

Principal Investigator

Name : Professor Sir David Lane

Appt : Executive Director

Tel : (65)

Fax : (65)

Email : d.p.lane@imcb.a-star.edu.sg

Employment History

- 1976-1977 Postdoctoral Research Fellow in the laboratory of Dr. L.V. Crawford, Imperial Cancer Research Fund, Lincoln's Inn Fields, London WC2A 3PX
- 1977-1981 Lecturer
Department of Zoology, Imperial College of Science & Technology, London, SW7 2AZ
- 1978-1980 *Leave of Absence*
Robertson Research Fellow/Cancer Research Institute Fellow, Cold Spring Harbor Laboratories, New York 11724, U.S.A.
- 1981-1985 Lecturer, Department of Biochemistry, Imperial College of Science & Technology
- 1985-1988 Senior Staff Scientist, Imperial Cancer Research Fund Head, Molecular Immunochemistry Laboratory I.C.R.F. Clare Hall Laboratories, South Mimms, Hertfordshire EN6 3LD
- 1988-1990 Principal Scientist, I.C.R.F. Continued at Clare Hall Laboratories
- 1990-present Personal Chair in Molecular Oncology, University of Dundee.
Director of the Cancer Research UK Cell Transformation Research Group, The Cancer Research UK Laboratories at Dundee.
- 1990-98: *Department of Biochemistry, Medical Sciences Institute, University of Dundee, Dundee DD1 4HN.*
- 1998-present *Department of Surgery and Molecular Oncology, Ninewells, Hospital and Medical School, University of Dundee, Dundee DD1 9SY*

Teaching Experience

- 1977-1985 Taught and convened an advanced third year course on molecular and cellular immunology. The course was taken by biochemists, microbiologists, zoologists and botanists. It consisted of some 25 lectures plus practicals and tutorials. In addition numerous individual lectures were given on first and second year courses.
- 1991-current Teaching final year module in molecular oncology. Additional lectures on immunology and cancer to third year biochemistry students and to medical students.

Other Appointments

Current

- Member of the Scientific Executive Board of Cancer Research UK
- Founder, Director and Chief Scientific Officer, Cyclacel Ltd
- Chairman of the SAB IMCB Singapore

- Member of the SAB of the IMP Vienna
- Chairman of the Translational Research Committee CRUK
- Chairman of the Cancer Research Portfolio Steering Group of the Chief Scientist Office Scottish Executive

Previously

- CRC Scientific Committee
- ICRF Council
- MRC Cell and Molecular Medicines Board
- Chairman of NTRAC

Research Interests

David Lane is distinguished for his original discovery of p53 and for over two decades of subsequent research through which he has brought p53 all the way from a basic discovery through to the clinic. The p53 protein is of enormous significance. Selected as Science Magazines “Molecule of the Year” over 20,000 papers on the protein have been published. The p53 gene is the most frequently mutated gene in human cancer as more than half of human tumours contain mutations in the gene. In many other tumours the p53 pathway is inactivated by other processes. Sequencing of the p53 gene and mutation analysis has given insight into the molecular epidemiological basis of Human cancer. The status of the p53 pathway is now used to guide therapy of Bladder cancer and treatments based on p53 ranging from gene therapy to small molecule activators are now in advanced Clinical trial. Indeed p53 gene therapy now has marketing approval in China. The Onyx virus designed to replicate only in p53 negative tumours has shown clear efficacy in Head and Neck cancers. Recently the p53 response has been shown to be important in many other human diseases including most dramatically the phenomena of early aging.

David Lane has clear priority for the discovery of p53 through his description in Nature (1) of the complex between SV40 large T antigen and p53. This paper published in early 1979 was based on the development (2) of novel mono-specific antibodies to SV40 T antigen (published in 1978) that allowed Lane to establish that p53 was precipitated by anti-T antibodies not because of cross reaction but because of the molecular complex between the viral and host protein . Lane’s paper was submitted in 1978 and had to revised before acceptance.

Other key papers in 1979 (Linzer and Levine, the May group in Paris and the Old group at Sloan Kettering) all followed this work and were not submitted until 1979.

David Lane has made consistent observations to the p53 field since his original discovery and is widely acknowledged as a key contributor. In the 1980’s he produced and distributed widely the key monoclonal antibody reagents that have defined the protein analysis of p53 conformation (for example 3). He showed how p53 could act to limit SV40 replication by blocking the SV40 T DNA polymerase interaction (4). He in 1990 published the first paper (5) to link over expression of the p53 protein in tumours with mutation in the p53 gene and then went on to confirm this phenomena in a wide range of cell lines and a comprehensive set of Human tumours (for example 6). In this time he developed the key reagents used in the immunohistochemical analysis of p53 in human cancer (7).

His studies of the regulation of the stability of p53 lead ultimately to his establishment that this is due to loss of expression of functional mdm2 protein in p53 mutant tumours thus explaining the link between mutation and over expression of p53 (8).

Lane was the first to show that DNA damage activated p53 dependant transcription and that the response to different damaging agents showed variable kinetics (9). He went on to show that this response occurred in human tissues and physiologically relevant doses of UV light (10). From this work stemmed his key commentary in Nature “ p53 guardian of the genome”(11) which for the first time clearly explained the role of p53 in normal cells as a damage induced checkpoint and pro-apoptotic protein and has become a citation classic.

More recently Lane’s research has been dedicated to finding ways of using the p53 system to develop new treatments for cancer. His detailed work on the p53-Mdm2 interaction (12,13,14,) established that disruption of this interaction would trigger the p53 response non-genotoxically. Improving peptide activators from 10⁻⁴ M to 5nM by peptide libraries, phage display and peptide chemistry this work is now seen as a paradigm in the analysis of protein protein interaction and many pharmaceutical companies are now working on small molecule mimics of these peptides. Lane’s work on the folding of mutant p53 (15,16,17) and its potential reactivation has similarly been widely vindicated most recently by work with small molecules from a number of groups including Alan Fersht’s group in Cambridge. Lane’s group have continued to work on p53 regulation discovering its modification by SUMO (18) subcellular localization (19) in control of degradation and activation by inhibitors of nuclear export. Lane founded a company, Cyclacel Ltd in 1996 which now has a potent non-toxic inducer of the p53 response in phase 11 clinical trials. This molecule acts by blocking the activity of the cdk/cyclin family and Lane has done extensive work on the molecular basis of inhibition by small molecules of this important class of enzymes leading up to the clinical trials and development of second generation compounds and discovered a novel route to inhibition by blockade of the substrate binding site on the cyclin subunit. (for example 20).Cyclacel has 70 employees and is seen as one of the most promising European spin out companies.

Lane has done much to encourage the translation of basic science into clinical practice and is currently playing a key role in the promotion of this approach both locally and nationally especially within the UK government and the combined UK cancer charity CRUK. Lane has won many international prizes for his research and was Knighted for his contribution to medical research in 2000.

Academic Qualifications

- 1963-1970 John Fisher School, Purley, Surrey
- 1970-1973 BSc in Microbiology (upper second class honours). University College London, London WC1E 6BT
- 1973-1976 PhD in immunology (Faculty of Medicine), Department of Zoology & Comparative Anatomy, University College London.
Thesis Title: "F: A Liver Specific Antigen".
Supervisor: Prof. N. A. Mitchison, F.R.S.

Publications

1. Lane, D.P. and Crawford, L.V. (1979) SV40 T antigen is bound to a host protein in V40 transformed cells. *Nature* 278, 261-263.
2. Lane, D.P. and Robbins, A.K. (1978) An immunochemical investigation of SV40 T antigens. *Virology* 87, 182-193.
3. Yewdell, J.W., Gannon, J.V. and Lane, D.P. (1986) Monoclonal antibody analysis of p53 expression in normal and transformed cells. *J. Virol.* 59. 444-452.
4. Gannon, J.V. and Lane, D.P. (1987) p53 and DNA polymerase α compete for binding to SV40 large T antigen. *Nature* 329, 456-458.
5. Iggo, R., Gatter, K.G., Bartek, J., Lane, D., and Harris, A.L., (1990) Increased expression of mutant forms of the p53 oncogene in primary lung cancer. *Lancet* 335, 675-679.
6. Rejthar, A., Kovarik, J., Midgley, C.A., Gannon, J.V. and Lane, D.P. (1991) Aberrant expression of the p53 oncoprotein is a common feature of a wide spectrum of human malignancies. *Oncogene* 6, 1699-1703.
7. Vojtesek, B., Bartek, J., Midgley, C.A. and Lane, D.P. (1992) An immunochemical analysis of the human nuclear phosphoprotein p53. New monoclonal antibodies and epitope mapping using recombinant p53. *J. Immun. Meth.* 151, 237-244.
8. Midgley, C.A. and Lane, D.P., (1997) p53 protein stability in tumour cells is not determined by mutation but is dependent on Mdm2 binding. *Oncogene* 5 (10) 179-1189.
9. Lu, X. & Lane, D.P. (1993) Differential induction of transcriptionally active p53 following UV or ionizing radiation: defects in chromosome instability syndromes? *Cell* 75, 765-778.
10. Hall, P.A., McKee, P.H., Menage, H du P., Dover, R., Lane, D.P. (1993) High levels of p53 protein in UV irradiated normal human skin. *Oncogene* 8, 203-207.
11. Lane, D.P. (1992) Cancer - p53, Guardian of the Genome. *Nature*, 358, 15-16.
12. Picksley, S.M., Vojtesek, B., Sparks, A. & Lane, D.P. (1994) Immunochemical analysis of the interaction of p53 with MDM2; - fine mapping of the MDM2 binding site on p53 using synthetic peptides. *Oncogene* 9, 2523-2529.
13. Bottger, V., Bottger, A., Howard, S.F., Picksley, S.M., Chene, P., Garcia-Echeverria, C., Hochkeppel, H-K., and Lane, D.P. (1996) Identification of novel mdm2 binding peptides by phage display. *Oncogene* 13 2141-2147
14. Bottger, A., Bottger, V., Sparks, A., Liu, W.L., Howard, S., and Lane, D.P. (1997) Design of a synthetic Mdm2-binding mini protein that activates the p53 response in vivo. *Curr Biol.* 7(11) 860-869
15. Gannon, J., Greaves, R., Iggo, R. and Lane, D.P. (1990) Activating mutations in p53 produce common conformational effects. A monoclonal antibody to the mutant form. *EMBO J.* 9, 1595-1602.
16. Hupp, T.R., Meek, D.W., Midgley, C.A. and Lane, D.P. (1992) Regulation of the DNA binding function of p53. *Cell* 71, 875-886.
17. Hupp, T.R., Sparks, A. and Lane, D.P. (1995) Small peptides activate the latent sequence specific DNA binding function of p53 *Cell* 83 237-245
18. Rodriguez, M.S., Desterro, J.M., Lain, S., Midgley, C.A., Lane, D.P., Hay, R.T., (1999) SUMO-1 modification activates the transcriptional response of p53. *EMBO Journal* 15;18(22):6455-6461.
19. Xirodimas, D. P., Stephen, C. W., and Lane, D. P. (2001). Cocompartmentalization of p53 and Mdm2 is a major determinant for Mdm2-mediated degradation of p53. *Exp Cell Res* 270, 66-77

20. McInnes, C., Andrews, M.J.I., Zheleva, D.I., Lane, D.P., Fischer, P.M., (2003)
Peptidomimetic Design of CDK Inhibitors Targeting the Recruitment Site of the Cyclin
Subunit. *Current Med.Chem. – Anti-Cancer Agents* 3, 57-69

Prizes and Awards

- 1990 Gibb Fellow of the Cancer Research Campaign
1993 Charles Rodolphe Brupbacher Foundation Prize, Switzerland
1993-98 Howard Hughes International Scholar Award
1993 Joseph Steiner Prize, Switzerland
1994 Medal of the Swedish Society of Oncology
1995 Yvette Mayent Prize, France
1995 Black Prize, Thomas Jefferson University, USA
1995 Mayenberg Preis, Germany
1996 Silvanus Thompson Medal
1996 Henry Dryerre Prize Lecture
1998 Paul Ehrlich Prize, Germany
1998 Tom Connors Prize Lecturer
1998 Bruce-Preller Prize
1999 Hon. Doctor of Science, University of Abertay
2000 Hon. Doctor of Science, University of Stirling
2000 Knighthood
2002 Hon. Doctor of Science, University of Aberdeen
2002 Hon. Doctor of Science, University of Birmingham
2003 Medal of the Society of Chemical Industry

Elected Fellowships

- 1990 Member of European Molecular Biology Organisation
1992 Fellow Royal Society of Edinburgh
1996 Fellow of the Royal Society
1996 Fellow of the Royal College of Pathologists
1998 Fellow of the Academy of Medical Sciences
2000 Fellow of the Royal College of Surgeons (Edinburgh)
2001 Fellow of University College London

Principal Current Grants Held

- 2003-2004 Cancer Research UK – Gibb Fund Professorship. £122,769 per annum till retirement.
2000-2003 Cancer Research UK - '*Mechanism of p53 degradation in adenovirus mediated transformation*' (with Prof. Ron Hay, St Andrews) £259,839
2001-2005 Cancer Research UK Programme Grant University of Dundee, '*Exploiting tumour suppressor gene pathways for therapy*' £2,728,118
2001-2006 MRC Co-operative Group Grant (Principal Investigator) £663,088
2001-2004 MRC Grant – '*Analysis of the novel p53 induced gene "Scotin" that promotes apoptosis*' £316,840
2001-2004 Cancer Research UK Studentship – R. Berkson £69,711- '*Discovering novel non-genotoxic activators of the p53 response*'

2002-2003 Cancer Research UK - Equipment - £28,000
2002-2003 Cancer Research UK Screen for Inhibitors of Replication Licencing project
(Staff) £41,702
Cancer Research UK (formerly ICRF) *'The development of individualised
treatment through an understanding of the basis for variations in the outcome of
chemotherapy'* (with Profs' Elaine Rankin & Roland Wolf, University of Dundee)
£231,677
2003-2006 Tenovus – Dundee Cancer Therapeutic Discovery Facility - £300,000
2003-2005 Tenovus – *'Screening for Non-Genotoxic Activators of p53 Tumour Suppressor
Function'* - £54,875