



The Australian Centre for Blood Diseases (ACBD) is a leading national and international blood diseases centre with recognised research, treatment, and educational programs for blood diseases. ACBD is affiliated with Monash University, Alfred Health, Eastern Health and Southern Health, and is organised into three integrated divisions:

- Clinical and Diagnostic Haematology/Oncology
- Clinical and Basic Research Programs
- Teaching and Education

## Thrombosis Research Unit

### Head: Professor Shaun Jackson

Blood clotting diseases are Australia's major healthcare problem affecting more than 50% of the adult population and killing one Australian nearly every 10 minutes. Despite intense investigation over the last 40 years into the discovery and development of more effective anti-clotting drugs, the impact of these therapies on mortality rates has remained disappointingly low, with less than 1 in 6 patients taking anti-clotting therapies avoiding a fatal clotting event. This situation is likely to worsen in the future due to the rapidly growing incidence of obesity and diabetes. People with diabetes are typically more resistant to the benefits of anti-clotting therapy; thus there is a pressing need for the identification and development of more effective approaches in the prevention of blood clotting.

Underlying the formation of blood clots are platelets: small, specialised blood cells that stick to areas of injury in blood vessels in order to stop bleeding, in a process known as haemostasis. When triggered within diseased blood vessels, this normally protective process becomes exaggerated and results in an abnormal platelet plug that blocks blood flow through the vessel (arterial thrombosis). Thus, platelets represent a key ingredient in the development of blood clots (thrombosis) that lead to devastating diseases such as heart attacks and strokes.

The unit aims to further our understanding of the basic principles surrounding normal haemostasis, with the ultimate goal to discover a 'magic bullet' that selectively targets pathological thrombosis without compromising haemostasis. The laboratory also investigates the important cross-talk between blood clot formation and inflammation. A major highlight for 2010 was the award of an NHMRC Australia Fellowship to Professor Shaun Jackson.

### Current Projects

- Novel insights into platelet function and thrombus formation
  - Novel approaches to regulate blood clot contraction and arterial thrombolysis (S Schoenwaelder)
  - Mitochondrial pathways in procoagulant platelet function and survival (S Schoenwaelder)
  - The prothrombotic implications of diabetes (S Al-Daher)
  - Dynamic interplay between thrombus formation and inflammation (Y Yuan)
- Biochemical and physical factors regulating platelet function
  - A role for Dok2 proteins in regulating haemostasis and thrombosis (S Hughan)
  - Disturbed blood flow and blood clot formation (W Nesbitt)

- Type II PI 3-kinases in haemostasis and thrombosis (J Hamilton)
- The role of thrombin in blood clot formation (Z Kaplan)
- Platelet receptors and their roles in haemostasis and thrombosis
  - The vWf receptor – GPIb/V/IX (S Cranmer)
  - Thrombin and the protease-activated receptors (J Hamilton)

## Serpin Biology Unit

### Head: Professor Paul Coughlan

The prevention and treatment of blood clots is a delicate act: too much anti-platelet or anti-coagulant therapy can lead to unwanted bleeding, which can have catastrophic consequences (such as haemorrhagic stroke), while fibrinolysis therapy can cause brain damage. The unit examines alternative ways of treating and preventing blood clots, by focusing on the serpin (serine protease inhibitor) superfamily of proteins.

When blood clots form in response to injury, a naturally occurring process of dissolution is also activated. This leads to the clearance of clot from blood vessels during the healing process. Similarly, in diseases such as heart attack, stroke and deep vein thrombosis, clots are usually dissolved over time. In many people this mechanism is inefficient. In the past, activators of clot dissolution have been exploited to treat people with thrombosis. There is a balance in blood between the main clot dissolving factor, plasmin, and its regulator, antiplasmin. The unit studies the ways that these proteins recognise each other and bind together, and has shown that by interfering in this interaction, the clot dissolving process can be accelerated. Ongoing work involves the development of agents which will ultimately be used to treat blood clots and thereby hasten the recovery from thrombotic diseases.



*Clinical haematologist Dr Zane Kaplan commenced his PhD under the supervision of Professor Shaun Jackson in the Thrombosis Research Unit.*

## Fibrinolysis and Gene Regulation

### Head: Associate Professor Robert Medcalf

The removal of blood clots from the circulation and the turnover of extracellular matrix proteins are facilitated by specialised enzymes. One of the most important enzymes in this setting is plasmin, which is the end product of the fibrinolytic system. Plasmin performs many functions but it is generally accepted that its primary role is to degrade fibrin, the structural scaffold of a blood clot.

The main interests of the unit are in the molecular and cellular biology of this enzyme system, particularly in gene regulation in various cell types. Efforts are also devoted to understanding the biology and pathophysiology of the plasminogen activator system in the central nervous system, particularly in relation to ischaemic stroke and neurotrauma and modulation of the blood brain barrier.

### Current Projects

- Regulation of tissue-type plasminogen activator gene expression *in vitro* (R Medcalf)
- The role of t-PA in the central nervous system (R Medcalf, A Samson, M Sashindranath)
- To understand the means by which t-PA modulates the blood-brain barrier (R Medcalf, B Niego)
- Regulation of the plasminogen activator inhibitor type 2 gene expression (S Stasinopoulos)
- The modulatory effect of the plasminogen activating system on the immune response (R Borg, A Samson, R Medcalf)

## Malignant Haematology & Stem Cell Transplantation

### Head: Associate Professor Andrew Spencer

A diverse range of translational and clinical research activities exploring improved therapeutic approaches to a variety of blood cancers continued.

### Myeloma Research Group

- Epigenetic targeting of haematological malignancies (D Mithraprabhu, A Spencer)
- Small molecule development program (T Khong, A Spencer)
- Cell adhesion mediated drug resistance in multiple myeloma (K Monaghan, A Spencer)
- Tissue array as a predictive tool in multiple myeloma drug response (A Kalf, A Spencer)
- Heat shock proteins as targets for anti-myeloma therapy (E Nichols, A Spencer)
- Impact of CD45 expression on drug resistance and disease progression in multiple myeloma (C Lin, A Spencer)
- Dual kinase inhibitors to target acute myeloid leukemia (AML) (M Guthridge, A Wei)
- The role of inositol phosphatides in regulating PI3K in AML (A Wei, S Rijal, C Mitchell)
- A platform technology for prognostication in AML (A Wei, D Irwin, J McManus)

### Stem Cell Transplantation Research Group

- Late Effects Clinic (P Walker, S Avery)
- Immune reconstitution following novel reduced intensity conditioned stem cell transplantation (SCT) (P Walker, A Spencer)
- Longitudinal audit of invasive fungal infections in SCT and acute leukaemia induction (P Walker)

## Haematology Clinical Research Unit

Clinical trial activities remained at a high level in 2010, with 34 open trials, with an increasing proportion of Phase 1 and first-time-in-human studies being conducted. Throughout 2010 and into 2011, a suite of multicentre investigator-initiated trials of novel therapeutic approaches to both multiple myeloma and AML were initiated. The Clinical Research Unit acted as the national coordinating site for the ALLG-GIMEMA MM11 myeloma trial.

## Eastern Clinical Research Unit

The Eastern Clinical Research Unit (ECRU) is an initiative of the Monash University Department of Medicine and is based at Box Hill Hospital, Maroondah Hospital and The Alfred. ECRU has been involved in clinical trials since 1996 and employs over 50 medical and nursing staff who are involved in the management of over 150 clinical trials in both medical and surgical specialties. ECRU is now the largest multidisciplinary clinical trial unit in Australia. ECRU has particularly distinguished itself in its ability to recruit, collect statistical data and retain trial participants.

### ECRU Biotechnology Research Division

ECRU Biotechnology (ECRU Biotech), headed by Dr Anthony Dear, aims to expand the capabilities of ECRU beyond clinical research to a better understanding of the activity of existing pharmaceuticals and the development of new treatments. This in turn promises to deliver better treatment than is currently available. Active contributors to ECRU Biotech include members of several disciplines from the clinical activity at ECRU including endocrinology, neurology and oncology together with significant support from the pharmaceutical industry.

ECRU Biotech also seeks to foster an environment supportive of ongoing academic endeavour, offering biotechnology research projects for Honours and PhD students.

### Selected ECRU Biotechnology Collaborative Research Projects

- Assessment of novel small molecule treatments in *in vivo* models of abdominal aortic aneurysm, atherosclerosis and neointimal hyperplasia (R Widdop, Department of Pharmacology, Monash University)
- Effects of liraglutide on vascular endothelial peptide expression in *in vitro* and *in vivo* models of vascular disease (L Knudsen, Novo Nordisk A/S, Denmark)
- *In vivo* characterisation of novel histone deacetylase inhibitors (HDAC) in breast carcinoma (R Anderson, Peter MacCallum Research Institute)
- Effects of novel HDAC inhibitors on HIV latency (S Lewin, Burnet Institute; D Rhodes, AVEXA Pty Ltd, Melbourne)
- Effects of novel HDAC inhibitors and azacytidine in the myelodysplastic syndrome (J McKendrick, Department of Oncology, Box Hill Hospital; G Leone and M Voso, Catholic University, Italy; K Lynch, Celgene Corporation)
- Effects of incretins on severity of acute thromboembolic cerebrovascular accident (C Bladin, Department of Neurology, Box Hill Hospital)

### Postgraduate Students

22 PhD Students

### Publications

34 Journal Articles

1 Book Chapter