



Geoffrey Lindeman

BSc (Med) MBBS (Hons) PhD FRACP

Joined Institute: 1998

Date of Birth: 10 September 1959

Areas of Research: Mammary gland development and breast cancer

ACADEMIC QUALIFICATIONS

1983 University of Sydney BSc (Med)
 1984 University of Sydney MB BS (Hons)
 1990 Royal Australasian College of Physicians
 (Medical Oncology) FRACP
 1995 University of Melbourne PhD

CURRENT APPOINTMENTS

Group Leader, Victorian Breast Cancer Research Consortium Laboratory (Co-Head), Molecular Genetics of Cancer Division. NHMRC Senior Research Fellow

Medical Oncologist and Director, Royal Melbourne Hospital Familial Cancer Centre

Principal Fellow, Department of Medicine, Royal Melbourne Hospital, The University of Melbourne

PREVIOUS APPOINTMENT

1995–1997 Post-doctoral Research Fellow, The Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA USA

MAJOR PRIZES AND AWARDS

1982 Association of Commonwealth University, Travelling Fellowship

1983 Cedric Swanton Memorial Prize for Psychiatry

1984 Dunn Surgery Prize in Surgery and Clinical Surgery

1991–1994 NHMRC Medical Postgraduate Research Scholarship

1991–1992 University of Sydney Faculty of Medicine Postgraduate Travelling Fellowship

1992 Neupogen Young Investigator's Award, Clinical Oncological Society of Australia

1993 The Walter and Eliza Hall Institute Seminar Prize The Glaxo Travel Award

1995 Rhone-Poulenc Rorer Fellowship in Oncology Human Frontier Postdoctoral Fellowship (Declined)

1995–1998 NHMRC Neil Hamilton Fairley Fellowship

MOST SIGNIFICANT RESEARCH CONTRIBUTIONS AND PUBLICATIONS (up to 20)

Overexpression of the *myc*-partner, *max*, in transgenic mice

During During PhD studies I explored the biological relevance of *max*, the heterodimeric partner of the *myc* proto-oncogene, by generating transgenic mice. A key finding was that overexpressed *max* attenuated *myc*-induced lymphogenesis *in vivo* (1). I also showed that an insertional mutant strain, *max* 41, exhibited a remarkable phenotype, whereby B lymphoid cells are redirected to become granulocytes (2). I also contributed to important studies on Cyclin D1 transgenic mice, demonstrating that Cyclin D1 impeded lymphocyte maturation and collaborated in lymphomagenesis with the *myc* gene (3).

In vivo function of the cell cycle regulators E2F4 and E2F5

My postdoctoral studies were carried out at the Dana-Farber Cancer Institute/Harvard Medical School with Prof. David Livingston, an internationally recognised expert in the cell cycle field and on BRCA1 function. My research centred on the cell cycle/transcriptional regulators E2F4 and E2F5. These two members of the E2F family were shown to undergo nuclear export, revealing a novel mechanism of transcriptional regulation (4,7). I also generated E2F5 knockout mice and demonstrated that E2F5 was essential for post-natal survival. The phenotype of these mice revealed the first cell cycle-independent function for a member of the E2F family (5). Subsequent work utilising E2F5 knockout mice showed that E2F4 and E2F5 play an essential role in pocket protein-mediated growth control (6).

Positive and negative regulators of Prolactin-Stat5 signalling in the mammary gland

PrIR signalling is largely mediated by Stat5a, and since excessive Prolactin Receptor (PrIR) signalling can cause mammary tumorigenesis, we searched for modulators of Stat5a function in the mammary gland. We identified a novel cofactor, CPAP, which interacts with Stat5a and Stat5b, but not other members of the Stat family (11,21). We also identified the prolactin-responsive gene *Taxreb107*, a transcription factor involved in positive regulation of prolactin signalling (15). In collaboration with Drs Hilton and Alexander, we investigated the role of Suppressors of Cytokine Signalling (SOCS) in attenuating prolactin receptor signalling and demonstrated that SOCS1 is a negative regulator of the prolactin response *in vivo* since mice deficient in SOCS1 exhibited accelerated lobuloalveolar development during late pregnancy and precocious lactation. Further, the lactogenic defect in PrIR heterozygous

females could be rescued by deletion of a single *SOCS1* allele, indicating the importance of critical threshold levels for PrIR signalling in the mammary gland (8, 23). We explored the hypothesis that *SOCS* genes are tumour suppressor genes and found differential hypermethylation of *SOCS* genes in ovarian and breast carcinomas (18). We also recently identified 14-3-3 proteins as another possible class of negative regulators of prolactin signalling (14, 24).

Role of LMO4 in mammary gland development and cancer

LMO4 belongs to a family of LIM-only transcriptional regulators, the first two members of which are oncoproteins in acute T-cell leukaemia. LMO4 is believed to function as an adaptor protein and we identified the breast/ovarian tumour suppressor BRCA1 and the nuclear coregulatory molecule CtlP as LMO4-interacting proteins *in vivo*. LMO4 was shown to repress BRCA1-mediated transcriptional activation, suggesting a role as a repressor of BRCA1 activity in breast cancer (10, 22). LMO4 is developmentally regulated in the mammary gland and forced expression of this gene inhibited differentiation of mammary epithelial cells, suggesting that it may contribute to breast tumorigenesis (9). Upregulation of LMO4 was found to be transcriptionally regulated (12), although somatic mutations in LMO4 can occur, albeit infrequently (13). Loss of LMO4 in the mammary gland during pregnancy was found to impede mammary gland development (19). To formally test the hypothesis that LMO4 is an oncogene, we generated MMTV-LMO4 transgenic mice, and found that overexpression of a LMO4 transgene elicited mammary hyperplasia and mammary tumours. Knockdown of LMO4 levels in breast cancer cells was found to reduce cellular proliferation as well as cell migration and invasion, suggesting that deregulation of LMO4 in breast epithelium contributes to breast neoplasia by altering the rate of cellular proliferation and promoting cell invasion. Significantly, high nuclear levels of LMO4 were found to be an independent predictor of death from breast cancer (20, 25).

- LINDEMAN GJ, Harris AW, Bath ML, Eisenman R, Adams JM. Overexpressed *max* is not oncogenic and attenuates *myc*-induced lymphoproliferation and lymphomagenesis in transgenic mice. **Oncogene** 10(5): 1013–1017, 1995 (IF 6.50; 21 citations)
- LINDEMAN GJ, Adams JM, Cory S, Harris AW. B lymphoid to granulocytic lineage switch during hematopoietic differentiation in a transgenic mouse strain. **Immunity** 1(6): 517–527, 1994 (Article featured on cover) (IF 16.00; 21 citations)
- Bodrug SE, Warner BJ, Bath ML, LINDEMAN GJ, Harris AW, Adams JM. Cyclin D1 transgene impedes lymphocyte maturation and collaborates in lymphomagenesis with the *myc* gene. **EMBO J** 13(9): 2124–2130, 1994 (IF 10.50; 228 citations)
- LINDEMAN GJ, Gaubatz S, Livingston DM, and Ginsberg D. The subcellular localization of E2F-4 is cell-cycle dependent. **PNAS USA** 94(10): 5095–5100, 1997 (IF 10.30; 107 citations)
- LINDEMAN GJ, Dagnino, L, Gaubatz S, Xu Y, Bronson R, Warren HB, Livingston DM. A specific, non-proliferative role for E2F-5 revealed by gene targeting. **Genes Dev** 12(8): 1092–1098, 1998 (IF 17.00; 76 citations)
- Gaubatz S, LINDEMAN GJ, Jakoi L, Nevins JR, Livingston DM, and Rempel RE. E2F4 and E2F5 play an essential role in pocket protein-mediated G1 control. **Mol Cell** 6: 729–735, 2000 (IF 16.80; 80 citations)
- Gaubatz S, LINDEMAN GJ, Lees JA, and Livingston DM. E2F4 is exported from the nucleus on a *crml* dependent pathway. **Mol Cell Biol** 21: 1384–1392, 2001 (IF 8.10; 19 citations)
- LINDEMAN GJ, Wittlin S, Lada H, Naylor MJ, Santamaria M, Zhang JG, Starr R, Hilton DJ, Alexander WS, Ormandy CJ, Visvader JE. *SOCS1* deficiency results in accelerated mammary gland development and rescues lactation in prolactin receptor deficient mice. **Genes Dev** 15: 1631–1636, 2001 (IF 17.00; Citations 34)
- Visvader JE, Venter D, Hahm K, Santamaria M, Sum EYM, O'Reilly L, White D, Williams R, Armes J, LINDEMAN GJ. The LIM domain gene *LMO4* inhibits differentiation of mammary epithelial cells *in vitro* and is overexpressed in breast cancer. **PNAS USA** 98(25): 14452–14457, 2001 (IF 10.50; 32 citations)
- Sum EYM, Peng B, Yu X, Chen J, Byrne J, LINDEMAN GJ, Visvader JE. The LIM domain protein LMO4 interacts with the cofactor CtlP and the tumor suppressor BRCA1 and inhibits BRCA1-mediated transactivation. **J Biol Chem** 277(10): 7849–7856, 2002 (IF 6.50; 35 citations)
- Peng B, Sutherland KD, Sum EYM, Olayioye M, Wittlin S, Tang TK, LINDEMAN GJ, Visvader JE. CPAP is a novel Stat5-interacting cofactor that augments Stat5-mediated transcriptional activity. **Mol Endo** 16(9): 2019–2033, 2002 (IF 5.70; 8 citations)
- Wittlin S, Sum EYM, Jonas NK, LINDEMAN GJ, Visvader JE. Two promoters within the human *LMO4* gene contribute to its overexpression in breast cancer cells. **Genomics** 82(3): 280–287, 2003 (IF 3.50; 4 citations)
- Sutherland KD, Visvader JE, Choong DYH, Sum EYM, LINDEMAN GJ, Campbell IG. Mutational analysis of the *LMO4* gene, encoding a BRCA1-interacting protein, in breast carcinomas. **Int J Cancer** 107: 155–158, 2003 (IF 4.40; 1 citation)
- Olayioye MA, Guthridge MA, Stomski FC, Lopez AF, Visvader JE, LINDEMAN GJ. Threonine 391 phosphorylation of the human prolactin receptor mediates a novel interaction with 14-3-3 proteins. **J Biol Chem** 278: 32929–32935, 2003 (IF 6.50)
- Wittlin S, Sutherland KD, Visvader JE, and LINDEMAN GJ. Identification of *Taxreb107* as a prolactin-responsive gene in mammary epithelial cells. **Biochim Biophys Acta (Mol Cell Res)** 1642(3): 139–147, 2003 (IF 3.60)

16. Olayioye MA, Hoffmann P, Pomorski T, Armes J, Simpson RJ, Kemp BE, LINDEMAN GJ, Visvader JE. The phosphoprotein StarD10 is overexpressed in breast cancer and cooperates with ErbB receptors in cellular transformation. **Cancer Research** 64(10): 3538–3544, 2004 (IF 8.60; 2 citations)
17. LINDEMAN GJ, Hiew M, Visvader JE, Leary J, Field M, Gaff CL, Gardner RJM, Trainor K, Cheetham G, Suthers G, Kirk J. Frequency of the ATM IVS10-6T>G variant in Australian multiple-case breast cancer families. **Breast Cancer Research** 6(4): R401–R407, 2004 (IF 2.9)
18. Sutherland KD, LINDEMAN GJ, Choong DYH, Wittlin S, Brentzell L, Phillips W, Campbell IG, Visvader JE. Differential hypermethylation of SOCS genes in ovarian and breast carcinomas. **Oncogene** 23(46): 7726–7733, 2004 (IF 6.5)
19. Sum EYM, Shackleton M, Hahm K, Thomas RM, Wagner KU, LINDEMAN GJ, Visvader JE. Loss of the LIM domain protein Lmo4 in the mammary gland during pregnancy impedes lobuloalveolar development. **Oncogene** In Press (Accepted February 2005) (IF 6.50)
20. Sum EYM, Segara D, Duscio B, Bath ML, Field AS, Sutherland RL, LINDEMAN GJ, Visvader JE. Overexpression of LMO4 induces mammary hyperplasia, promotes breast epithelial cell invasion and is a predictor of poor outcome in breast cancer. **PNAS USA** Epub 9 May 2005 (IF 10.50)

Patents

1. Therapeutic and diagnostic molecules (CPAP - Stat5 coactivator). Jane VISVADER, GEOFFREY LINDEMAN. Priority Date 9/2/2000. Australia PQ5498/00 (Provisional Application).
2. A method of diagnosis and treatment and agents useful for same (LIM domain LMO4). Jane VISVADER, GEOFFREY LINDEMAN, Eleanor SUM and Lorraine O'REILLY. PCT/AU02/01246. Priority Date 12/9/2001. Australia PR7618 (Provisional Application); PCT International PCT/AU02/01246; New Zealand (National Application); Australia 2002322199 (National Application); Canada 2460092 (National Application); USA 10/799797 (National Application); Europe 2753953.5 (National Application); Japan 2003-527424 (National Application).
3. Differentiation and/or proliferation modulating agents and uses therefore (SOCS-1 - Breast). GEOFFREY LINDEMAN, Jane VISVADER. Priority Date 28/12/2001. USA 10/331695 (national application).
4. A Novel Phosphoprotein (StarD10). Monilola OLAYIOYE, Jane VISVADER, GEOFFREY LINDEMAN, Peter HOFFMAN, Thomas POMORSKI. PCT/AU03/01664. Priority Date 13/12/2002. Australia 2002953341 (Provisional Application); PCT International PCT/AU03/01664.
5. A method of cell isolation (Method of purifying mammary stem cells). Jane VISVADER, GEOFFREY LINDEMAN. Priority Date 12/5/2004. Australia 2004902525 (Provisional Application).

TOTAL PUBLICATIONS

Refereed Journal Articles 47, Reviews 3, Chapters 3, Other Publications 13

Total Patents 5

RESEARCH SUPPORT 1997–2005

1995–1998 NHMRC, Neil Hamilton Fairley Postdoctoral Fellowship \$50,000pa

1997–2002 Victorian Breast Cancer Research Consortium-Transcriptional and cell cycle regulators in mammary gland development and cancer \$600,000pa

2001–2003 NHMRC Project Clinical Outcomes in individuals with an inherited predisposition to breast cancer. \$200,000pa

2001 Cancer Council Victoria, kConFab: A national consortium for research into aspects of familial breast cancer. \$50,000

2002 Cancer Council Victoria, kConFab: A national consortium for research into aspects of familial breast cancer. \$55,000

2003–2006 Victorian Breast Cancer Research Consortium. Transcriptional and cell cycle regulators in mammary gland development and cancer \$600,000pa

2003 Multi-State Cancer Research Grant. kConFab: A national consortium for research into aspects of familial breast cancer. \$257,500pa

2003–2004 Cancer Council Victoria, SOCS genes in the mammary gland and other organs – potential tumour suppressor genes? \$30,000pa

2003–2005 NHMRC Project. In vivo role of LMO4 and isolation of an LMO4-containing proteosome in breast cancer. \$145,000pa

2003–2005 Breast Cancer Research Association. Tissue Micro-arrays – a key tool for evaluating gene expression and novel tumour markers in primary breast cancer. \$35,000pa

2004 Multi-State Cancer Research Grant. kConFab: A national consortium for research into aspects of familial breast cancer. \$276,500

2004–2006 NHMRC Project. Clinical outcomes in individuals with an inherited predisposition to breast cancer. \$167,600pa

COMMERCIAL ACTIVITY

2001–2002 Consultant to Bionomics Inc, Adelaide

2002 Consultant to Johnson and Johnson, Sydney

CLINICAL INVOLVEMENT

I have an appointment (20%) with the Royal Melbourne Hospital Department of Clinical Haematology and Medical Oncology, which is one of Australia's premier clinical oncology units, with a strong track record in the design and conduct of first-in-man Phase I and other clinical trials. I am Director of the Familial Cancer Centre, where my clinical and research focus is in the area of hereditary breast cancer, and am a member of the Department of Human Services Steering Committee for the Victorian Family Cancer Genetics Service.

I have strong links to clinical and translational research activities, including membership of the Board and Scientific Advisory Committee of the Australia and New Zealand Breast Cancer Clinical Trials Group, and membership of Cancer Trials Australia. In addition, I helped establish a tumour bank, which is a collaborative project between the VBCRC, The Ludwig Institute for Cancer Research and The Royal Melbourne Hospital. I Chairs The Victorian Tissue Bank Network, established by the Cancer Council, which was recently awarded \$7M to establish a statewide Cancer Tissue Bank.

LECTURES AT MAJOR SCIENTIFIC MEETINGS 1997–2005

National

1998

ASBMB Satellite Cell Cycle Symposium, Adelaide, *Invited Speaker*

1999

Medical Oncology Group of Australasia Annual Meeting, Hamilton Island, QLD, *Invited Speaker*

26th Annual Scientific Meeting Clinical Oncological Society of Australasia (COSA), Melbourne, *Invited Speaker*

VBCRC Annual Symposium *Speaker, Session Chair*

2000

Royal Melbourne Hospital Prostate Cancer Symposium, Melbourne, *Invited Speaker*

2002

Lorne Cancer Conference, Lorne, VIC, *Speaker*

2002

Fifth Australasian Conference on Familial and Genetic Aspects of Cancer, Barossa Valley, SA, *Invited Speaker*

2003

Royal Australasian College of Physicians Annual Meeting, Hobart, *Invited Speaker*

Australian New Zealand Breast Cancer Trials Group Annual Meeting, Adelaide, *Invited Speaker, Session Chair*

MOG (Medical Oncology Group of Australia), Canberra, *Invited Speaker*

Familial Cancer 2003 (combined kConFab, Familial Cancer

Clinic and Australian Ovarian Cancer Study meeting), Couran Cove, QLD, *Invited Speaker, Session Chair*

2004

Annual Scientific Meeting, Royal Australasian College of Surgeons, Melbourne, *Invited Speaker*

Sydney Breast Cancer Trials Symposium, Sydney, *Invited Speaker, Scientific Committee*

Familial Cancer 2004: Research and Practice, Couran Cove, QLD, *Invited Speaker, Session chair*

Australian Breast Cancer Conference, Melbourne, *Conference co-convenor, Speaker*

International

2000

International Gordon Conference on Mammary Gland Biology, Il Ciocco, Italy *Invited Speaker*

2002

International Gordon Conference on Mammary Gland Biology, Il Ciocco, Italy *Session Chair*

PROFESSIONAL ACTIVITIES**Membership of Executive/Policy Committees**

Genetics Advisory Committee, Victorian Cooperative Oncology Group, Cancer Council Victoria, Committee Member

Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer (kConFab), Committee Member

Department of Human Services Implementation Committee for the Victorian Family Cancer Genetics Service, Committee Member

Department of Human Services (Vic), Australian Bowel Cancer Screening Pilot Program, Familial Cancer Representative, Victorian Advisory Group

Human Research and Ethics Committee, WEHI, Scientific Secretary

Australasian and New Zealand Breast Cancer Trials Group, Scientific Advisory Committee Member and Board Member.

Victorian Tissue Bank Network, Cancer Council of Victoria, Committee Chairman

Genetics Advisory Group, Royal Melbourne Hospital, Committee Chair

Peer Review Committees

2002 NHMRC Grant Review Panel, Oncology

Executive Positions Held

Head, Royal Melbourne Familial Cancer Centre
Chair, Victorian Tissue Bank Network

Principal Investigator, Victorian Tissue Bank Initiative (\$7M Science Technology and Innovation-funded project)