Dr Geoffrey Brown BSc, PhD

Reader in Cellular Immunology

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About

Geoffrey Brown is Director of Postgraduate Taught, College of Medical Sciences and Director of Graduate Studies, Immunity and infection

Geoffrey has published 130 original research papers in scientific journals and 16 reviews/book chapters in the fields of blood cell development and leukaemia. In 2009, he edited the book entitled 'Cell Determination during Hematopoiesis' which included contributions from principle workers in this field from around the world.

Qualifications

- MA (status) Oxford 1975
- PhD Tumour Immunology London 1975
- BSc (Hons) Microbiology London 1972

Biography

Geoffrey Brown qualified with a BSc (Hons) in Microbiology from Queen Elizabeth College at the University of London in 1972. He studied for a PhD in Tumour Immunology at the Imperial Cancer Research Fund Tumour Immunology Unit, University College London. Geoffrey then went to work at the University of Oxford as the University IBM Fellow and Research Lecturer of the House, Christ Church College Oxford. He worked in the MRC Immunochemistry Unit, Department of Biochemistry followed by a period as a Leukaemia Research Fund Fellow in the Nuffield Department of Clinical Medicine, Radcliffe Infirmary Oxford. Brief spells abroad have been work at the University of Toronto (as a Leukaemia Research Fund Travel Fellow), the National Institutes of Health, Washington DC (as a Visiting Senior Scientist), and the University of Chicago (as an Anne Wall Travel Fellow).

In 1979, Geoffrey came to the University of Birmingham where he has continued to work on blood cell development and leukaemia and other malignancies. From 1996 to 2000, Geoffrey was Co-Director of the Leukaemia Research Fund Differentiation Programme at both Birmingham and the University of Wales College of Medicine and also worked from 1998 to 2004 as a consultant to Allergan Pharmaceuticals, USA.

Geoffrey was awarded MA status in 1975 by the University of Oxford, and in 2009 made a Paul Harris Fellow (of the Rotary Foundation of Rotary International) for contributions to leukaemia studies. In 2002, he was elected to The Lunar Society of Birmingham.

Teaching

Teaching Programmes

- **BMedSci (/students/courses/undergraduate/med/medical-sci.aspx)**
- **MBChB (/students/courses/undergraduate/med/medicine.aspx)**

Postgraduate supervision

Geoffrey is interested in supervising doctoral research students in the following areas:

- The development of blood cells
- The use of retinoids to modulate the behaviour of normal and malignant cells

If you are interesting in studying any of these subject areas please contact Geoffrey on the contact details above, or for any general doctoral research enquiries, please email: **dr@contacts.bham.ac.uk (mailto:dr@contacts.bham.ac.uk)** or call +44 (0)121 414 5005.
For a full list of available Doctoral Research opportunities, please visit our Doctoral Research programme listings.

Research

RESEARCH THEMES

Blood Cell Development, Cell Fate Determination, Leukaemia Cell Biology, Therapeutic Use of Novel Synthetic Retinoids

RESEARCH ACTIVITY

Since 1972, the core aims of my research have been to define the nature of blood cell types, to understand their development and to define the cellular origins of, and possible treatments for, leukaemia and other malignancies.

Current research interests:
Modelling the development of haematopoietic cells
The mammalian blood cell system provides biologists with one of the best models for unravelling how one stem cell – the haematopoietic stem cell – gives rise to the many different types of cells of the blood and immune systems. The classic model for this process depicts two families of cells; lymphoid and myeloid. This dichotomy has been increasingly challenged – and an accumulation of new findings culminated in a Nature commentary suggesting that "the latest research will necessitate revision of textbook accounts". I proposed the 'Pair-Wise Model' of haematopoiesis, which is an updated version of my 'Sequential Determination Model' (from 1985). The model groups the pair-wise relationships between lineage fates around a broken circle: to date there aren't findings that refute this model. Ongoing studies are examining whether the Pair-Wise model is a correct representation of haematopoiesis by extending understanding of the events that govern commitment of haematopoietic stem cells to becoming one particular type of cell.

Controls on cell behaviour
Endeavours to understand cell differentiation are also focused on signals that arise from all-trans retinoic acid (ATRA) and vitamin D3 (with Dr Hughes). It is well known that retinoids are important to the development of many tissues. Work has investigated the effects of novel synthetic retinoids that agonize and antagonize sub-types of retinoic acid receptors (RAR), including unique □-selective compounds, on the growth and differentiation of various normal and malignant cells. Findings are that: (i) RAR antagonists potently induce growth arrest, followed by apoptosis, in patients' prostate and colon carcinoma cells and breast carcinoma cell lines, (ii) antagonizing RARs improves the recovery of neutrophils in leukopenic mice and provides protection to these mice from Staphylococcus aureus infection, and (iii) pan-RAR antagonism enhances expansion of haematopoietic stem cells in liquid culture (~40 fold). Current interests are to explore the potential therapeutic uses that are indicated by these findings. Vitamin D3 studies have described the importance of rapid 'non-genomic' responses that involve interaction of the vitamin D3 receptor with 'non-genomic' signalling pathways that are usually growth-factor driven.

Previous related research activity:
The cellular origins of leukaemias
Early work described human B and T lymphocyte antigens which contributed towards the definition of B and T lymphocytes in man, and to the description of B-acute lymphoblastic leukaemia (B-ALL) and T-ALL. Cells from 76% of childhood and 50% of adult cases of ALL exhibited neither a B nor T cell phenotype. The nature of this leukaemia was resolved by the discovery of the 'common Acute Lymphoblastic Leukaemia Antigen' (cALLA, now CD10) - the leukaemia is designated common ALL (cALL). Identification of cALLA was a forerunner of the immunophenotyping of leukaemia cells that is now routine clinical practice.

A monoclonal antibody approach to the identification of blood cells
With Galfre and Milstein, I produced the first monoclonal antibodies to human cell surface antigens, including the leukocyte common antigen CD45. Subsequently, monoclonal antibodies were produced to MHC class I molecules; various myeloid-associated antigens; the transferrin receptor; a novel haemopoietic precursor cell antigen; the MHC class molecules DR, DP, DQ; a novel nuclear envelope protein; and nucleoplasmin.

Fundamental aspects of cellular inositol polyphosphates
Studies of HL60 cells, with Bob Michell, revealed three important characteristics of inositol polyphosphates: (i) they are present in the cytosol of mammalian cells in much larger quantities than the Ca2+-mobilising second messenger inositol 1,4,5-trisphosphate; (ii) the concentrations of several inositol polyphosphates, especially Ins(1,3,4,5,6)P5, increase substantially during myeloid differentiation; and (iii) normal haematopoietic progenitors and malignant cells such as HL60 display similar changes during differentiation.

Differentiation and proliferation are separately regulated
I showed that myeloid cells can undergo commitment and differentiation to neutrophils and to monocytes under conditions that permit no proliferation. Moreover, differentiation is initiated rapidly in cells arrested in early G1, at G1/S or during S phase of cell cycle. These studies revealed that differentiation and proliferation are separate processes that can be concurrently regulated.

Novel strategies for differentiation therapy of myeloid leukaemias
ATRA is widely used to treat acute promyelocytic leukaemia. The sensitivity of myeloid cells to ATRA (and to vitamin D3) can be increased by simultaneous treatment with several agents, such as indomethacin. The steroid-metabolizing enzyme aldoketoreductase e, which was cloned with colleagues in Cardiff, is a cellular 'target' for some of the 'sensitizing' agents. Sensitization of leukaemia cells to the differentiative effect of ATRA by inhibiting the activity of aldoketoreductase e provides a novel type of combination differentiation therapy for leukaemias.

Other activities

- 1998-2004 Consultant to Allergan Pharmaceuticals, Irvine, California
- A founder member of the Rotary Club of Edgbaston Convention

Publications

BROWN G, HUGHES PJ, MICHELL RH, ROLINK A and CEREDIG R (2007). The sequential determination model of hematopoiesis. Trends in Immunology 28: 442-448.

HUGHES PJ, LEE JS, REINER NE and **BROWN G** (2008). The vitamin D receptor-mediated activation of phosphatidylinositol 3-kinase (PI3Ka) plays a role in the 1a,25-dihydroxyvitamin D_3-stimulated increase in steroid sulphatase activity in myeloid leukaemic cell lines. Journal of Cellular Biochemistry 103: 1551-1572.

QIN S, OKAWA Y, ATANGAN L, **BROWN G**, CHANDRARATNA RAS and ZHAO Y (2008). Integrities of A/B and C domains of RXR are required for rexinoid-induced caspase activations and apoptosis. Journal of Steroid Biochemistry and Molecular Biology 112: 25-31.

HUGHES PJ, MARCINKOWSKA E, GOCEK E, STUDZINSKI GP and **BROWN G** (2009). Vitamin D_3-driven signals for myeloid cell differentiation – Implications for differentiation therapy. Leukemia Research 34, 553-565.

BROWN G, MICHELL RH, HUGHES PJ, ROLINK A and CEREDIG R (2009). A pair-wise relationship model of hematopoietic fate determination. Chapter 10 in: "Cell Determination during Hematopoiesis". eds: **G Brown** and R Ceredig. Nova Science Publishers Inc., New York. pp: 261-284.

CEREDIG R, ROLINK T and **BROWN G** (2009). Opinion Models of haematopoiesis: seeing the wood for the trees. Nature Reviews Immunology 9, 293-300.

BROWN G and CEREDIG R (2009). Lineage determination in haematopoiesis: *Quo Vadis*. Trends in Immunology 30, 465-466.

BROWN G, HUGHES PJ, MICHELL RH and CEREDIG R (2010) The versatility of haematopoietic stem cells: implications for leukaemia. Critical Reviews in Clinical Laboratory Sciences. 47: 171-180.

BOOK

Cell Determination during Hematopoiesis. eds: **G Brown** and R Ceredig (2009). Nova Science Publishers Inc., New York.

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