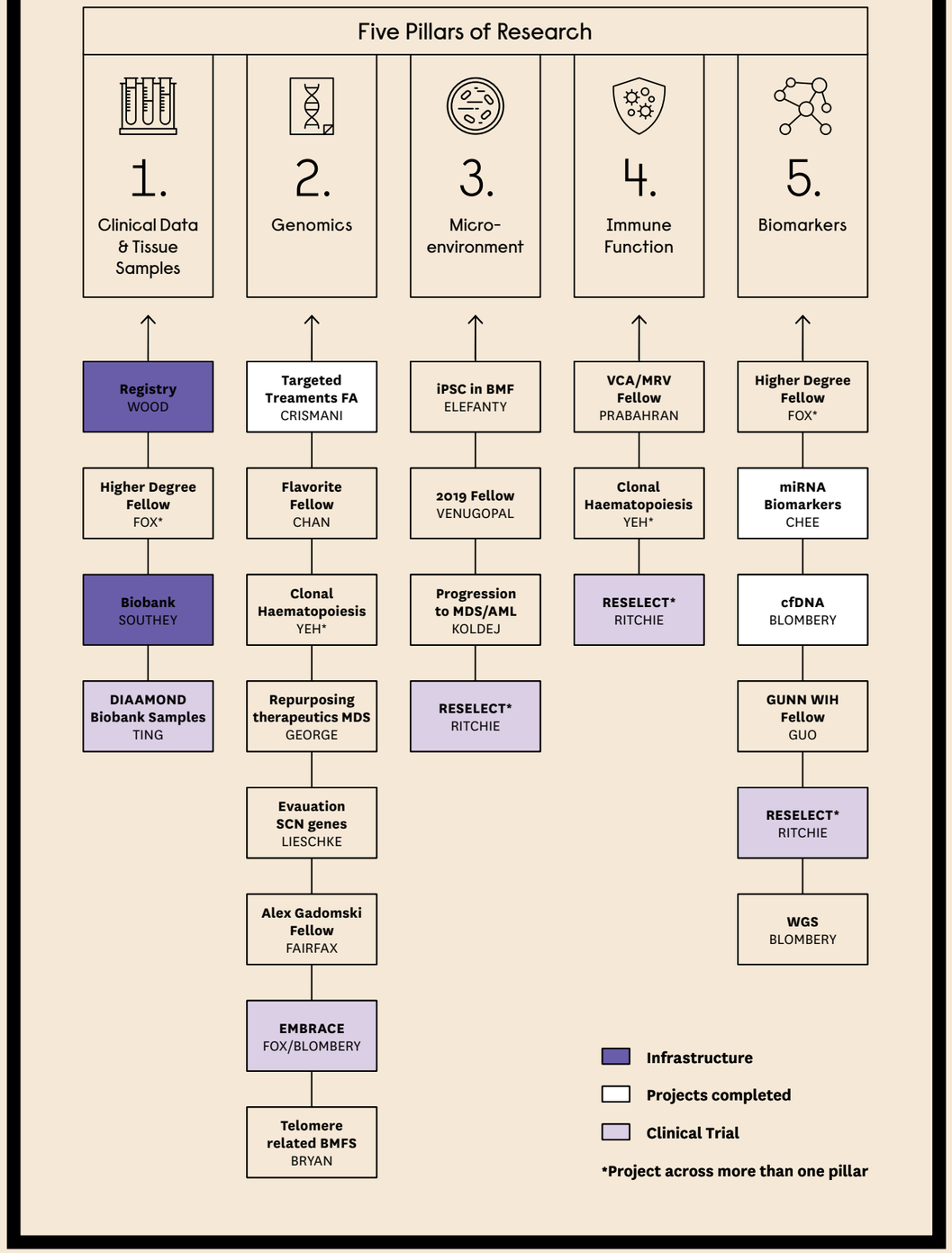
3. The components and control of the HSC niche (Microenvironment) within the bone marrow.

4. Abnormalities of Immune Function.

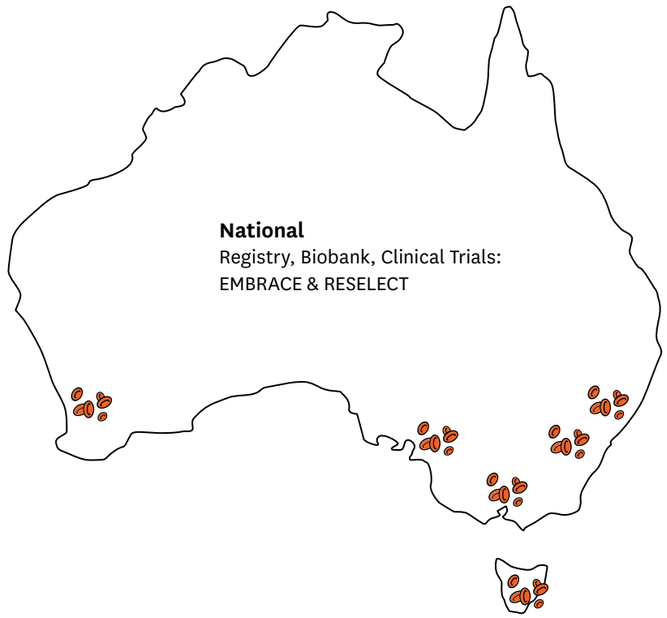
5. Monitoring and predictors (Biomarkers) of prognosis, response to treatment and disease evolution.

# CRE schematic structure



# Where are our projects?




**Melbourne**
14

**Hobart**
2

**Canberra**
1

**Sydney**
1

**Adelaide**
1

**Perth**
1


# National Symposium on Bone Marrow Failure Syndromes

# 3.

# Inaugural National Symposium on Bone Marrow Failure Syndromes

A major milestone event took place over 24 to 26 May 2019 – Australia's first ever Bone Marrow Failure Syndrome Symposium. Proudly hosted by our Centre of Research Excellence in Bone Marrow Biology the symposium brought together 180 national and international delegates. Representatives from every possible stakeholder group attended, including adult and paediatric haematologists & clinicians, research scientists and technicians, Victorian State Government members, patients and their families, nurses, genetic counsellors, pharmaceutical representatives and not-for-profit colleagues.

## Our inaugural symposium featured two highly esteemed international guest speakers, Professor Akiko Shimamura and Dr Austin Kulasekararaj.

Dr Akiko Shimamura is a Professor of Paediatrics at Harvard Medical School and Director of the Bone Marrow Failure and MDS Program at the Dana Farber/Boston Children's Cancer and Blood Disorders Centre. Her research spans laboratory and clinical studies to improve diagnosis and treatment of bone marrow failure and predisposition to myeloid malignancies. Dr Shimamura founded and directs the North American Shwachman Diamond Syndrome Registry. She serves on the Executive Committee of the North American Paediatric Aplastic Anaemia Consortium (NAPAAC), a working group of over 30 paediatric haematology centres. Her work has led to the identification of genetic causes of bone marrow failure and leukaemia predisposition. Her studies have informed evidence-based integration of genomic testing into diagnostic algorithms for these disorders.

Dr Austin Kulasekararaj is a Consultant Haematologist working at King's College Hospital, London, under the myeloid, allogeneic transplant and bone marrow failure services. He also leads the King's National PNH service. Dr Kulasekararaj's special interest is acquired Bone Marrow Failure Syndromes - Aplastic Anaemia and Myelodysplastic Syndrome. His research interest is in molecular pathogenesis of myelodysplastic syndromes (MDS), especially the role of TP53 and other somatic

Left to right: Professor Akiko Shimamura, Dr Piers Blombery and Dr Austin Kulasekararaj at the official opening welcome event.


Opening night, Mr Frank McGuire, Parliamentary Secretary for Medical Research

mutations. He has contributed to key publications in the field of molecular and immunological aspects of bone marrow failures, especially MDS.

Dr Kulasekararaj visited Melbourne as an Expert-In-Residence of Melbourne Genomics Health Alliance

**Melbourne Genomics**
Health Alliance

*Global knowledge. Individual care.*

## Opening Night

The symposium was officially opened on the Friday evening by Parliamentary Secretary for Medical Research, Mr Frank McGuire MP, at an elegant and intimate event at Crown Hotel. Dr Lucy Fox was the master of ceremonies for the welcome program, and guests were treated to an exceptional 'Meet the Expert' panel with our international guests, compered by Dr

Piers Blombery. Dr Blombery asked a series of questions that prompted wonderful insight, a little humour, and remarkable wisdom from our international guests, despite having landed in Australia only hours earlier. The evening was closed by Ms Georgie Crozier MLC, Shadow Minister for Health, Shadow Minister for Ambulance Services and Deputy Leader of the Opposition in the Council.

## Scientific Content

Saturday and Sunday delivered 22 scientific presentations, including dedicated case study discussions, over a one-and-a-half-day program that incorporated all aspects of both acquired and inherited Bone Marrow Failure Syndromes. Professor David Ritchie, Director of the CRE in Bone Marrow Biology, chaired the opening session, welcoming the ground-breaking gathering of bone marrow failure expertise into a single room. Professor Ritchie provided detail of the CRE's strategic objectives, and emphasised the overarching goal to provide a critical synchronisation of all current and future research opportunities, and to accelerate and amplify research outcomes.

Left to right: Professor Akiko Shimamura, Dr Austin Kulasekararaj, Dr Lucy Fox, Professor David Ritchie and Dr Simonne Neil

Professor Shimamura delivered three outstanding lectures focussed on inherited BMFS: **Bone Marrow Failure – progress and challenges, Bone Marrow Failure and MDS, and Challenges for clinical research on rare diseases ( including the Metformin Study for FA and the North American Paediatric Aplastic Anaemia Consortium).** Professor Shimamura emphasised the importance of registries and consortia to facilitate the collection and curation of patient clinical data and research specimens. She also stressed the necessity to forge partnerships and nurture both national and international collaborations in the context of rare disease, warmly encouraging the involvement of Australian sites in international clinical trials.

Dr Kulasekararaj presented two impressive lectures concentrating on acquired BMFS: **Clinical aspects of Idiopathic Aplastic Anaemia – pathophysiology, current diagnostic strategies, prognostic indicators and treatments and Paroxysmal Nocturnal Haemoglobinuria clones in BMF patients, and recent developments including ravulizumab.** Dr Kulasekararaj enthralled the audience on Sunday morning with an excited report of his first ever visit to the Melbourne Cricket Ground and AFL game the previous night (enormous thanks to Joe Riewoldt for organising and hosting), and even managed to feature the persistent MCG seagulls in his presentation – surely a world first!

The program featured oral or abstract presentations from all Maddie's Vision grantees, and reflected the diversity and breadth of research being currently supported by the overarching strategic aims of the CRE, within the 5 Pillars of Research identified as necessary to enhance understanding of bone marrow biology. The opportunity to hear from young investigators with obvious passion, enthusiasm and intelligence provided appreciation for the remarkable work, at the forefront of scientific endeavour, currently being performed nationally.

## Closing Panel

The scientific program concluded with a panel Q&A, hosted by Professor Ritchie and comprising Professor Shimamura, Dr Kulasekararaj, Maddie's Vision CEO Nicky Long, Dr Wayne Crismani – Senior Research Fellow at St Vincent's Institute of Medical Research, and Ms Jessica Bond OAM – Executive Director of the Captain Courageous Foundation.


Dr Lucy Fox, master of ceremonies, at the official opening welcome event.



The panel considered areas of unmet need and barriers to progression. The discussion was both lively and perceptive, and contributions from a variety of stakeholders bestowed multi-dimensional input on how to optimise collaboration amongst clinicians and scientists, how to ensure adequate infrastructure is secured (registries and biobanks), how to prioritise clinical trials, and how to ensure sustainable funding.

The inaugural Symposium was an overwhelmingly successful educational and networking event, promoting our CRE for national and international collaboration, and providing evidence and reassurance that with ongoing financial support from Maddie's Vision and co-ordination by the CRE, Australia is phenomenally placed to lead the world in BMFS research.


Scientific Symposium audience

Scientific Symposium, Maddie's Vision CEO Nicky Long and Professor Akiko Shimamura in the audience

## Thanks to Steering Committee and Organising Committee

Gratitude is extended to Dr Lucy Fox, chair of the Symposium Steering Committee. Members of the Steering Committee were Professor David Ritchie, Professor Erica Wood, Dr Anthea Greenway, Dr Pasquale Barbaro, Dr Piers Blombery, Dr Simonne Neil, Nicky Long and Maggie Lynch. The Organising Committee worked diligently to ensure the weekend ran smoothly and much appreciation is proffered to Dr Simonne Neil (chair), Lou Johns, Annabel Banks, Elizabeth Zamanis-Robinson and Maggie Lynch. We also are extremely grateful to the sponsors - Melbourne Genomic Health Alliance, Amgen, MSD, Crown, Jigsaw Travel and Carman's.

# Second National Symposium on Bone Marrow Failure Syndromes

The second National Symposium on Bone Marrow Failure Syndromes was scheduled to take place in 2020, but due to the COVID-19 pandemic, will proceed in May, 2021. In addition to an impressive program of presentations from Australasian clinicians and researchers, we look forward to welcoming two exceptional international guest speakers, Professor Neal Young and Associate Professor Alison Bertuch, who have both contributed to the field of Bone Marrow Failure Syndromes in extraordinary ways.

## Professor Neal Young, Chief, Haematology Branch National Heart, Lung and Blood Institute, National Institutes of Health (NIH), Bethesda, Maryland.

Neal S Young, MD, is Chief of the Hematology Branch of the National Heart, Lung and Blood Institute, and a world expert in the study of bone marrow failure. His clinical and research interests include Aplastic Anaemia, telomeropathies and other inherited Bone Marrow Failure Syndromes, myelodysplastic syndromes, paroxysmal nocturnal hemoglobinuria, and parvovirus B19. His scientific investigations have spanned basic science and translational research, epidemiology and molecular biology, and especially pivotal clinical treatment protocols. His work has led to understanding the pathophysiology of Aplastic Anaemia as immune-mediated and the development of effective immunotherapy that has dramatically improved survival in this devastating disease. Most recently, his group has discovered that eltrombopag can stimulate haematopoietic stem cells in bone marrow failure and that danazol is both effective in the treatment of telomeropathies and elongates telomeres. During the course of his career, he has trained over 100 postdoctoral and clinical fellows and mentored many junior faculty members. He has published over 500 original research articles, reviews, book chapters, and monographs.

Professor Neal Young

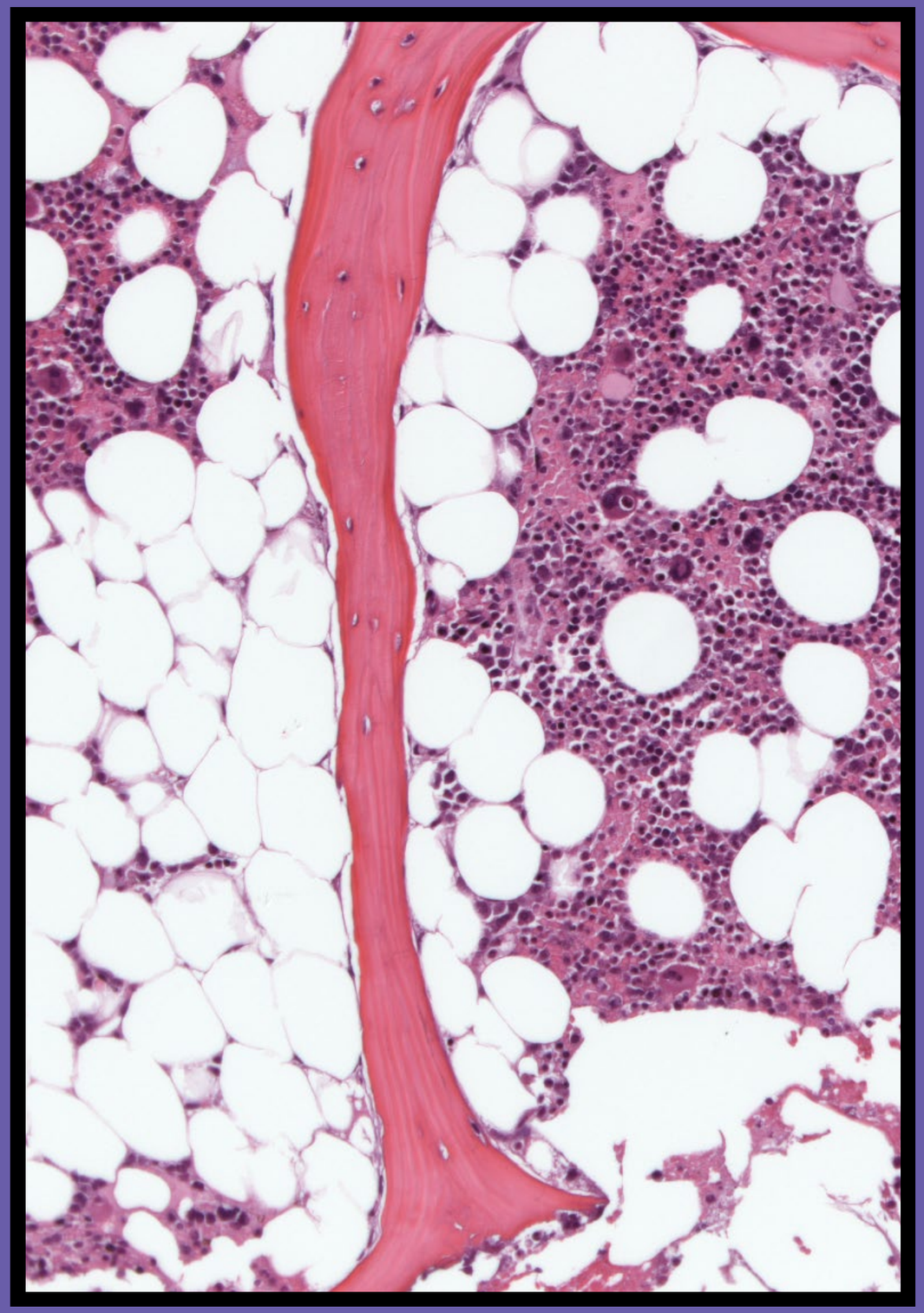
## Dr Alison Bertuch, Associate Professor, Department of Paediatrics, Haematology/Oncology Section, Department of Molecular & Human Genetics, Huffington Centre on Aging and Director, Bone Marrow Failure Program, Texas Children's Cancer and Haematology Centres, Texas Children's Hospital.

Dr Bertuch is the director of the Bone Marrow Failure Program at Texas Children's Hospital, the largest children's hospital and among the top-ranked paediatric hematology/oncology centres in the United States. She is also Associate Professor of Paediatric Hematology/Oncology and Molecular & Human Genetics at Baylor College of Medicine.

She has a long-standing interest in telomere biology and her research contributions have spanned from the basic science of telomeres to translational and clinical studies on the telomere biology disorders, such as the bone marrow failure predisposition syndrome dyskeratosis congenita. She is particularly interested in the complexity of the molecular genetics underlying these disorders.

Dr Bertuch has served in several leadership roles including as a Co-leader of the Clinical Care Consortium for Telomere Associated Ailments, as an inaugural Executive Committee member of the North American Paediatric Aplastic Anaemia Consortium, and recent Chairperson of the American Society of Hematology Scientific Committee on Bone Marrow Failure. She is on the Medical Advisory Board of Team Telomere and the Scientific Advisory Board of the Shwachman-Diamond Syndrome Registry. She has received several honours including election to the American Society for Clinical Investigation and the American Paediatric Society.

Associate Professor Alison Bertuch



# Project Reports

# 4.

# The Aplastic Anaemia and other Bone Marrow Failure Syndromes Registry

2015 Ongoing

Registry Steering Committee Members L to R Professor Frank Firkin (chair), Professor Jeff Szer, Associate Professor Merrole Cole-Sinclair, Professor Erica Wood and Dr Lucy Fox

The Australian Aplastic Anaemia and other Bone Marrow Failure Syndromes Registry (AAR) was established to capture the epidemiology, current treatment and clinical outcomes of these important but rare Bone Marrow Failure Syndromes (BMFS).

Most patients with Aplastic Anaemia (AA) develop anaemia, bleeding (due to low platelet counts) and infections, which can be life-threatening. Usual treatment includes immunosuppressive therapy (IST), with haematopoietic stem cell transplantation (HSCT) an option for some (usually younger) patients. Many patients depend on ongoing transfusion support, with red blood cells and platelets, as well as measures to prevent and manage infection.

AA is a diagnosis of exclusion and can be confused with other acquired and inherited BMFS (IBMFS) which can mimic the presentation of AA. Both AA and IBMFS are rare conditions but are increasingly recognised as distinct entities, especially now with greater access to molecular diagnostics.

## Why do we need a registry for these conditions?

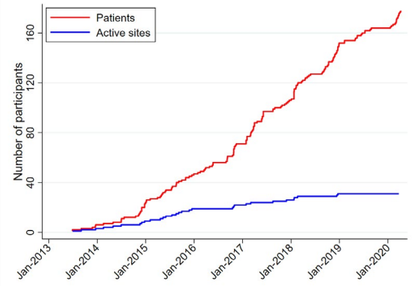
The absence of coordinated data collection has created barriers to comprehensive research, at national and international levels. Conducting clinical trials is difficult due to the rarity of the conditions, so registries play important roles in understanding the clinical journey and long-term outcomes of patients with BMFS. Currently, few Australian data are available on the incidence, treatment or clinical outcomes of acquired AA and IBMFS.

## What is the AAR doing?

The AAR was first established as the Aplastic Anaemia Registry in 2013 to address these evidence gaps. The registry collects data on adult and paediatric patients with AA. Excitingly, from 2020, the registry has been expanded and now collects data on other BMFS, including IBMFS. The project is overseen by a national Steering Committee of clinical and registry experts, chaired by Professor Frank Firkin of St Vincent's Hospital Melbourne, and managed by the Transfusion Research Unit in the School of Public Health and Preventive Medicine at Monash University, which is noted for its registry expertise.

The AAR now has 39 paediatric and adult sites participating across Australia, and to date approximately 180 patients, with a range of diagnoses, have joined the registry. As patients are enrolled and follow-up data accrue, the registry will be able to provide a better picture of the natural history of both AA and inherited BMFS. Information is collected following diagnosis, at six months and then annually. Data are collected onto a secure, web-based data collection form designed specifically for this research. It records data for each patient in the following categories:

- Demographic details (including ethnicity)
- Clinical context including possible precipitants
- Family history (including IBMFS)
- Clinical presentation
- Laboratory test results at initial presentation and during follow-up
- Therapy (details of IST, HSCT, and supportive therapy)
- Clinical outcomes including details of any relapse, complications (of therapy or condition), performance status indicators and disease progression.




Recruitment of participating hospitals and patients to the AAR. The graph demonstrates that once a critical number of key sites are recruited, patient recruitment can follow – these are both vital for research in rare conditions.

Data on each patient are entered at multiple time-points over a period of years, to allow monitoring of changes in treatment and outcomes over time and will provide vital long-term outcome data for these important conditions.

## Registries can serve as platforms to support a wide range of research

Better treatments for BMFS are urgently needed. Registries offer clinical networks and infrastructure to efficiently conduct observational and interventional clinical research, and importantly to monitor changes in clinical practice, including the uptake of new therapies and use of clinical guidelines.[1] Monash University's registries are currently being used for a number of clinical trials and other research projects in a range of blood disorders.[2]

Leveraging the AAR's national clinical network and infrastructure, the DIAAMOND-Ava clinical trial, Diagnosis of Aplastic Anaemia, Management and Outcomes utilising a National Dataset, was recently opened, an interventional clinical trial of a second-generation thrombopoietin-receptor agonist, avatrombopag in both upfront (treatment-naïve) and relapsed/refractory AA. Importantly, this is the first trial of a new therapy in this condition to be conducted in Australia for some decades. The trial is funded by Federal Government's Medical Research Future Fund. Eight hospitals have so far opened to recruitment, with more in the process of joining, and 13 patients have already been enrolled to the trials.

Registry data and activities have been highlighted during 2019 in a poster presentation at the annual "BLOOD" conference in 2019, and a review article for the Internal Medicine Journal – the journal of the Royal Australasian College of Physicians, to reach a national clinical audience.[3,4]

## How you can help

If you are a patient, please consider joining the AAR. Your information is vital to help paint a picture of BMFS across Australia. Your data will be held securely and confidentially by Monash University.

If you are a treating clinician, please discuss the AAR with your patients and families and encourage them to participate.

If you have an idea for a research project using the AAR, or if you are an individual or organisation who can support the AAR with funding or other resources, please get in touch:

**AAR: AAR@monash.edu**
**DIAAMOND trial: sphpm.diaamond@monash.edu**

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# Towards targeted treatments for Fanconi Anaemia

Dr Wayne Crismani

Fellowship 2016 - 2019 / Grant-in-Aid 2017 - 2019

Dr Wayne Crismani

Dr Wayne Crismani from the St Vincent's Institute (SVI) of Medical Research is undertaking research focussed on dissecting the molecular biology of an inherited Bone Marrow Failure Syndrome and cancer predisposing condition called Fanconi Anaemia. In the 1990s, the life expectancy of a patient with Fanconi Anaemia was horrifically less than 10 years of age. Thankfully, with advances in all fields of science, the current life expectancy of an individual with Fanconi Anaemia has improved and is approximately 35 years, but this statistic is still appalling. Dr Crismani emphasises, "There is no cure for Fanconi Anaemia, nor are there targeted treatments that address the root cause of the condition. The scientific gains have come from flow on effects in other fields. We investigate the fundamental biology of what goes wrong in Fanconi Anaemia and we are working towards translating this fundamental knowledge to effective treatments and early detection."

The SVI laboratory is made up of diverse people, generally in their 20s or 30s, with a range of skills - biochemists, biologists, data scientists and a nurse. It requires great expertise to work in a high standard of molecular biology today and collaborations are imperative, both nationally and internationally. Dr Crismani's team has a number of projects underway that include drug development, genetic studies with individuals with FA, early detection of cancer and fertility studies. While these projects may seem diverse, they all stem from the root cause of Fanconi Anaemia which is what is referred to as "genomic instability". Dr Crismani's team use multi-disciplinary approaches with a variety of methods including biochemistry, cell culture, mouse models, whole genome sequencing and epidemiology.

The research covers a number of stages in the research pipeline, "We ask many fundamental scientific questions, but we also have projects that are clinical and can result in the early detection of a cancer. There is a lot that needs to be done. Some areas that I see a need for include early and accurate detection of genetic conditions. A lot of genetic testing is currently being performed, but more investment is required in the laboratories that can provide validation of the results and the predictions that come out of these reports. I also feel that we are now in a position to develop targeted treatments including specific pharmaceutical products and also gene therapy. Gene editing with CRISPR/Cas9 technology is the discovery of a generation for molecular biologists. It offers the realistic chance of altering genetic mutations that cause disease to alleviate or prevent serious health conditions. These are just a few examples. It is extremely important that more money is directed towards basic and applied research."

Dr Crismani wishes to make a meaningful difference. "I think that the area that I am in makes the best use of my skills, and those of my team, to help individuals who truly need it. Our research will lead to early and accurate detection of serious health conditions. I do not want to give false hope as the roads to cures are long and very challenging. But we work hard towards creating transformative treatments for people affected by conditions such as Fanconi Anaemia."

One of the major barriers to researchers according to Dr Crismani is the severe lack of available funding. "The current prospects for a bone marrow failure researcher, and all academic scientists, is that their contracts are short, and their futures are uncertain. It is understandably tempting to leave for greener pastures in a completely different area of society where they can have a stable job, have a family and a mortgage. The answer seems so simple: put more money into research. In reality this is very hard to achieve but a number of countries do this simply by pledging a far superior amount of their gross domestic product to research. Unfortunately, Australia is below average for OECD countries and investment in science."

Dr Crismani is originally from Adelaide and attended university in South Australia. He has lived in a number of countries for his scientific career and spends most of his free time with his young family, enjoying traveling locally and abroad whenever possible. Dr Crismani has been extraordinarily generous devoting energy and time to Maddie's Vision; he is a current member of the 2021 National Symposium Steering Committee, and has recently taken on the role of chairing the Gene and Cellular Therapies Subcommittee. He has also been instrumental in securing funding from the US based Fanconi Anaemia Research Foundation to assist with establishing Fanconi Anaemia Support Australasia, a membership-driven volunteer organisation which aims to unite and inform the FA community in Australia and New Zealand.

# Identification of miRNA biomarkers predictive of clinical outcomes in AA/MDS

Dr Lynette Chee

Grant-in-Aid 2016 - 2018

Dr Lynette Chee

The Royal Melbourne Hospital

Dr Lynette Chee's research is conducted at the Australian Cancer Research Foundation (ACRF) Translational Laboratory at The Royal Melbourne Hospital, and specifically focusses on the role microRNAs, non-coding molecules that can affect gene expression, play in treatment responses and disease progression in Aplastic Anaemia (AA). Aplastic Anaemia has an incidence of 2-4 per million / year and although two-thirds of patients respond to current treatments, about one-third of responders will experience disease recurrence. Approximately 10-15% of patients with AA progress to myelodysplasia (MDS) and acute myeloid leukaemia (AML). MicroRNAs have been shown to correlate with clinical outcomes in MDS and AML.

Interestingly, in Dr Chee's exploratory cohort, she discovered that AA patients who had progressed to MDS/AML had a similar microRNA expression profile to patients who develop MDS without prior AA. In addition, specific microRNAs at diagnosis and post-treatment were associated with disease progression and treatment response. These findings now need to be validated in a larger cohort of patients and will have implications for identifying mechanisms underlying inferior treatment outcomes in AA and how we can improve these outcomes by targeting these specific pathways.

Dr Chee is particularly fascinated by the way the field of haematology led the way in the concept of 'targeted therapies' with the discovery of tyrosine kinase inhibitors, which specifically target the dysfunctional protein that results from the abnormal fusion gene responsible for the blood cancer chronic myeloid leukaemia. She explains "Following completion of my specialist training in haematology, the development of 'targeted therapies' piqued my interest in pursuing PhD studies in investigating novel retinoid treatments in acute myeloid leukaemia. As we unravel and understand more about the genetics and molecular mechanisms underpinning AA and related haematological malignancies, we can aim to discover novel ways of targeting aberrant pathways to improve efficacy of current treatments while reducing off-target side effects from the treatment."

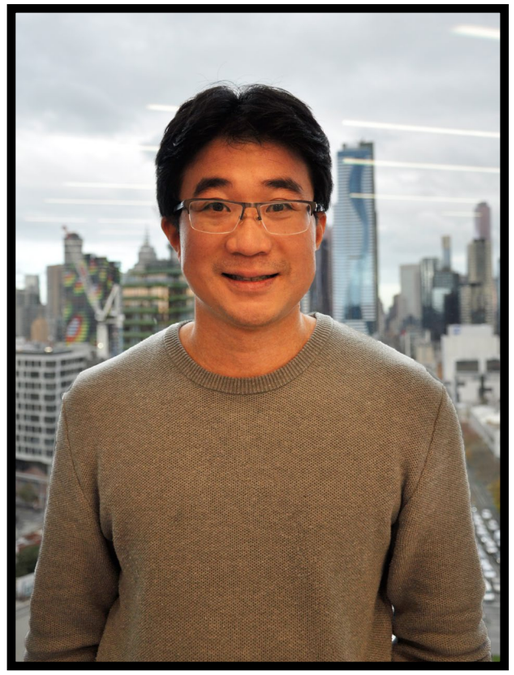
# Genome editing of haematopoietic stem and progenitor cells to uncover novel therapeutics for Aplastic Anaemia and other Bone Marrow Failure Syndromes.

Dr Yih-Chih Chan

Flavorite Fellowship 2017 - 2020

Dr Yih Chih Chan is a senior postdoctoral researcher at the Peter MacCallum Cancer Centre with expertise in both laboratory research and computational biology. He completed his PhD at the University of Auckland, NZ, in Molecular Medicine and Pathology, investigating regulation of immune cells in inflammatory diseases. Following his PhD, he took up a postdoctoral fellow at King's College London, UK, studying the role of the immune system in a non-allergic subtype of asthma. For the past 5 years, he has been working in Professor Mark Dawson's group at the Peter MacCallum Cancer Centre, focussing on the epigenetic regulation of blood disorders. In 2017, he was awarded the Maddie Riewoldt's Vision Flavorite Fellowship to discover novel therapeutic avenues to treat Bone Marrow Failure Syndromes.

Dr Chan explains, "In Bone Marrow Failure Syndromes, the body is unable to generate certain blood cell types. There are many different types of mature blood cells which are all thought to be derived from blood stem cells through sequential steps, known as differentiation, in a hierarchical manner. One of the main goals of this project is to understand the epigenetic process involved in each step of normal blood development."



Dr Yih Chih Chan

The fascinating area of research that Dr Chan is currently focussed in is epigenetics. Within a single person, every cell, whether it is cells from the skin, eyes, heart or brain, have the exact DNA sequence. Despite the same genetic makeup, all these cells look and function very differently, and this control is termed epigenetics. Epigenetics is the precise control of the genetic sequence, to tell a cell to turn on or off particular genes which in turn affects how a cell behaves and function. Epigenetics research is therefore very complicated, but at the same time very powerful with enormous potential.

By understanding the epigenetic regulators of normal blood development, Dr Chan hopes to discover the main determining factors that generate each specific cell type, and therefore also understand what may have gone wrong in Bone Marrow Failure Syndromes. This understanding will also provide tools to assist with new ways in overcoming this group of diseases.

Dr Chan's project involves both complex bioinformatics analysis and cutting-edge laboratory research techniques. He has isolated different populations of cells that correspond to each main blood cell type and has looked at their gene expression profiles using next generation sequencing. This has enabled his team to compare and find differences in each of the different blood cell types. He has then used a variety of genome editing tools to see if he can control how a cell behaves by turning on or off specific genes. "We are beginning to unravel the complexity of blood development; we have identified key epigenetic genes that are required for long-term blood stem cells and important epigenetic complexes in the different cell types. Using this knowledge, we hope to be able to use the same signals to control cell fate decisions and allow us to direct cells to become a specific blood cell type that is absent in disease. If we can manipulate cell fate at will, this will be an incredibly powerful tool and provide new therapeutic avenues to achieve our ultimate goal of finding a cure."

Dr Chan believes the advances in science and technology in the last decade have been truly amazing. The advent of next generation sequencing technology has provided unprecedented insights into the genetics, gene expression and epigenetic regulation of cells. "This has provided us with a massive amount of information, even from just a single cell!"

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

Dr Piers Blombery

Grant-in-Aid 2017 - 2019

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

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

Dr Piers Blombery

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.

# Bone Marrow Failure Syndromes in Australia: improving diagnosis to inform strategies for better care and outcomes

Dr Lucy Fox

Higher Degree Fellowship (Doctoral Degree Scholarship) 2019 ongoing

Dr Lucy Fox is completing a higher degree focussing on patient outcomes in Bone Marrow Failure Syndromes (BMFS). She is the clinical research fellow at the Australian Aplastic Anaemia and other Bone Marrow Failure Syndromes Registry (AAR) and is working on analysis of the comprehensive dataset housed within the registry as part of her higher degree. She has recently launched a new AAR database and is excited to both expand the scope of the registry and continue collaborative projects, aiming to offer every Australian patient, both paediatric and adult, experiencing both acquired Aplastic Anaemia and inherited Bone Marrow Failure Syndromes the opportunity to participate in this important project. Dr Fox's additional role, as the Bone Marrow Failure Fellow at Peter MacCallum Cancer Centre, focusses on both the inherited and acquired genetic changes that accompany the different BMFS and the way these genetic results can offer diagnostic certainty and also prognostic information to assist with clinical decision making. Her two roles described here are highly complementary and share the common primary goal of improving outcomes for all Australian patients with BMFS.

Dr Fox is intently focussed on the curation of clinical data in order to make significant contributions to clinical decision making and scientific literature. She wishes to follow and document patients over the course of their disease in order to learn about which patients do well and why, and why some patients do poorly. She elaborates, "We have heard from many patients of the comfort that they derive from knowing that their story is not 'lost', and that the particulars of their experience may one day help another family. We strive to develop our relationships with local, interstate and international colleagues so we can discuss the best testing and treatment strategies for patients, including multidisciplinary team discussion of complex cases. The importance of shared learnings and collaboration in this complex, rapidly evolving field cannot be overstated. Ultimately, we want to facilitate enrolment of Australian patients in clinical trials both locally and internationally."

Dr Lucy Fox

Dr Fox's first project in this area was her involvement with the Melbourne Genomics Health Alliance Bone Marrow Failure Flagship at Peter MacCallum Cancer Centre. During this project, she met many patients with BMFS and gained an appreciation of their often long and difficult diagnostic journeys and how these diseases profoundly impact daily life. She became aware of how daunting complex 'genetic' conversations can be and learned how important it was to ensure improvements were instituted to the counselling and everyday support of these patients. "This is a patient group at risk of experiencing very poor outcomes, and we have much to learn in order to improve both the length and the quality of life of BMF patients. These are individually rare and diverse diseases, but share several commonalities in terms of diagnostic strategies and management. It is enormously apparent that outcomes for patients experiencing BMFS will only be improved by collaborative efforts by researchers and clinicians around the country, and indeed the world. I am grateful for the opportunities afforded by Maddie's Vision which have permitted me to engage with interested BMF researchers both nationally and internationally."

Dr Fox's commitment to the Maddie's Vision mission is impressive, extending her professional energy beyond her core research to a myriad of other Maddie's Vision activities. In 2019, she expertly chaired the Steering Committee of Australia's inaugural National Symposium, was a poised master of ceremonies at the welcome event, and presented multiple times over the one and half day scientific program. In 2020, she has agreed to chair the Steering Committee for the second National Symposium (postponed till May 2021), and is chairing the subcommittee for the first ever Maddie's Vision Patient and Family Forum, a virtual event scheduled for August 28, 2020. She is often a warm and lively face in the crowd at Maddie's Vision fundraising events, including in 2019 the Bloody Good Dinner and Purple Ladies Lunch. Dr Fox has been instrumental in a deliberate and focussed effort to open an Australian site for the Pilot Study of Metformin in Fanconi Anaemia trial conducted at the Boston Children's Hospital, and was the successful recipient of the opportunity to present the Maddie Riewoldt's Vision lecture at the 10th International Congress on Shwachman Diamond Syndromes in Cambridge (now rescheduled to March 2021). Maddie Riewoldt's Vision is delighted to be supporting her Higher Degree Fellowship.

# Influences of clonal haematopoiesis in allogeneic bone marrow transplantation

Dr Paul Yeh / Professor Mark Dawson

Grant-in-Aid 2018 ongoing
Co-funded with the Snowdome Foundation

Dr Dr Paul Yeh

Dr Paul Yeh's research focusses on using genetic testing to study clonal haematopoiesis (CH) and how it influences therapies in bone marrow failure. CH is a phenomenon that occurs when a genetic mutation is acquired in the haematopoietic (blood forming) stem cells of healthy individuals. At least 10-15% of 'healthy' people over 60 years of age have CH, and presence indicates increased risk of developing haematological malignancies and also Bone Marrow Failure Syndromes, as well as an increased risk of heart disease, stroke and death from other cancers. The first stage of Dr Yeh's research has used highly sensitive and targeted genetic sequencing to determine if CH influences bone marrow transplant outcomes.

"Bone marrow transplantation is one of the only potential curative strategies for Bone Marrow Failure Syndromes. However, the procedure carries a significant risk of death. Also, transplant resources are extremely precious and there is a need to find better ways of improving transplant outcomes. I am using sophisticated genetic sequencing techniques to look for CH in stem cell transplant donors. I will then look to see if the presence of CH can predict the outcome of the stem cell transplant."

The first part of Dr Yeh's research focussed on CH and stem cell transplantation. Importantly, CH itself can be part of, or can evolve to, Bone Marrow Failure Syndromes. Not all individuals with CH will develop or progress, and it is not precisely understood how CH leads to bone marrow failure. The next steps of his research are to explore these unanswered questions, ultimately creating a better biological understanding of how CH evolves into bone marrow failure. Much of the genetic testing component of the research has already been completed and Dr Yeh is now focussed on how this has affected stem cell transplantation. There is a large amount of data that has been generated via the genomic sequencing of samples, which requires analysis and integration with carefully curated clinical transplant databases.

Dr Yeh is the recipient of a prestigious National Health and Medical Research Council Investigator Grant, Medical Research Future Fund Priority Round 2020. As his mentor and supervisor Professor Mark Dawson commented "Paul is definitely one of our finest next generation clinician-scientists, and we are very proud of him." Maddie's Vision and Snowdome similarly share this pride as he toils to discover factors that can predict transplant outcomes, significantly impacting on the lives of patients with Bone Marrow Failure Syndromes by both improving outcomes and also providing better allocation of valuable transplant resources.

# Functional evaluation of candidate genes and mutations that cause failure of bone marrow neutrophil production

Professor Graham Lieschke

Grant-in-Aid 2018 ongoing

White blood cells come in many shapes and types. A failure to make white blood cells leads to the recurrent infections that are problematic for Bone Marrow Failure Syndrome patients. Professor Graham Lieschke, from Monash University's Australian Medicine Regenerative Institute, is particularly interested in phagocytes, the white cells that repair tissue damage and fight infection. Professor Lieschke elaborates, "Phagocytes perform the process of phagocytosis – cleaning up debris and foreign invaders by engulfing them - gobbling them up. We study how the two types of phagocytes, neutrophils and macrophages, form during embryonic development, function to do their job, and how their supply is maintained through life."

Fascinatingly, the animal model system Professor Lieschke's laboratory uses is the zebrafish. Zebrafish are small tropical fish native to South East Asia, approximately 2.5 – 4 cm long. Zebrafish have similar white blood cells to humans, possess conserved genetic and molecular regulatory pathways, and as they are transparent, are exceptionally good at providing high resolution imaging in living tissues. Zebrafish genetics provides a tool for studying the regulation of white blood production.

Professor Lieschke's project has enabled the exploration of the consequence of mutations in genes identified in patients with white blood cell development problems. For a selected number of gene changes, he is trying to answer the question: are these just incidental findings, or are these genetic mutations actually the cause of the patient's problems with white blood cell development? With advances in sequencing whole genomes, that is all the DNA encoded in an individual's genes, clinicians and scientists are now aware of the enormous genetic variation in humans. Understanding functional consequences of each particular variant is one of the great challenges. Professor Lieschke is chipping away at this, one variant at a time, for a selection that are strong candidates to be important in particular patients and their families. "It would be great if there wasn't such a bottle neck," he laments. "Current methods including ours are research-intensive and very focussed on individual variants. Ultimately, a functional proof of disease-causation is needed to supplant a presumption of involvement. As the database of genetic mutations that are causative of disease accumulates, predictions based on prior information will become more and more accurate."

Professor Lieschke's work is vitally important, "Knowing that a genetic change is the cause of the problem provides diagnostic precision for patients and their families, and opens the path to rational design of curative genetic and/or pharmacological approaches."

Professor Lieschke's career spans an amazing period in clinical haematology, from first knowing about blood cell growth factors as just an activity in a laboratory dish (his Bachelor of Medical Science BMedSci project) through to standing at the bedside of some of the first patients to receive them as drugs (as a Clinical Research Fellow), and then seeing their use become routine for supporting white blood cell counts as treatment of some forms of bone marrow failure and during cancer chemotherapy delivery. He is a Melbourne University BMedSci and Medicine graduate, and undertook his specialist clinical training in Parkville. His post-doctoral training took him to Boston and New York, but otherwise he has devoted his professional life to working in Melbourne hospitals and institutes. His free time interest is rather quirky though – he possesses a mad passion for the organ and choral music of J.S. Bach and is an outstanding pipe organist and conductor.

Professor Graham Lieschke

Central to the work being undertaken in the Lieschke laboratory is the brilliant mind of Dr Vahid Pazhakh, who performs the genetic work that is at the core of the Maddie's Vision funded project. Dr Pazhakh obtained his PhD from Monash in the Lieschke laboratory as an international student, and is now here to stay in Australia. In 2020, a Master of Biotechnology student, Lingge Tu, is also working on the zebrafish genetics and helping to score the blood cell numbers in the experiments that disrupt the genes of interest. It is rather remarkable to conceive that the humble zebrafish, a small and robust creature, is assisting in unlocking the answers of Bone Marrow Failure Syndromes!

# Identifying therapeutics which can be repurposed for the treatment of Myelodysplastic Syndrome and other Bone Marrow Failure Disorders

Dr Amee George

Grant-in-Aid 2018 ongoing

Australian National University

Dr Amee George is situated at the Australian National University, Canberra. Her specific research interest is understanding the molecular basis of bone marrow failure (BMF) disorders, in particular, rare congenital BMF disorders such as Diamond-Blackfan Anaemia (DBA), as well as myelodysplastic syndrome (MDS), with a view to finding alternative treatment strategies.

The identification, discovery and development of drugs can be a long process. Dr George is utilising high-throughput screening technologies, which include cutting-edge robotics and instrumentation, to screen many thousands of known drugs and gene candidates simultaneously and rapidly. Conducting these screens provides lists of potential drugs and genes which influence the biology of the disease. Possible candidates are further tested in preclinical models of BMF diseases. The final steps aim to move appropriate candidates that pass pre-clinical validation into clinical trials to assess how effective they are in patients, hopefully providing further therapeutic options for patients

Dr George has completed screens for DBA, and is currently conducting screens for MDS. She explains "It takes quite a bit of time to optimise screening experiments first before we venture into conducting the full large-scale screens. Ironically, the actual screens themselves are usually the quickest part! Whilst bone marrow transplantation is currently the only definitive cure, not all patients have this option, and alternative therapeutic options are limited. Our research aims to identify therapeutics that could be used for the treatment of these diseases, potentially reducing the burden of disease and enhancing quality of life."

Dr George became interested in BMF research in 2013, when she met an extraordinary family in Australia whose child was diagnosed with DBA. The family had set up a foundation, the Captain Courageous Foundation, to raise research funding to identify new therapies to treat DBA. She elaborates. "After hearing their story, and the medical treatments their young child had to endure, it immediately inspired me to work in this area, aware that the research I was undertaking could make a difference. Since then, I have met many other incredible families (including the Riewoldt family) who are passionate advocates for research and are a continuous source of inspiration; this along with my interest in understanding the molecular basis of these diseases drives me to continue working in this field."

Dr George believes that one of the greatest challenges faced by researchers in the field is access to funding for 'high risk' projects. "Whilst there are always obstacles to obtaining adequate patient samples, by far the most difficult problem faced by those working in an academic setting is obtaining research funding from traditional sources for 'blue-sky' discovery projects – particularly screening projects - because these approaches can be seen as too risky. I remind myself of the Thomas Jefferson quote, "With great risk comes great reward" and the potential to identify the next drug or next cure will likely come from taking these calculated risks. Therefore, many of us rely on funds from foundations such as Maddie Riewoldt's Vision in order to continue this vital and potentially ground breaking research into BMF."

Dr George completed her BSc (Hons) and then went on to complete a PhD within the Faculty of Medicine, Dentistry and Health at the University of Melbourne in 2007. She has worked across multiple research

Dr Amee George in the laboratory at the Australian National University

institutions (University of Melbourne, University of Queensland, Peter MacCallum Cancer Centre) before moving to the Australian National University in Canberra in 2015. As an academic, she works within Professor Ross Hannan's team at the John Curtin School of Medical Research. She also leads a small team which manages the ANU Centre for Therapeutic Discovery, a purpose built high-throughput screening facility. Within the Hannan laboratory, research focusses on the process of making ribosomes, the protein factories contained within cells. This process is called ribosome biogenesis. The laboratory is specifically researching avenues for how to target ribosome biogenesis for the treatment of cancer and other diseases including ribosomopathies and BMFS disorders. Intriguingly, while these diseases are different and present differently in patients, there are common elements. Much of the work performed in the laboratory helps to piece together the molecular puzzle across a number of disease types.

Outside of research, she enjoys photography, baking, coaching her daughters' basketball team and of course, being from Victoria, loves watching the footy!

ACTD Cabinet

# Using induced pluripotent stem cells to find causes and cures for bone marrow failure in children and young adults

Professor Andrew Elefanty

Grant-in-Aid 2018 ongoing

murdoch children's research institute

The work of Professor Elefanty's project represents a collaborative effort between three laboratories at the Murdoch Children's Research Institute; the Blood Development (Andrew Elefanty and Elizabeth Ng) and Immune Development laboratories (Ed Stanley), who have worked together on the blood differentiation and genetic manipulation of human pluripotent stem cells for 18 years, and the Translational Bioinformatics group, headed by Cas Simons, who have the necessary expertise in analysis of genomic sequencing that is required to complement cell and molecular biology skills.

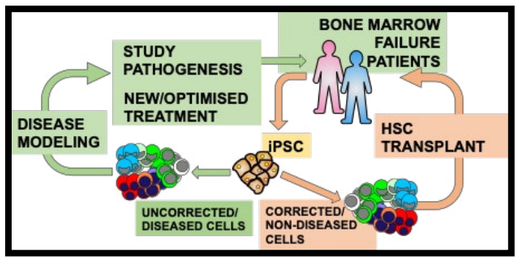
Bone marrow failure is not one disease, but a complex mixture of many disorders that have a similar end point– the inability of the bone marrow to make sufficient blood cells. In some cases, there are mutations in genes that are required for normal blood formation, but in many other instances the cause is not known, and it appears that the immune system functions abnormally and attacks the body's own blood cells.

Professor Elefanty's research aims to explore the causes of bone marrow failure, and therefore to discover new approaches to treatment and cure. His team is comparing the blood forming ability of stem cell lines made from patients with bone marrow failure with lines made from their unaffected relatives. These stem lines are made from bone marrow samples harvested at diagnosis from young patients with bone marrow failure and also from blood samples given by their parents, who serve as 'controls' against which the patients samples can be compared.

The bone marrow or blood cells from patients and their parents are first turned into stem cells – called induced pluripotent stem cells, or iPSCs – using a Nobel Prize-winning genetic 'trick' involving the transient, enforced expression of four genes. The process takes about a month, leading to the generation in the laboratory of normal cell lines that are immortal, can be cryopreserved and thawed as required, and can be directed to turn into any cell type in the body, including new blood cells (a process called 'differentiation'). Professor Elefanty explains, "For many years our laboratories have been studying the process of differentiating iPSC into blood stem cells, and we have become progressively more proficient as we understand more about the process. For example, we can now make blood cells from iPSC that resemble the blood cells made during human development – they express the same genes and the cells display similar functions, in some cases including an ability to engraft into the bone marrow of laboratory mice."

This extraordinary progress has enabled Professor Elefanty's laboratory team to perform similar differentiations and analyses on blood cells made from the iPSCs of patients with bone marrow failure. These analyses will include sequencing the genomes of these patients and their relatives to determine whether there are differences in the patient's genes that might explain their inability to robustly make sufficient blood cells. In cases in which genetic abnormalities are found, his team are aiming to determine how this causes the bone marrow to fail, and how to treat or cure the problem. "Eventually, we would like to use our skills in genetic manipulation to 'correct' the genetic problem in the patient iPSCs, and therefore to be able to make non-diseased blood cells to transplant back into these patients."

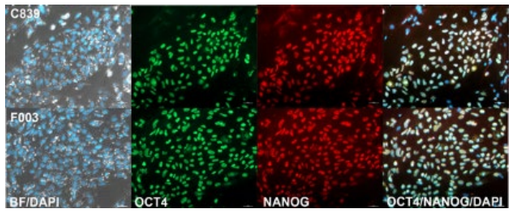
Professor Andrew Elefanty




Applications of patient iPSCs in the study and treatment of Bone Marrow Failure. Correction of underlying mutations or use of non-diseased iPSCs followed by differentiation produces blood stem cell (HSCs) for replacement cell therapy. Diseased iPSC cells facilitate study of pathogenesis and enable screening for new therapies.

For the larger proportion of patients who do not appear to have a genetic abnormality, Professor Elefanty's work will compare the ability of the patient and parent iPSC lines to differentiate into blood cells – to determine whether the patient samples are intrinsically poor at making blood cells, or whether they are normally fine, and some secondary event (an abnormality in immune cell function, for example) was to blame for their bone marrow failure. This information will be most important, since it is not clear whether there is a problem in blood formation in patients with bone marrow failure even when there is not a clearly identified genetic abnormality.

Currently, iPSC lines from 6 patients with bone marrow




Immunostaining of iPSC lines derived from patient (C839) and parent (F003), showing robust expression of the pluripotency genes OCT4 and NANOG.

DNA samples for patients and their parents for sequencing studies to identify genetic abnormalities are also being performed, and studies to determine whether these patient iPSCs differentiate normally into blood cells or whether this function is impaired are underway. The information generated from the blood forming studies with the results from the DNA sequencing will then be correlated for analysis.

Professor Elefanty's work excitingly contributes to two areas of research and therapy for patients with bone marrow failure. Firstly, the ability to differentiate stem cells enables the study of abnormalities in blood formation in these patients, and subsequently to trial various therapies on cells in the laboratory before they are used in patients. Secondly, if genetic abnormalities can be identified in some patients, there is potential to correct these defects and then generate sources of blood cells in the laboratory that could be used as a transplantation therapy for these patients. These options are shown schematically in the figure, and offer incredible hope in achieving the Maddie's Vision mission.

# Functional interrogation of loci associated with the regulation of haematopoiesis

Dr Kirsten Fairfax

Alex Gadomski Fellowship 2019 ongoing

Dr Kirsten Fairfax is the recipient of the Alex Gadomski Fellowship, and undertakes her work at the Menzies Institute for Medical Research, University of Tasmania, Hobart. Her main area of interest is to try to understand if there are new drug targets that can be found for Bone Marrow Failure Syndromes (BMFS). She is achieving this by studying how the genetic code of each individual changes the way their blood cells develop and is using an exciting new technology called single cell RNA sequencing where the genes in every single cell are individually studied. So far, she has examined over one million cells from blood samples and collected bone marrow samples from 72 individuals to map the developing blood stem cells.

Dr Fairfax expands, “The blood forming stem cells, known as haematopoietic stem cells, that reside in the bone marrow are truly extraordinary. The stem cells are capable of generating in a healthy adult approximately 600 billion cells per day! These cells are composed of red blood cells, which carry oxygen around the body, platelets which are important for clotting the blood, and white blood cells which fight infection. Bone Marrow Failure Syndrome occurs when the bone marrow stem cells are no longer able to generate the cells of the blood that we need to lead a healthy life. By studying how the genetic code of each person impacts on blood cell development, we will find ways to alleviate the defects in patients with BMFS and additionally, will uncover novel genetic mutations that are causative of Bone Marrow Failure.”

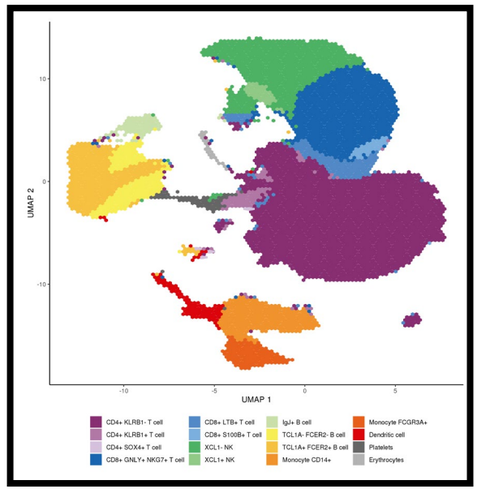
Dr Fairfax and her team are using gene technology to use the information generated from analysing specific sections of the genetic code to change the way stem cells behave when they are grown in a laboratory dish. This is the first step in demonstrating what each bit of the genetic code is doing. Whilst the research is currently at an early stage, she is delighted that the bone marrow sample collection is complete and has received confirmation that the genetic material is very high quality. Her team is collaborating with scientists at The Garvan Institute in Sydney, who are generating all the single cell data, and demonstrates a productive association between leading scientists from around Australia to work on a common problem. Additions to the team will be recruited to ensure the information generated will be translated into possible new therapies for patients as quickly as possible.

Dr Fairfax is very excited about the possibilities of gene therapies as cures for BMFS and was instrumental in initiating the Gene and Cellular Therapies Subcommittee of the CRE Executive. “I think gene therapy could really change the face of therapies for BMFS. As they are such a rare group of diseases, and because there are multiple causative genes, it is very difficult to convince biotechnology or pharmaceutical companies to be involved. This means that we need our academic institutes to step into the void and generate the clinical grade therapeutics that are needed to establish the safety profiles for these therapeutics. However, this is quite different to the typical model of science research, and as such it is quite difficult to get funding for. We are currently trying to secure funding to conduct safety testing on some gene therapy products for use in BMFS.”

Dr Fairfax’s background in immune cell development was a perfect fit for the Alex Gadomski Fellowship. “I was approached to consider being involved in the work going on in Tasmania. I like a good challenge and am very passionate about using scientific research to develop new therapeutics, so I think I was a great addition to the project team and was thrilled to become involved. There is an amazing family here in Tasmania, the Gadomski’s, who work together with Maddie Riewoldt’s Vision to fundraise for research into BMFS. The Gadomski’s work tirelessly, not only to fundraise, but also to promote awareness of the need for research into BMFS, so that scientists can deliver new therapeutics for sufferers of these rare diseases. They do this in memory of their beautiful son and brother Alex, in the hope that other families do not tragically lose a child or sibling as they lost Alex.”

Dr Kirsten Fairfax in the laboratory at the Menzies Institute of Medical

Dr Fairfax grew up in Launceston, Tasmania, and kept herself out of trouble as a youngster by exhausting her energy running in the hills and rowing on the Tamar River. Leaving Tasmania at the end of school, she headed to Melbourne on a National Undergraduate Scholarship to study science, majoring in genetics and biochemistry, and then furthered her education with an Honors and PhD at the Walter and Eliza Hall Institute through the University of Melbourne. During this time, she held a Dora Lush Fellowship. Subsequently, she held a NHMRC CJ Martin Fellowship to complete post-doctoral studies in Cambridge and at Monash University. A further appointment at The Walter and Eliza Hall Institute ensued before returning to Tasmania in 2019. She is delighted to call the The Menzies Institute for Medical Research and Hobart her home, and remarks, “Hobart is a not only a fantastic place to do my research but a most fabulous and picturesque location to go running and hiking in the hills!”




A total of 1,300,902 peripheral blood mononuclear cells have been analysed from 981 individuals. Clustering of cell types differentiated CD4 and CD8 T lymphocytic, B lymphocytic and monocytic cell clusters. Each colour represents a cell type from multiple individuals; T cells are in purple and blue, NK cells in green, monocytes are orange and dendritic cells are red.

# Novel immunological assessment of Aplastic Anaemia and post transplant graft dysfunction for the purpose of targeted therapeutic intervention

Dr Ashvind Prabahran

International Travelling Fellowship 2018 ongoing
Co-funded with the Victorian Cancer Agency

In order to understand Dr Ashvind Prabahran's research, one first needs to understand the process of bone marrow transplantation and its role in the treatment of blood diseases. Bone marrow transplantation is a curative procedure for many blood related diseases and is most commonly used in adults for the treatment of blood cancers. It involves the transplantation of bone marrow from a matched donor into a recipient. The bone marrow is the organ involved in producing blood and can be a source of many blood cancers. Transplantation allows for the abnormal bone marrow of a recipient to be replaced. The donor bone marrow will also produce important immune cells. These immune cells will hopefully recognise any recipient cancerous cells as abnormal and remove them from the body. Doctors are able to measure how much of a patient's cells are their own and how many are from their donor through a process called chimerism.

After transplantation, patients can have a reduction in blood cell production, leaving them susceptible to fatigue, bleeding and infection. This can occur despite the blood production being of donor origin. This is a condition called poor graft function, a serious complication of transplantation which carries a high mortality rate, and is the focus of Dr Prabahran's research.

Aplastic Anaemia is a rare condition that occurs due to the body's own immune cells turning against the bone marrow, interfering with the bone marrow's ability to produce blood. Dr Prabahran believes the underlying process that leads to Aplastic Anaemia is the same that leads to poor graft function. As poor graft function is more common than Aplastic Anaemia, it can be utilised as a model to study in more detail the cause of both conditions and assess the effectiveness of different therapies.

Dr Prabahran is undertaking a clinical trial with the purpose of trying to understand more about the interactions between immune cells and the bone marrow which ultimately gives rise to poor graft function. Simultaneously, he is applying a cutting-edge method of analysis, called Nanostring Digital Spatial Profiling, to the bone marrow specimens of patients with poor graft function to identify potential targets for treatment. Using this information, he will undertake further clinical studies to study the effectiveness of new therapies in patients with poor graft function and Aplastic Anaemia. He explains, "In order to demonstrate the effectiveness and safety of a therapy, it needs to be tested in clinical trials. As Bone Marrow Failure Syndromes are rare, enrolling adequate numbers of patients with bone marrow failure in clinical trials is difficult. Multiple sites need to collaborate to recruit suitable numbers of patients."

Whilst Maddie's Vision is spending significant energy forging both national and international collaborations, Dr Prabahran's wish is to similarly establish "a national and international trial network with the purpose of evaluating new treatments for the spectrum of bone marrow failure disorders." His interest in this area was piqued as patients with Bone Marrow Failure Syndromes often have difficult journeys and the limited treatments available, such as bone marrow transplantation, are effective but often fraught with risk. For this reason, he became interested in bone marrow failure research because he is intent on improving the safety and effectiveness of treatments.

Dr Prabahran  grew up in Melbourne and studied medicine on the Gold Coast at Bond University. He underwent his training in internal medicine at the Royal Melbourne Hospital and his specialty training in haematology across the combined Clinical Haematology Department of The Royal Melbourne Hospital / Peter MacCallum Cancer Centre and Austin Hospital. As part of his fellowship, he is undertaking a PhD through Melbourne University and is currently a member of the Australian Cancer Research Fund (ACRF) Translational Research Laboratory. In his free time he enjoys spending time with his wife and 2 young children, particularly reading, trips to the zoo or pool, and playing with Lego. One of his passions is Capoeira, a unique martial art from Brazil.

Dr Ashvind Prabahran

# Novel blood biomarkers for predicting bone marrow failure in Myeloproliferative neoplasms (MPN)

*(Taking an unusual approach to understand what causes bone marrow failure in patients with blood cancers)*

Dr Belinda Guo

The Gunn Family Women in Haematology Fellowship 2018 ongoing
Co-funded with the Snowdome Foundation

Dr Belinda Guo, front centre, and the full project team from The University of Western Australia

Belinda is the recipient of the inaugural Gunn Family National Career Development Fellowship for Women in Haematology (co-funded by Maddie Riewoldt's Vision and Snowdome) and works in the Translational Cancer Pathology Laboratory at the University of Western Australia in Perth.

From a young age, Belinda was always fascinated by how diseases develop and the many ways that scientists and doctors can help overcome the disease. Following her curiosity, she studied protein biochemistry at the University of Canterbury in Christchurch New Zealand before moving to complete a PhD at the University of Melbourne at the Bio21 Institute. There she explored how infectious misfolded proteins that cause prion disease (e.g. Creutzfeldt-Jakob disease and mad cow disease), exploit our body's normal functions to help them spread. During her PhD, she attended a dinner which was held to bring patients, researchers and doctors together where she gained a true appreciation of the impact that research can have on the community. When she completed her PhD, she was determined to transition into applied research and was fortunate to have an opportunity to join the translational laboratory at UWA as a Cancer Council WA Postdoctoral Fellow in 2014.

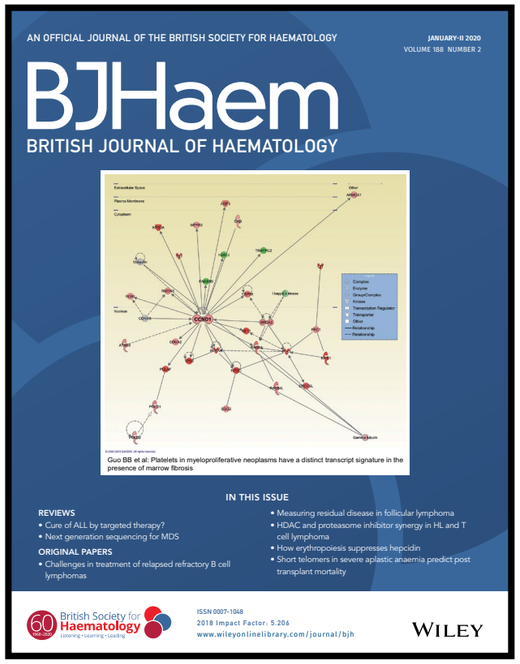
She has since been developing new and improved methods to help earlier detection of blood cancers and disorders using cutting-edge technologies such as next-generation sequencing. She works with a fantastic and integrated team of clinicians, scientists and community representatives. This team is led by Professor Wendy Erber, a haematologist with a career-long interest in blood and bone marrow cancers. Professor Erber has been a strong mentor for Belinda and is a champion for early career researchers and clinicians, and a leader in blood cancer research.

Over the past six years, Belinda's research has provided new workflows to examine specialised cells in the bone marrow and blood, and she is interested in using these new approaches to improve detection of and understand what causes bone marrow failure. Belinda's Fellowship project, entitled **'Novel blood biomarkers for predicting bone marrow failure in myeloproliferative neoplasms'** focusses on myeloproliferative neoplasms (MPN), a group of bone marrow cancers where the marrow's ability to produce blood cells is affected. Up to 20% of these patients will unfortunately develop bone marrow failure, as a result of their bone marrow becoming progressively replaced by scar tissue. Despite major advances in other aspects of MPN, there is still

Dr Belinda Guo and core members of her team at The University of Western Australia, L to R Associate Professor Matthew Linden, Associate Professor Kathy Fuller, Prof Wendy Erber, Dr Belinda Guo and Mr Bob Mirzai. Absent Ms Lynne Wilson

poor understanding of how this happens, why it is in some patients and not others, and, when it will occur. Clinicians need a way to predict which patients are at risk of progressing, and when, so that informed decisions can be made about their management. Belinda has taken a novel approach to address this problem by focussing on a component of the blood, platelets. Platelets are small cells that helps us form clots to stop bleeding. Her research has shown that these cells are highly unusual in patients with MPN and contain a unique genetic profile, which can be used to discriminate between patients at different stages of the disease with high accuracy. This discovery was recently published and featured on the cover of the British Journal of Haematology in January 2020. Belinda aims to use this unique approach to better understand the causes of bone marrow failure in these patients, and to establish a blood test that can be used to detect and/or predict bone marrow scarring and failure in patients with MPN. This will provide opportunities for personalised and early intervention, and hopefully lead to better outcomes and quality of life for patients.

Belinda acknowledges a significant challenge faced by bone marrow failure researchers is lack of government funding due to the rarity of the disease and the immense contribution philanthropic organisations provide in order to support the research and discoveries that will lead to new treatments and cures for bone marrow failure. She is incredibly honoured to be a part of the fight against bone marrow failure.




A figure from Dr Guo's publication was chosen as the cover illustration for the British Journal of Haematology in January 2020. The figure illustrates a cluster of 31 molecules identified using network analysis by Ingenuity Pathway Analysis, based on the list of differentially expressed genes that are unique to platelets from patients with fibrosis. The colours indicate up- (in red) or down-regulation (in green) of the genes in platelets.



# The EMBRACE Trial Evaluating MultidisciplinaRy Bone maRrow fAilure CarE trial

Principal investigators: Dr Lucy Fox and Dr Piers Blombery

2020 ongoing

The Evaluating MultidisciplinaRy Bone maRrow fAilure CarE (EMBRACE) trial is a prospective observational clinical trial being undertaken by the combined Clinical Haematology Department at the Peter MacCallum Cancer Centre and The Royal Melbourne Hospital. The trail is open to patients from one month old, and offers molecularly-guided individualised care to Australian patients with a either a suspected Bone Marrow Failure Syndrome (BMFS) or an inherited predisposition to blood cancer, and expert management advice to clinicians referring these patents.

Patients enrolled on the trail will undergo molecular genetic testing for approximately 90 known current genes responsible for inherited BMFS and predisposition to haematological malignancy. Prior to the availability of genomic testing, establishing an accurate diagnosis was extraordinarily complicated, and only achieved in a proportion of cases with traditional testing. Patient stories of the 'diagnostic odyssey' (the time taken from the onset of symptoms to the receiving a definitive diagnosis) are absolutely heartbreaking – families who had no idea what was so desperately wrong with their child for years, enduring multiple hospital admissions, failure to thrive, and only a generic diagnosis of 'ugly bone marrow'.

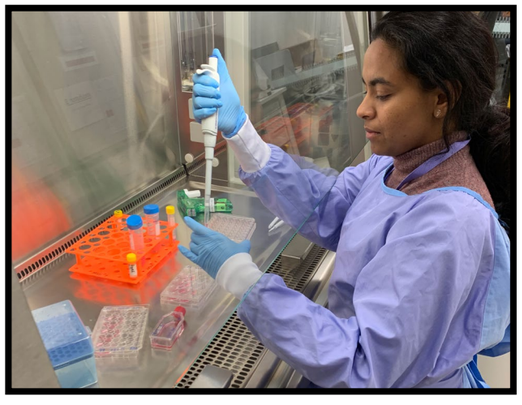
Access to genomic testing has revolutionised the ability to provide an accurate clinicogenomic diagnosis in a matter of weeks. The EMBRACE trail will ensure positive and lasting impact to Australian patients by providing a co-ordinated and efficient approach to case identification, diagnosis, multidisciplinary management, and genetic counselling and management to affected family members

# 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."

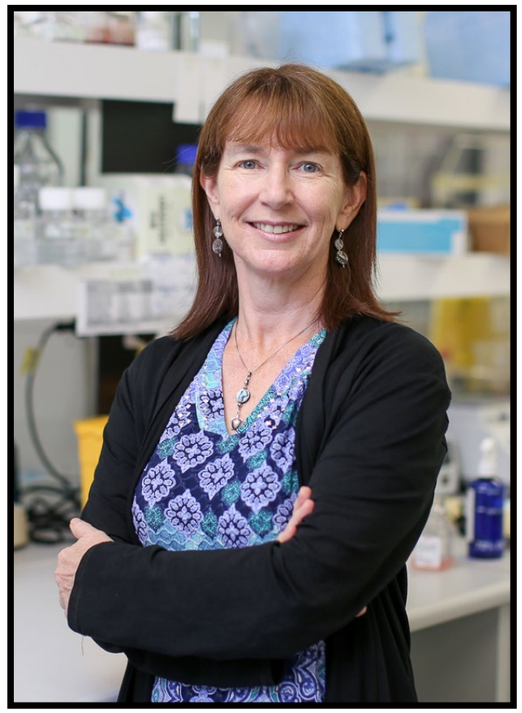
To better understand the mechanism, Dr Venugopal aims to induce correction in an inherited bone marrow failure mouse model, and to identify conditions to help corrected cells expand to re-populate the bone marrow to cure symptoms of disease, thereby determining conditions required to restore and maintain 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.

# Establishing an *in vivo* humanised mouse model for telomere related Bone Marrow Failure Syndromes

Professor Tracy Bryan

Grant-in-Aid 2020 ongoing



Professor Tracy Bryan, CMRI

CHILDREN'S MEDICAL RESEARCH INSTITUTE

Jeans for Genes®

For the last 25 years, Professor Tracy Bryan has been performing research aimed at understanding how the protective tips at the ends of chromosomes, called telomeres, are linked to cancer, aging and other diseases. Her research team is particularly interested in understanding how an enzyme called telomerase functions to prevent telomeres from shortening. This is relevant to cancer, because a majority of cancers produce too much telomerase – this enables them to keep lengthening their telomeres, overcoming the signals that tell healthy cells to stop dividing. However, in patients with inherited mutations in telomerase genes, the telomerase in their stem cells is defective or present at low levels, which means their telomeres become too short and these cells die prematurely.

Many families with inherited BMF caused by short telomeres have not yet had their causative mutation(s) identified. Professor Bryan is therefore collaborating with Drs Lucy Fox and Piers Blombery, and other haematologists around Australia, to determine whether any telomerase mutations found in these families are likely to be causing their disease. Experimental procedures Professor Bryan has developed over the last 20 years to recapitulate the patient's mutation in cancer-derived cells in culture are utilised to determine whether the mutated telomerase is defective. However, these experimental systems have limitations, since telomerase in cancer cells does not always behave the same as telomerase in bone marrow stem cells.

Excitingly, however, gene editing technology is rapidly advancing. Clustered regular interspaced short palindromic repeats (CRISPR) based genome editing of human bone marrow stem cells has matured a lot in recent years. This project aims to use these techniques for setting up a much more clinically-relevant model of telomere-related BMF. Professor Bryan explains, "We are introducing patient mutations into the genomes of blood stem cells from healthy donors, and we can then determine the impact of the mutation on the ability of telomerase to maintain telomeres in the cell type that is most relevant to this disease. This will also allow us to make fundamental discoveries about how short telomeres lead to bone marrow failure, which is not fully understood."

About 30 – 40% of patients with inherited BMF do not know the identity of the mutation causing their disease. The current experiments will assist in providing definitive molecular diagnoses to individual families, allowing them to understand what is causing their disease and helping their clinicians make treatment-related decisions. For example, it is known that patients with short telomeres often experience high levels of toxicity from standard bone marrow transplant procedures, so identifying such patients would allow use of modified procedures that would spare them this toxicity.

Professor Bryan's research is completely aligned with the mission of Maddie's Vision, to ultimately find a cure for bone marrow failure, "Currently, patients with bone marrow failure are given transplanted stem cells. However, the five year survival rate after bone marrow transplant in short-telomere patients remains only approximately 65%, with complications including graft-versus-host disease. It would be preferable to use a gene-corrected version of the patient's own cells for the transplant, but such strategies are challenging in BMF patients. However, very recent progress in the success rate of CRISPR-based gene editing in human blood stem cells raises the exciting possibility that the technology has matured sufficiently to make gene therapy a viable strategy for inherited BMF syndromes. The techniques we are refining while introducing telomerase gene mutations into healthy human stem cells will theoretically be able to be applied in reverse to fix the same mutations in patient cells, and we want to test this as the next stage in this research. Furthermore, these techniques won't only be applicable to telomere-related BMF, but also may be applied to fix genes causing other forms of BMF. We would warmly welcome collaborations with other CRE Executive member researchers to test this!"

Professor Bryan undertook an undergraduate Bachelor of Science degree in biology at Macquarie University in Sydney, before travelling to Johns Hopkins University in the USA to gain hands-on experience

in a world-renowned cancer genetics laboratory. She returned to Australia to do a PhD on the role of telomeres in cancer cells with Professor Roger Reddel at Children's Medical Research Institute (Westmead), before travelling back to the USA for postdoctoral training in the lab of Professor Tom Cech at the University of Colorado, Boulder. Professor Cech's laboratory had just identified the gene for human telomerase and it was a fantastic opportunity for her to be involved in the initial investigations into how telomerase works. While in the Cech laboratory, she developed a huge appreciation for the powerful role of fundamental biochemical analysis of molecular machines, and how much information they impart about disease mechanisms. This has shaped the research she is now undertaking in her own laboratory at the Children's Medical Research Institute, Westmead, Sydney.

When she returned to Australia, she also brought back her husband, whom she had met in the Cech laboratory, Dr Scott Cohen, a fellow telomerase researcher, "Even more than our shared love of science, we also shared a love of hiking in the Colorado mountains, and now our favourite way to unwind is bushwalking in the Sydney area, often with our two dogs."

Professor Bryan's project is very collaborative, involving a large Australian and international team with complementary expertise. The research team at CMRI led by both Professor Bryan and Dr Cohen, brings expertise and technology related to telomeres and telomerase, "Many of the techniques for studying this enzyme were developed or refined by us. We also have fantastic colleagues at our institute, including Associate Professor Karen MacKenzie, whose expertise relates to understanding telomerase specifically in human blood cells. Professor Ian Alexander and Dr Leszek Lisowski at CMRI are among Australia's leading experts in gene therapy approaches for treating disease, and their expertise will be vital for this project. We are also collaborating with Professor Matthew Porteus at Stanford University in the USA, who has developed the most recent techniques for genome editing of human blood cells. Through Maddie Riewoldt's Vision, we have also made linkages with other Australian researchers aiming to apply gene therapy approaches to other subsets of inherited BMF patients, using complementary techniques, so we are very excited about the possibility of pooling all of our expertise and working together towards this goal in the coming years."

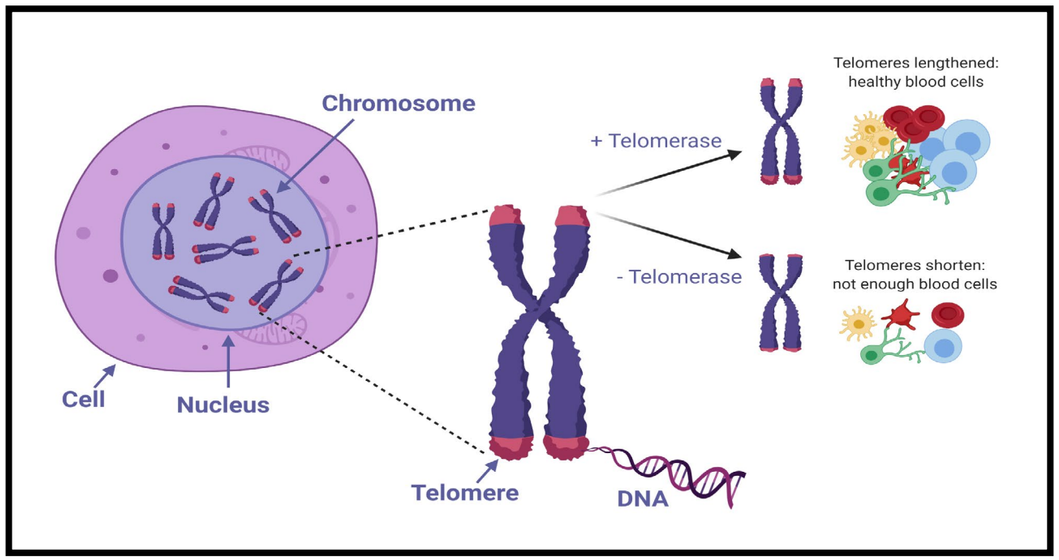



Illustration depicting location of telomeres and function of telomerase

# Microenvironmental determinants of Aplastic Anaemia progression to MDS/AML

Dr Rachel Koldej

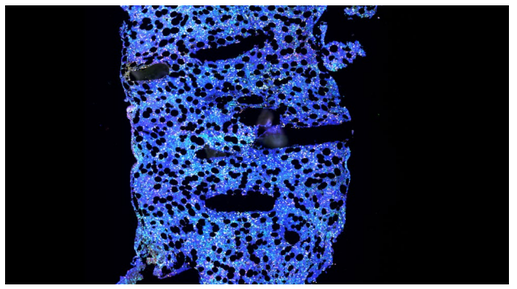
Grant-in-Aid 2020 ongoing

The Royal Melbourne Hospital

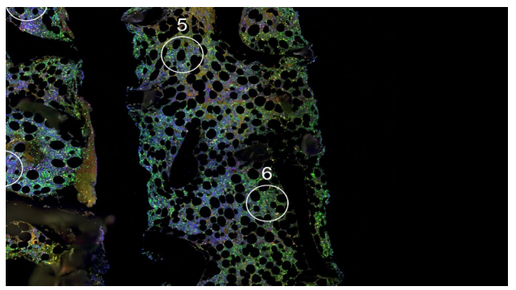
The Australian Cancer Research Foundation (ACRF) Translational Research Laboratory is a unique collaborative environment bringing together research scientists, higher degree students (both clinical and science based), nursing and clinical staff. Established in 2013 by Professor David Ritchie (Director) and Dr Rachel Koldej (Senior Scientist), the laboratory has the mission of undertaking projects utilising clinically derived samples from well-defined clinical cohorts of patients, applying high quality investigational assays and investigating the factors that determine clinical outcomes, treatment efficacy and exploring ways of improving the treatment of disease. Ultimately, the laboratory's goal is to improve the lives of people with blood conditions including Bone Marrow Failure Syndromes (BMFS).

One of the single biggest issues facing researchers in the field of BMFS is that the low incidence of these diseases means that patient samples for research are very difficult to obtain in large enough numbers for meaningful research discoveries to be made and translated into improved patient care.

One of the founding principles of the ACRF Translational Research Laboratory is to unlock the potential of existing sample sets for correlative translational research. The laboratory identified that while fresh samples from patients with BMFS are very rare and therefore slow to collect, there is often stored specimens collected over many years as part of routine care. At the ACRF laboratory, enormous effort has been made to identify these stored specimens as a means of fast tracking research that might otherwise take many years to complete. This approach was applied to Dr Lynette Chee's project into the use of circulating microRNA as a determinant of outcome in Aplastic Anaemia. The approach was further extended by accessing a repository of bone marrow samples (trephines) collected from patients as a part of routine clinical care to diagnose and monitor their disease. These trephine samples collectively represent over 30 years of patients with full clinical outcome data and are an untapped resource for BMF research. However, the way that they had been processed has previously limited the ways in which they could be analysed.



Bone Marrow Trephine tissue stained with immunofluorescent markers to allow selection of regions of interest for analysis using digital spatial profiling




Bone Marrow Trephine tissue stained with immunofluorescent markers to allow selection of regions of interest (circled) for analysis using digital spatial profiling

In a world first study Dr Koldej demonstrated that a new technique, Digital Spatial Profiling (DSP), could be used to simultaneously examine the expression of multiple proteins in BM trephine samples (Koldej and Ritchie, Immuno-oncology Technology, 2020). This exciting discovery has allowed the incorporation of DSP into a number of studies to analyse the immune microenvironment in trephine samples including:

- Dr Koldej's project Microenvironmental determinants of Aplastic Anaemia progression to MDS/AML,
- Dr Ashvind Prabahran's International Travelling Fellowship project Novel immunological assessment of Aplastic Anaemia and post bone marrow transplant Graft Dysfunction for the purposes of targeted therapeutic intervention, and
- The Royal Melbourne Hospital/Fight Cancer Foundation Fellowship awarded to Dr Koldej for her project High multiplex analysis of the immune microenvironment in BM trephine samples using DSP.

Dr Rachel Koldej, ACRF

The central hypothesis to these studies is that acquired BMF and graft dysfunction post bone marrow transplantation, whereby there is evidence of donor engraftment but persistent cytopenias (low blood cell counts), occur via similar mechanisms and treatments that are applicable to one condition could also be used to treat the other. To this end, DSP is also being incorporated as an analysis technique into the prospective RESELECT clinical trial to treat both Aplastic Anaemia and Graft Dysfunction with combinations of drugs designed to target the dysfunctional immune microenvironment in these conditions.

As this project utilises archival BM trephines, which exist in pathology departments in their thousands, there are large numbers of patient samples that could be accessed to perform validation and translation studies in the future without requiring new patient samples to be collected, which would take a significant amount of time. In this way, the use of DSP will significantly increase the speed at which new treatments and monitoring methods are developed for BMFS and translated to the clinic.

Ultimately, this project will lead to a greater understanding of the contribution of the immune microenvironment to the biology and clinical course of BMF disorders. It will identify new therapeutic targets and new improved methods of disease monitoring that complement other techniques currently under development and those already used in the clinic.

# The following projects are scheduled to commence in the latter half of 2020:

## Alex Gadomski Postgraduate Scholarship
HDR Agreement with UTAS/Menzies

## Australian Marrow Failure Biobank
Biobanking Victoria

## The RESELECT Trial
Principal investigator: Professor David Ritchie
REscuing bone marrow function in patients with relapsed acquired aplaStic anaEmia and/or bone marrow failure post aLlogeneic stEm Cell Transplantation

## Using whole genome sequence analysis to find answers for unsolved cases of inherited Bone Marrow Failure Syndrome
Dr Piers Blombery

## Curation of the DIAAMOND-based Aplastic Anaemia Biobank
Associate Professor Stephen Ting

# Publications

# 5.

# List of Publications to June 2020

(in chronological order):


**1.** van Twest S, Murphy VJ, Hodson C, Tan W, Swuec P, O'Rourke JJ, Heierhorst J, Crismani W, Deans AJ. Mechanism of Ubiquitination and Deubiquitination in the Fanconi Anemia Pathway. Mol Cell. 2017 Jan 19;65(2):247-259. doi: 10.1016/j.molcel.2016.11.005. Epub 2016 Dec 13.

**2.** Agarwal R, Chan YC, Tam CS, Hunter T, Vassiliadis D, Teh CE, Thijssen R, Yeh P, Wong SQ, Ftouni S, Lam EYN, Anderson MA, Pott C, Gilan O, Bell CC, Knezevic K, Blombery P, Rayeroux K, Zordan A, Li J, Huang DCS, Wall M, Seymour JF, Gray DHD, Roberts AW, Dawson MA, Dawson SJ. Dynamic molecular monitoring reveals that SWI-SNF mutations mediate resistance to ibrutinib plus venetoclax in mantle cell lymphoma. Nat Med. 2019 Jan;25(1):119-129. doi: 10.1038/s41591-018-0243-z. Epub 2018 Nov 19.

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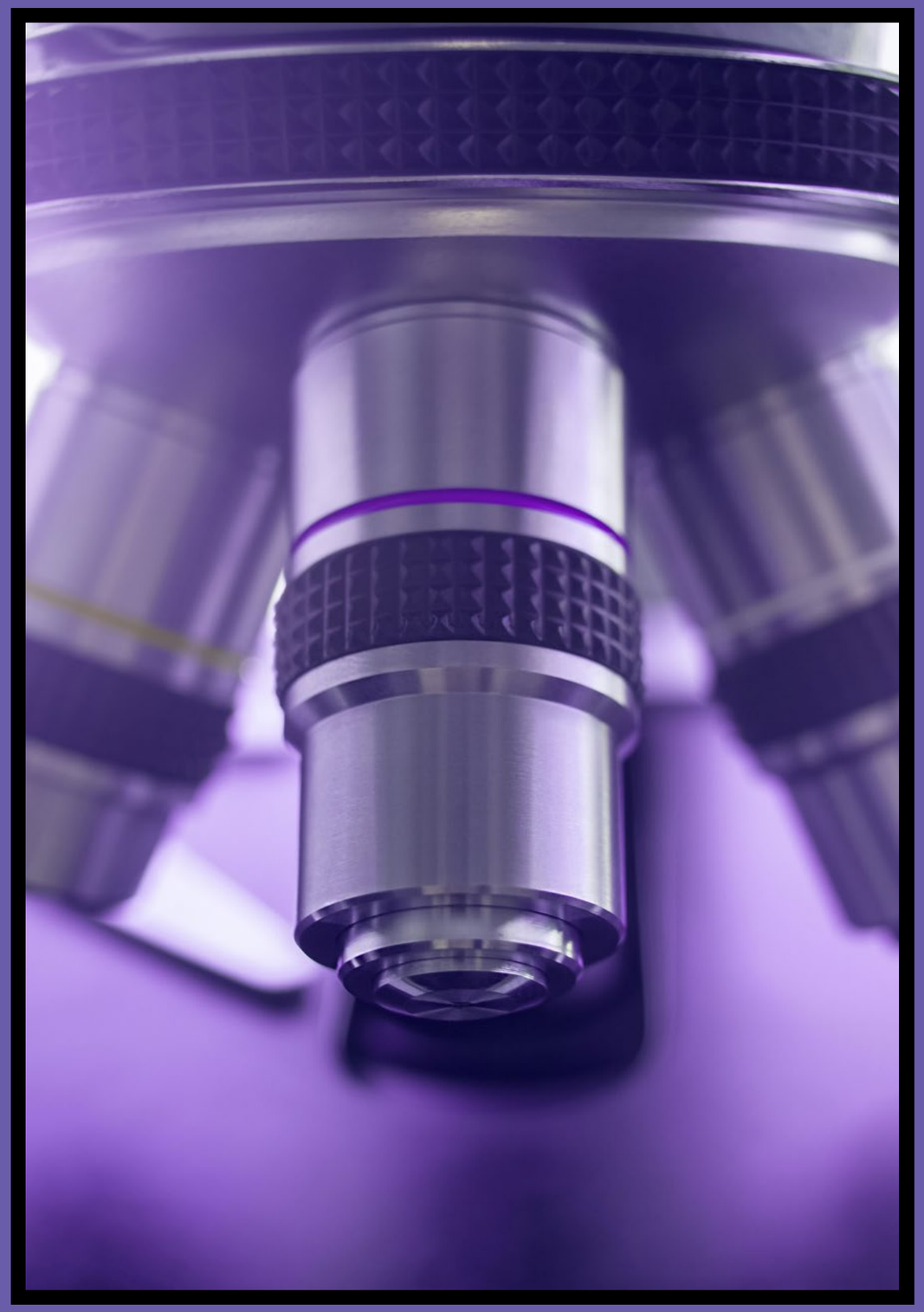

# Appreciation

# 6.

# Thank you

## to the Scientific Advisory Committee

The Centre of Research Excellence is indebted to the Maddie's Vision Scientific Advisory Committee (SAC), who willingly volunteer their time and expertise, and have provided long term commitment to determining the scope and timing of granting rounds, reviewing grant applications, monitoring active grants, providing strategic and scientific direction to the CRE, and evaluating and advising in regard to grant opportunities.

The SAC is currently comprised of:

- Professor David Ritchie (Chair)
- Professor David Haylock
- Associate Professor Steven Lane
- Associate Professor Rachel Conyers
- Associate Professor Ingrid Winkler
- Associate Professor Andy Moore
- Dr Duncan Purtill

Maddie's Vision wholeheartedly thanks each member for their ongoing involvement and dedication.



# Thank you

## to Collaborative Research Institutes

The CRE is enormously appreciative for the partnership of our nationwide Collaborative Research Institutes, who provide support to the CRE Executive to enable their projects to occur.

# Thank you

## to the Victorian State Government

The CRE extends immense gratitude to the Victorian State Government, whose support in providing for the CRE's establishment powerfully and immeasurably assists in our mission to find new treatments and ultimately cures for both acquired and inherited Bone Marrow Failure Syndromes.

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