



Andrew Roberts

MBBS (Hons I) FRACP FRCPA PhD

Joined Institute: 1998

Date of Birth: 13 July 1961

Areas of Research: Molecular Haemopoiesis, Cytokine Biology, Translational Research

ACADEMIC QUALIFICATIONS

1984 University of Queensland, *MBBS (Hons I)*
 1993 Royal Australasian College of Physicians *FRACP*
 1993 Royal College of Pathologists of Australasia *FRCPA*
 1997 University of Melbourne, *PhD*

CURRENT APPOINTMENTS

NHMRC Practitioner Fellow, Laboratory Head, Cancer and Haematology Division
 Physician, Bone Marrow Transplantation Service, Department of Clinical Haematology and Medical Oncology, The Royal Melbourne Hospital

APPOINTMENT PRIOR TO WEHI

1997–1998 Visiting Scientist (Neil Hamilton Fairley Fellow) and Research Associate, Howard Hughes Medical Institute, Herman B Wells Center for Pediatric Research, Indiana University School of Medicine, USA

MAJOR PRIZES AND AWARDS

1993–1996 NHMRC Postgraduate Medical Scholarship
 1993–1996 Michael Pearson Fellowship in Leukaemia Research, Cancer Council Victoria
 1995 Albert J. Baikie Memorial Medal, Haematology Society of Australia
 1997 Bushell Travelling Fellowship, Royal Australasian College of Physicians
 1997–2000 NHMRC Neil Hamilton Fairley Postdoctoral Fellowship
 1998 Bowman Award for Excellence in Postdoctoral Research in Biochemistry and Molecular Biology, Indiana University School of Medicine (2nd Prize)
 2000–2005 Sir Edward Dunlop Clinical Fellowship, Anti-Cancer Council of Victoria
 2001 Haematology Society of Australia and New Zealand GlaxoSmithKline Travel Award
 2002 Best of Health Medical Award, Royal Melbourne Hospital
 2004 Burnet Prize of The Walter and Eliza Hall Institute of Medical Research
 2005–2009 NHMRC Practitioner Fellowship

MOST SIGNIFICANT RESEARCH CONTRIBUTIONS AND CONTRIBUTIONS (up to 20)

Characterisation of the biology of peripheral blood progenitor cells

While a PhD student of Don Metcalf investigating the biology of peripheral blood haemopoietic progenitor (and stem) cells (PBPC), I was the first to show that circulating blood progenitor cells are a highly selected sub-population of bone marrow progenitor and stem cells. The PBPC population was shown to be highly enriched for megakaryocyte progenitor cells, explaining in part the markedly accelerated platelet recovery observed after clinical PBPC transplantation (1). In contrast to bone marrow progenitors, PBPC were also discovered to be exclusively in the G₀/early G₁ phase of the cell cycle (2). Recognition of this fact led to modifications in protocols for retroviral gene transfer into PBPC (addition of in vitro stimulation to recruit cells into cycle), and facilitated the development of clinical gene therapy trials.

Phase I study of G-CSF in normal stem cell donors

In collaboration with Andrew Grigg at Royal Melbourne Hospital, I led a pivotal clinical trial of safety and efficacy of G-CSF in normal donors (3). This helped pave the way for the introduction of G-CSF-mobilised PBPC allogeneic transplantation into international clinical practice. Leukapheresis of G-CSF-mobilised PBPC has subsequently succeeded bone marrow harvesting as the standard method for collection of haemopoietic stem cells for allogeneic transplantation. Apart from safety considerations, such a study was required because of my initial observation of wide inter-individual variation in the magnitude of the progenitor cell mobilisation response to G-CSF amongst patients with malignancy (4).

Definition of function of Rac2

During post-doctoral studies in David Williams' laboratory, I defined the physiological requirement for the small GTPase Rac2 in neutrophil function. Rac2 is expressed only in haemopoietic cells and prior to my work was thought to be required primarily for the generation of superoxide by phagocytes. I discovered that Rac2 was essential for normal chemotaxis, rolling, spreading and superoxide production by neutrophils in response to specific extracellular cues and for normal cell trafficking and resistance to fungal infection in the whole animal (5). Since the publication

of this work, paediatric patients with an unexplained neutrophil immunodeficiency of similar phenotype have been investigated by my collaborators and Rac2 deficiency has been confirmed as a rare cause of lethal neutrophil dysfunction in humans. Rac2 deficient mice were the first knockouts of any member of the Rho GTPase family and our further analyses of these animals confirmed the physiological involvement of members of this family in such diverse cellular functions as actin cytoskeletal rearrangement, proliferation, apoptosis, transcriptional activation and differentiation in haemopoietic cells (6–8).

Characterisation of the physiological function of Socs3

In close collaboration with other members of the Cancer and Haematology Division, I have investigated the role of SOCS-3 in haemopoiesis via creation of *socs3* null mice and mice with tissue-specific deletion of *Socs3*. Expression analysis and functional assays in overexpression systems had implicated SOCS-3 in the negative regulation of signalling downstream of a wide range of cytokine and haemopoietin-family receptors including erythropoietin, G-CSF, and IL-6. Mice deficient in SOCS-3 die in utero by day E12. Analysis revealed this premature death to be a consequence of placental failure (reflecting dysregulation of LIF-signaling), rather than abnormalities of haemopoiesis (9). Through conditional gene targeting strategies, we have developed multiple models of tissue-specific deficiency of *Socs3*. Using these in vivo models, complemented by in vitro assays, we have proved that *Socs3* is a critical physiological regulator of IL-6 and G-CSF signalling (10–12). Further, *Socs3* is required by adult mice to prevent the spontaneous development of inflammatory diseases. In collaboration with Ian Wicks at WEHI, and at Geoff Hill at QIMR, my research has identified *Socs3* as a major suppressor of acute arthritis and graft-versus-host-disease in murine models of these human diseases (13,14).

1. ROBERTS AW, Metcalf D. Granulocyte colony-stimulating factor induces selective elevations of progenitor cells in the peripheral blood of mice. *Exp Hematol* 22: 1156–1163, 1994 (IF 4.00; 34 citations)
2. ROBERTS AW, Metcalf D. Non-cycling state of peripheral blood progenitor cells mobilized by granulocyte colony-stimulating factor and other cytokines. *Blood* 86: 1600–1605, 1995 (IF 10.10; 100 citations)
3. Grigg AP*, ROBERTS AW*, Raunow H, Houghton S, Layton JE, Boyd AW, McGrath KM, Maher D. Optimising dose and scheduling of filgrastim (granulocyte colony-stimulating factor) for mobilization and collection of peripheral blood progenitor cells in normal volunteers. *Blood* 86: 4437–4445, 1995 *joint first authors (IF 10.10; 143 citations)
4. ROBERTS AW, DeLuca E, Begley CG, Basser R, Grigg AP, Metcalf D. Broad inter-individual variations in circulating progenitor cell numbers induced by granulocyte colony-stimulating factor therapy. *Stem Cells* 13: 512–516, 1995 (IF 5.80; 34 citations)
5. ROBERTS AW, Kim C, Zhen L, Lowe JB, Kapur R, Petryniak B, Spaetti A, Pollock J, Borneo JB, Bradford GB, Atkinson SJ, Dinauer MC, Williams DA. Deficiency of the hematopoietic cell-specific Rho-family GTPase Rac2 is characterized by abnormalities in neutrophil function and impaired host defense. *Immunity* 10: 183–196, 1999 (IF 16.00; 151 citations)
6. Li B, Yu H, Zheng W, Voll R, Na S, ROBERTS AW, Williams DA, Davis RJ, Ghosh S, Flavell RA. The small G protein Rac2 mediates Th1 cytokine expression through synergistic activation of multiple signaling pathways. *Science* 288: 2219–2222, 2000 (IF 29.20; 57 citations)
7. Yang FC, Atkinson SJ, Gu Y, Borneo JB, ROBERTS AW, Zheng Y, Pennington J, Williams DA. Rac and Cdc42 GTPases control hematopoietic stem cell shape, adhesion, migration and mobilization. *PNAS* 98: 5614–5618. 2001 (IF 10.30; 38 citations)
8. Croker BA, Tarlinton DM, Cluse LA, Tuxen AJ, Light A, Yang F-C, Williams DA, ROBERTS AW. The Rac2 GTPase regulates B lymphocyte antigen receptor responses and chemotaxis and is required for establishment of B-1a and marginal zone B lymphocytes. *J Immunol* 168: 3376–86, 2002 (IF 6.70; 26 citations)
9. ROBERTS AW, Robb L, Rakar S, Hartley L, Cluse L, Nicola NA, Metcalf D, Hilton DJ, Alexander WS. Placental defects and embryonic lethality in mice lacking suppressor of cytokine signaling 3. *PNAS* 98: 9324–9329, 2001 (IF 10.30; 38 citations)
10. Croker BA, Krebs DL, Zhang J-G, Wormald S, Willson TA, Stanley EG, Robb L, Greenhalgh CJ, Förster I, Clausen BE, Nicola NA, Metcalf D, ROBERTS AW, Alexander WS. SOCS3 negatively regulates interleukin-6 signaling in vivo. *Nature Immunology* 4: 540–545. 2003 (IF 28.20; 64 citations)
11. Croker BA, Metcalf D, Robb L, Wei W, Mifsud S, DiRago L, Cluse LA, Sutherland KD, Hartley L, Williams E, Zhang J-G, Hilton DJ, Nicola NA, Alexander WS, ROBERTS AW. SOCS3 is a critical physiological negative regulator of G-CSF signaling and emergency granulopoiesis. *Immunity* 20: 153–165, 2004 (IF 16.00)
12. Patent – Active compounds and uses thereof, filed 4/6/2003
13. Lawlor KE, Campbell IK, Metcalf D, O'Donnell K, van Nieuwenhuijze A, ROBERTS AW, Wicks IP. Critical role for granulocyte colony-stimulating factor in inflammatory arthritis. *PNAS* 101: 11398–11403, 2004
14. Patent – A method of treatment and prophylaxis, filed 23/8/2002

TOTAL PUBLICATIONS

Refereed Journal Articles 44, Reviews 2, Chapters 3

Total Patents 2

RESEARCH SUPPORT 1997–2005

2000–2005 Cancer Council Victoria , Sir Edward Dunlop Clinical Fellowship \$93,000pa
 2001–2006 Leukemia and Lymphoma Society of America Specialized Center of Research. Apoptosis in Haematopoiesis, Leukemogenesis and Therapy' \$1,925,000pa total, Roberts Lab \$100,000pa
 2002–2006 NHMRC Program Grant Molecular regulation of blood cell formation \$2,750,000 total, Roberts Lab \$225,000pa
 2005–2009 NIH CA22556 (MERIT Award) Differentiation of Granulocytes and Macrophages TBA

COMMERCIAL ACTIVITY

I serve as a consultant to CSL Ltd.

CLINICAL INVOLVEMENT

I have a half-time appointment as Physician, Bone Marrow Transplantation Service, Department of Clinical Haematology and Medical Oncology, The Royal Melbourne Hospital. My duties as a Consultant Clinical Haematologist are the inpatient and outpatient care of patients with haematological illnesses. The majority of patients have haematological malignancies ie leukaemia, lymphoma, myeloma or related conditions (myelodysplasias and myeloproliferative disorders). Half my clinical time is spent managing allogeneic and autologous transplant patients. In addition to these direct service responsibilities, my position involves significant involvement in clinical trials (local, national and international; Phases I, II and III). In this capacity, there is a substantial interface with my laboratory research at WEHI, with several current research projects being active collaborations with the clinical team. I lead the clinical core of the Leukemia and Lymphoma Society Specialised Centre for Research Excellence, chair the Clinical Advisory Group at WEHI, and am on the management committee for the Cancer Trials Australia translational research laboratory, as well as its Clinical Trials Advisory Committee. I also serve on the Executive Committees of the Cancer Council Victoria and the Haematology Society of Australia and New Zealand, and am co-chair of the Laboratory Science Committee of the Australasian Leukaemia and Lymphoma Society.

LECTURES AT MAJOR SCIENTIFIC MEETINGS 1997–2005**National**

2001
 HSAZ ASM, Brisbane, *Invited speaker*
 2004
 HSAZ ASM, Melbourne, *Organising committee, Invited speaker*
 16th Lorne Cancer Conference, Lorne, VIC, *Invited speaker*

International

1998
 11th Symposium Molecular Biology of Hematopoiesis, Bormio, Italy, *Invited speaker*
 2000
 World Apheresis Association Scientific Meeting, Perth, *Invited speaker*
 2002
 International Society of Experimental Hematology Annual Scientific Meeting, Montreal, Canada, *Presidential symposium speaker*
 2003
 International Society of Experimental Hematology Annual Scientific Meeting, Paris, France, *Presidential symposium speaker*
 12th International Congress of Radiation Research, Brisbane, *Invited speaker*
 2005
 10th International Myeloma Workshop, Sydney, *Symposium chair; Scientific advisory committee*

PROFESSIONAL ACTIVITIES**Peer Review Committees**

2001–2003 Discipline Panel for Project Grant Reviews, NHMRC
 2002–2003 Leukaemia Foundation Australia, Grant Review Panel for NSW
 2004 Deputy Chair, NHMRC Discipline Panel for Project Grant Reviews
 2004 Leukaemia Foundation Australia, National Grant Review Panel
 2005 Chair, NHMRC Discipline Panel for Project Grant Reviews

Membership of Executive/Policy Committees

1999–2005 Scientific Committee, Australasian Leukaemia and Lymphoma Group (ALLG)
 2000–2003 Committee of Management, Centre for Developmental Cancer Therapeutics (CDCT), Melbourne.
 2000–present Member, Scientific Committee, HSAZ
 2001–present Tissue Bank Management Committee, ALLG
 2003–present Clinical Trials Advisory Committee, Cancer Trials Australia
 2003–present Member, Executive Council, Haematology Society of Australia and New Zealand
 2004–present Member, Executive Committee (Board), The Cancer Council Victoria
 2005–present Co-Chair, Scientific Committee, Australasian Leukaemia and Lymphoma Group

Executive Positions Held

2005–present Co-Chair, Scientific Committee, Australasian Leukaemia and Lymphoma Group