Douglas J Hilton

BSc (Hons) PhD FAA

Joined Institute: 1986

Date of Birth: 13 June 1964

Areas of Research: Molecular regulation of blood cell formation and function

ACADEMIC QUALIFICATIONS

1985 Monash University *BSc*

1986 The University of Melbourne *BSc (Hons)*

1990 The University of Melbourne *PhD*

CURRENT APPOINTMENTS

NHMRC Senior Principal Research Fellow, Laboratory Head, WEHI

Professor, The University of Melbourne

APPOINTMENT PRIOR TO WEHI

1997–2001 Director, Cooperative Research Centre For Cellular Growth Factors (held concurrently with my position at WEHI).

MAJOR PRIZES AND AWARDS

1984 Australian National University Vacation Scholarship

1986 Macfarlane Burnet Prize, Ormond College, University of Melbourne

1987–1990 Anti–Cancer Council of Victoria, Postgraduate Scholarship

1989 SEC Science and Technology Award

Victorian Young Achiever of the Year

1991–1993 Lucille P. Markey Visiting Fellowship

1993–1996 Queen Elizabeth II Postdoctoral Fellowship

1994 & 1996 Anti –Cancer Council of Victoria, Hillcrest Friendship Club Research Award

1996 Anti - Cancer Council of Victoria, Graham Middleton Research Award

1997 Burnet Prize of The Walter and Eliza Hall Institute of Medical Research

1998 Gottshcalk Medal, Australian Academy of Science

1999 Australian Institute of Political Studies, Victorian "Tall Poppy"

2000 Amgen Medical Researcher Award, ASMR

Inaugural Commonwealth Health Minister's Award for Excellence in Health and Medical Research

2003 The GlaxoSmithKline Australia Award for Research Excellence

2004 Fellow Of The Australian Academy Of Science

MOST SIGNIFICANT RESEARCH CONTRIBUTIONS AND PUBLICATIONS (up to 20)

Purification, cloning and characterization of LIF.

As an undergraduate and PhD student, my mentor Nick Nicola and I purified mouse and human leukemia inhibitory factor (LIF), allowing it to be cloned and produced as a recombinant protein (1–3). Studies I performed in collaboration with members of this program and others led to the realization that LIF regulates a diverse array of biological effects, providing one of the first demonstrations of cytokine pleiotropy. Among the important effects of LIF that we discovered are its capacity to inhibit ES cell differentiation and its ability to protect neurons from cell death (4,5). We have built up a strong patent portfolio covering uses of LIF. This patent base has led to LIF, marketed as ESGRO, being sold internationally.

Identification and Analysis of Cytokine Receptors.

As a Postdoctoral Fellow at the Whitehead Institute at MIT, in collaboration with another fellow, Dr Stephanie Watowich, I provided evidence for the importance of cytokine receptor dimerization in initiating signal transduction (6,7). In addition, we revealed the role that an extracellular motif (WSXWS), which defines members of the cytokine receptor family, plays in protein folding.(8). On returning to Australia, I developed a method for cloning novel cytokine receptors using short degenerate oligonucleotides encoding the WSXWS motif. Two of these receptors were shown to encode the interleukin–11 receptor α–chain (9) and a shared component of the interleukin–4 and interleukin–13 receptors termed IL–13Rα1 (10). Matter of substance and use patents covering these receptors were lodged, and in collaboration with AMRAD and Merck, we are testing IL–13 and IL–4 receptor antagonists for their ability to ameliorate allergic disease.

Suppressors of Cytokine Signaling

Over the last ten years my research has focused on the regulation of cytokine signal transduction. In 1997, Robyn Starr and I expression cloned a novel negative regulator of signalling, which we named Suppressor of Cytokine Signalling–1 (SOCS–1). SOCS–1 contains a central SH2 domain and a previously undescribed C–terminal motif we termed the SOCS box (11). By performing database searches (12) we identified 6 other novel SOCS proteins with SH2 domains and SOCS boxes (SOCS–2–7) and three novel protein families with ankyrin repeats and a SOCS box (ASB1–18), SPRY domains and a SOCS box (SSB1–4) and WD40 repeats and SOCS box (WSB1– 2). We have demonstrated that SOCS proteins act as part of a classic negative feedback loop to regulate cytokine signalling and have started to define the biochemical mechanisms by which SOCS proteins act (13,14). Through this work, we have also demonstrated that the SOCS box plays an important general role in targeting proteins for ubiquitination and degradation. (15). In addition to unravelling the biochemical mechanisms by which SOCS proteins act, we have explored the physiological role of SOCS proteins through the generation and analysis of SOCS deficient mice. To date we have demonstrated that SOCS–1 plays an important role in regulating IFNγ signalling, SOCS–2 regulates the GH/IGF1 axis and SOCS3 regulates signalling by cytokines such as IL6, which act through gp130, and G–CSF (16–19).

Modifier Screens In The Mouse

As part of a broader program to use mouse genetics to dissect the molecular regulation of hemopoiesis and to identify prospective pharmaceutical targets, we executed the first modifier screen carried out in a vertebrate (19, 20). This screen showed that it was possible to identify mutations that can ameliorate a mouse model of human disease, in this case thrombocytopenia caused by deletion of the Mpl gene, which encodes the receptor for the platelet regulating cytokine thrombopoietin.

1. HILTON DJ, Nicola NA, Metcalf D. Purification of a murine leukemia inhibitory factor from Krebs Ascites cells. ***Anal. Biochem*** 173: 359–367, 1988 (IF 2.20; 107 citations)
2. Gearing DP, Gough NM, King JA, HILTON DJ. Nicola NA, Simpson RJ, Nice EC, Kelso A, Metcalf D. Molecular cloning and expression of cDNA encoding a murine myeloid leukaemia inhibitory factor (LIF). ***EMBO J*** 6: 3995–4002, 1987 (IF 10.50; 374 citations)
3. Gough NM, Gearing DP, King JA, Willson TA, HILTON DJ, Nicola NA, Metcalf D. Molecular cloning and expression of the human homologue of the murine gene encoding myeloid leukemia inhibitory factor. ***PNAS USA*** 85: 2623–2627, 1988 (IF 10.30; 168 citations)
4. Williams RL, HILTON DJ, Pease S, Willson TA, Stewart CL, Gearing DP, Wagner EF, Metcalf D, Nicola NA, Gough NM. Myeloid leukaemia inhibitory factor maintains the developmental potential of embryonic stem cells. ***Nature*** 336: 684–687, 1988 (IF 31.00; 642 citations)
5. Murphy M, Reid K, HILTON DJ, Bartlett PF. Generation of sensory neurons is stimulated by leukemia inhibitory factor. ***PNAS USA*** 88: 3498–3501, 1991 (IF 10.30; 170 citations)
6. Watowich SS, Yoshimura A, Longmore G, HILTON DJ, Yoshimura Y, Lodish HF. Homodimerization and constitutive activation of the erythropoietin receptor. ***PNAS USA*** 89: 2140–2145, 1992 (IF 10.30; 260 citations)
7. Watowich SS, HILTON DJ, Lodish HF. Activation and inhibition of erythropoietin receptor function: The role of receptor dimerization. ***Mol. Cell. Biol.*** 14: 3535–3549, 1994 (IF 8.10; 141 citations)
8. HILTON DJ, Watowich SS, Katz L, Lodish HF. Saturation mutagenesis of the WSXWS motif of the erythropoietin receptor. ***J. Biol. Chem***. 271: 4699–4708, 1996 (IF 6.50; 43 citations)
9. HILTON DJ, Hilton AA, Raicevic A, Rakar S, Harrison–Smith M, Gough NM, Begley CG, Metcalf D, Nicola NA, Willson TA. Cloning of a murine IL–11 receptor alpha chain; requirement of gp130 for high affinity binding and signal transduction. ***EMBO J.*** 13: 4765–75, 1994 (IF 10.50; 206 citations)
10. HILTON DJ, Zhang J-G, Metcalf D, Alexander W, Nicola NA, Willson TA. Cloning and characterization of a novel shared component of the interleukin–4 and interleukin–13 receptors. ***PNAS USA*** 93: 497–501, 1996 (IF 10.30; 253 citations)
11. Starr R, Willson TA, Viney EM, Murray LJL, Rayner JR, Jenkins BJ, Gonda TJ, Alexander WS, Metcalf D, Nicola NA, HILTON DJ. A family of cytokine inducible inhibitors of signal transduction. ***Nature*** 387: 917–921, 1997 (IF 31.00; 803 citations)
12. HILTON DJ, Richardson RT, Alexander WS, Viney EM, Willson TA, Sprigg NS, Starr R, Nicholson SE, Metcalf D, Nicola NA. Twenty proteins containing a cterminal SOCS box comprise five structural classes. ***PNAS USA*** 95: 114– 119, 1998 (IF 10.30; 267 citations)
13. Adams TE, Hansen JA, Starr R, Nicola NA, HILTON DJ, Billestrup N. Growth Hormone preferentially induces the rapid, transient expression of SOCS–3, a novel inhibitor of cytokine receptor signaling. ***J Biol Chem***. 273: 1285–1287, 1998 (IF 6.50; 166 citations)
14. Nicholson SE, Willson TA, Farley A, Starr R, Zhang J-G, Baca M, Alexander WS, Metcalf D, HILTON DJ, Nicola NA. Mutational analyses of SOCS–1 and SOCS–3 suggest a dual domain requirement but distinct mechanisms for inhibition of LIF and IL–6 signal transduction. ***EMBO J***. 18: 375–385, 1999 (IF 10.50; 197 citations)

15. Zhang J-G, Farley A, Nicholson SE, Willson TA, Zugaro LM, Simpson RJ. Moritz RL, Cary D, Richardson R, Hausmann G, Kile BT, Kent SBH, Alexander WS, Metcalf D, HILTON DJ, Nicola NA, Baca M. The conserved SOCS box motif in suppressors of cytokine signalling binds to elongins B and C and may couple proteins to proteasomal degradation. ***PNAS USA*** 96: 2071–2076, 1999 (IF 10.30; 214 citations)
16. Alexander WS, Starr R, Fenner JE, Scott CL, Handman E, Sprigg NS, Corbin JE, Cornish AL, Darwiche R, Owczarek CM, Kay TWH, Nicola NA, Hertzog PJ, Metcalf D, HILTON DJ. SOCS1 is a critical regulator of interferon gamma signalling and prevents the potentially fatal neonatal actions of this cytokine. ***Cell*** 98: 597–608, 1999 (IF 26.60; 229 citations)
17. Metcalf D, Greenhalgh CJ, Viney E, Willson T, Nicola NA, HILTON DJ, Alexander WS. Gigantism in mice lacking suppressor of cytokine signaling–2. ***Nature*** 405: 1069–1073, 2000 (IF 31.00; 136 citations)
18. Croker BA, Krebs DL, Zhang JG, Wormald S, Willson TA, Stanley EG, Robb L, Greenhalgh CJ, Forster I, Clausen BE, Nicola NA, Metcalf D, HILTON DJ, Roberts AW, Alexander WS. SOCS3 negatively regulates IL–6 signaling in vivo. ***Nature Immunol*** 4: 540–545, 2003 (IF 28.20; 65 citations)
19. Carpinelli MR, HILTON DJ, Metcalf D, Antonchuk JL, Hyland CD, Mifsud SL, Di Rago L, Hilton AA, Willson TA, Roberts AW, Ramsay RG, Nicola NA, Alexander WS. Links Suppressor screen in $Mpl^{-/-}$ mice: c–Myb mutation causes supraphysiological production of platelets in the absence of thrombopoietin signaling. ***PNAS USA*** 101:6553–8, 2004 (IF 10.30; 7 citations)
20. Kile BT, HILTON DJ. The Art And Design Of Genetic Screens: Mouse. ***Nature Reviews Genetics*** (in press), 2005

TOTAL PUBLICATIONS

Refereed Journal Articles 95, Invited Reviews 30, Invited Commentaries and Editorials 1, Books 1, Book Reviews 1, Conference Proceedings 6,

Total Patents 20

RESEARCH SUPPORT 1997–2005

1993–1998 Queen Elizabeth II Postdoctoral Fellowship and Support $70,000pa

1997–2001 CRC–CGF Director's Discretionary Allocation $100,000pa

1997–1999 AMRAD, Hemopoietic Growth Factors $900,000pa

1997–2002 Cooperative Research Centres Grant, CRC Cellular Growth Factors $700,000pa

1997–2002 AMRAD/GSK grants (NR4, NR6, SOCS, LIF/IL–6) $600,000

2003–2007 NH&MRC Program Grant Molecular regulation of blood cell formation $2,750,000pa total, Hilton Lab $400,000pa

2005–2006 Australian Stem Cell Centre TBA

2005–2010 NIH Merit Award CA–22556, Differentiation of Granulocytes and Macrophages TBA

COMMERCIAL ACTIVITY

Leukemia Inhibitory factor (LIF)

1987 Human and mouse LIF are purified and cloned and patents covering LIF are lodged and assigned to AMRAD.

1988–present LIF shown to inhibit ES cell differentiation, patent filed and assigned to AMRAD. AMRAD forms subsidiary, AMRAD Biopharmaceuticals, to manufacture and distribute LIF under the product name ESGRO. AMRAD Biopharmaceuticals sold to Chemicon P/L. License to LIF for inhibition of ES Cell Differentiation transferred to Chemicon.

1988–1990 LIF licensed by AMRAD to Merck and Co. to investigate role in bone biology.

1990–1995 LIF licensed by AMRAD to Sandoz Pharma AG to investigate LIF's potential in amelioration of thrombocytopenia.

1996 AMRAD begins preclinical and clinical development of LIF for amelioration of neurological impairment associated with chemotherapy. Phase I clinical trials completed successfully with the initial Phase II completed in 2002 with no effect of LIF observed.

2000–2003 LIF licensed to Ares–Serono for use in the area of reproductive biology. Initial phase II trial yields promising results however larger scale follow–up does not demonstrate a beneficial effect on implantation rates.

IL–13Rα1

1994–1999 Cloning of novel hemopoietin receptors forms major focus of A$16M research collaboration between Division of Cancer and Haematology, AMRAD and Chugai. Patents covering IL-11Rα, leptin receptor, IL-13Rα1 and NR6 are lodged. Chugai decline opportunity to develop intellectual property.

1999 Division of Cancer and Haematology,AMRAD and Medarex execute research agreements to derive human anti–human IL13Rα1 antibodies with a view to testing their efficacy in treating asthma and allergic disease. AMRAD and Division of Cancer and Haematology collaborate to humanize a mouse anti-human IL13Rα1 monoclonal antibody.

2003 AMRAD license package of intellectual property including more than 40 antibodies to Merck in a deal announced at BIO2003 in Washington DC, that would yield US$112M plus royalties on sale if pharmaceuticals reach the market. An upfront license fee and three milestone payments totalling US14$M has paid in the first 18 months of the project.

SOCS

1997 SOCS proteins are discovered and matter of substance and utility patents are lodged.

1998 IP covering some of the SOCS molecules is licensed to AMRAD for commercial development. Research collaboration between AMRAD and members of the Division of Cancer and Haematology begins. In collaboration with AMRAD and the AMRAD spin–out company Cerylid, high throughput screens are performed to find small molecular weight SOCS inhibitors.

2000 AMRAD sublicenses a part of the SOCS IP to GSK in order to bolster drug discovery efforts. Research collaboration expands to approximately 70 scientists in GSK, AMRAD and the Division of Cancer and Haematology. GSK pullout of collaboration after post-merger restructuring.

Genetics

1999 Co-Founder, Murigen Pty Ltd (with Prof Nick Nicola, Dr Warren Alexander and Prof Simon Foote).

2000 MuriGen signs 4 year $7M contract with an International Agricultural Company.

2003 MuriGen obtains BIF grant.

2004 MuriGen executes collaborative research and development agreements with WEHI, Melbourne Health and AMRAD.

2004 MuriGen obtains START grant.

Formal Industry Involvement And Consultancies

1992–1993 Consultant, Arris Pharmaceutical Company

1993–1995 Consultant, AMRAD Corporation

1995–1997 Director, Cytokine Research, AMRAD Corporation

1995–1997 Member Scientific Committee Overseeing Collaboration with Chugai Pharmaceutical Co.

1997 Consultant AMRAD Corporation

1997 Consultant to a range of venture capital and "angel" investors

1997–2001 Director, CRC–CGF

1999–2000 Consultant, AMGEN through Wray and Associates (Patent Lawyers)

2000–2001 Member Scientific Committee Overseeing Collaboration with AMRAD and GSK

LECTURES AT MAJOR SCIENTIFIC MEETINGS 1997–2005

National

1997

Lorne Cancer Conference, Lorne, VIC, Invited Speaker

1998

Australian Institute of Medical Scientists, National Scientific Meeting, Hobart, *Invited Speaker*

2000

Australia's Science Future, Australian Academy of Science, Canberra, *Invited Speaker*

GeneOz, Heron Island, QLD, *Invited Speaker*

1st WAIMR Symposium, Busselton, WA, *Invited Speaker*

Sydney Transcription and Protein Groups Symposium, Sydney, *Invited Speaker*

2001

ComBio Canberra, *Invited Speaker and Session Chairman*

2002

10th Australian Vascular Biology Society Meeting, Newcastle, NSW, *Invited Speaker*

Endocrine Society of Australia Annual Meeting, Adeliade, *Invited Speaker*

ComBio, Sydney, *Invited Speaker, Session Chairman*

Australian Society for Medical Research Annual Meeting, Melbourne, *Invited Speaker*

2004

Monash Inflammation Symposium, Clayton, VIC, *Invited Speaker*

International

1997

International Cytokine Society Meeting, Lake Tahoe, Nevada, USA, Invited Speaker

Chugai Research Symposium, Gotemba, Japan, *Invited Speaker*

1998

Keystone Symposium on JAKs and STATS, Tamaron, Colorado, USA, *Invited Speaker*

American Society of Haematology, Miami, USA, *Invited Speaker*

1999

Endocrine Society Annual Meeting, San Diego, USA, *Invited Speaker*

Gordon Research Conference, New Hampshire, USA, *Invited Speaker*

24th European Symposium on Hormones and Cell Regulation, Mount St Odile, France, *Invited Speaker*

2000

2nd Aachen Cytokine and Signal Transduction Workshop, Aachen, Germany, *Invited Speaker*

Gordon Research Conference, New Hampshire, USA, *Invited Speaker*

International Society of Experimental Hematology, Florida, USA, *Invited Speaker*

2001

Keystone Symposium on Hemopoiesis, Whistler, British Columbia, Canada, *Invited Speaker*

Gordon Research Conference, New Hampshire, USA, *Invited Speaker*

2002

Keystone Symposium on JAK/STAT Signalling, Snowbird, Utah, USA, *Invited Speaker and Session Chairman*

Gordon Research Conference, New Hampshire, USA, *Invited Speaker*

American Nephrology Society Annual Meeting, Philadelphia, Pennsylvania, USA, *Invited Speaker*

Japanese Society for Immunology Annual Meeting, Tokyo, Japan, *Invited Speaker*

2003

International Cytokine Society Meeting, Dublin, Eire, *Invited Speaker*

American Society of Haematology, San Diego, California, USA, *Invited Speaker*

2004

Keystone Symposium on Hemopoiesis, Whistler, British Columbia, Canada, *Invited Speaker*

Keystone Symposium on JAK/STAT Signalling, Lake Tahoe, California, USA, *Invited Speaker and Session Chairman*

PROFESSIONAL ACTIVITIES

Editorial Boards

2000–present Cytokine and Growth Factor Reviews.

Editorships

2002–present Journal of Biological Chemistry

Peer Review Committees

1997 CRC for Bio–pharmaceuticals, 5th year review.

1998 CSIRO Pharmaceuticals & Health Sector Forum.

1999–2000 NH&MRC Grants Committee.

2000–2003 NHMRC New Program Grant Committee.

2004–present Australian Academy of Science Asia Exchange Committee

Membership of Executive/Policy Committees

2001–2002 Prime Minister's Science, Engineering and Innovation Council, Working Group on New Fields of Medicine

2003–present NHMRC Working Group on Measuring Record of Research Achievement

2004–present NHMRC Workshop on Research Partnership Models

2004–present NHMRC Workshop on Commercialisation

2005–present Australian Academy of Science Working Group on the RQF

Executive Positions Held

1997–2001 Director, Cooperative Research Centre For Cellular Growth Factors

2002–present Co–convenor, Lorne Cancer Conference