fusion

THE NEWSLETTER OF THE SIR WILLIAM DUNN SCHOOL OF PATHOLOGY

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Editorial

Anyone reading William James's article on the history of Virology at the Dunn School will not fail to notice his 'aside' speculation on why the Dunn School has been such a successful contributor to medical science and fundamental biology. It has always been an Institute without Divisions, and has consequently fostered strong interdisciplinary science.

Our strong publication record and success in raising grant funding attests to the success of that philosophy. This is, of course, a structure which carries some risks, as certain important areas may go through periods when the "active mass" in a given area would seem small. In recent years the department has had the satisfaction of seeing that some of its star scientists have moved to occupy important leadership positions in other British Universities and research Institutions. The challenge for us has been to be able to recruit new scientists to bring new disciplines to the Dunn School, so as to keep Oxford science as innovative and productive as ever. In recent years that has been achieved by the recruitment of David Greaves, Quentin Sattentau and Chris Norbury to lectureship positions, the appointment of Nicholas Proudfoot to the newly endowed Brownlee-Abraham Chair of Molecular Biology, and the decision of Keith Gull to take up a Wellcome PRF position in this department. In addition we have been privileged to welcome a number of young and talented research fellows Akoulitchev, Saunders, Blocker, Harder, Ginger, Fodor, Murphy, Powrie, Malloy and Patton who have all established their own special interests in the department so keeping us alive and alert to new themes.

Our goals of remaining a strong interdisciplinary department that interfaces well with the rest of Oxford science, while ensuring that we fulfil the best standards in teaching, do require that we attract senior figures in the areas of the molecular basis of cancer, and in cell-signalling. To achieve the former the Division has agreed to allow the department to fundraise for the creation of the César Milstein Chair in Molecular Basis of Cancer. César Milstein was an old friend of the department, and his discovery of monoclonal antibodies opened up many fields of medical science for which many of his friends here are enormously grateful. We are delighted that Celia Milstein will be the Honorary President of the fundraising committee and that César's long-term close friend Claudio Cuello (McGill University) will act as its Chairman. We look forward to working with both Celia and Claudio to honour César's contributions and leave a lasting legacy of them here in Oxford.

Herman Waldmann, FRS, Head of Department

Malik Peris returned to the Dunn School to give a departmental symposium in Novemeber 2005. See pages 4–6 for a review of Virology in the Department

News

Awards

Professor Herman Waldmann, Head of the Sir William Dunn School of Pathology, has been awarded the prestigious José Carreras Award 2005, bestowed jointly by the European Haematology Association and the José Carreras Foundation. He will be giving the José Carreras Award Lecture at the Opening Ceremony of the European Haematology Association Annual Congress in Stockholm on 2 June 2005.

Gillian Griffiths

Gillian Griffiths, Professor of Experimental Pathology, has been elected fellow of the Academy of Medical Sciences.

Prizes

Congratulations to:

Abigail Stevenson, a third year D.Phil student in Chris Norbury's lab, won the poster prize at the Biochemical Society meeting on RNA Structure and Function in Edinburgh (December 4-6, 2004), for her work on targets and protein partners of the Cid1 poly(A) polymerase.

Saddif Ahmed from Nigel Saunders' lab who won the poster competition at the International Pathogenic Neisseria Conference 2004 in Milwaukee last June for his poster entitled "Lps mediated meningococcal serum resistance in the presence and absence of capsule"

Subhankar Mukhopadhyay, from Siamon Gordon's lab, who won second prize in the Promega Young Immunologist of the Year 2004 award at the British Society for Immunology meeting in Harrogate in December 2004.

Congratulations also to **Richard Daniel**, BBSRC Research Fellow in Jeff Errington's group, who has been appointed University Research Lecturer.

Sixth form study day – penicillin

The first study day organized by the Museum of the History of Science was on the topic of Penicillin: the Wonder Drug and appropriately took place at the MSTC lecture theatre behind the Dunn School. Local school students listened to presentations on the history of penicillin, developments in fungal biotechnology, clinical applications and resistance, and antibiotic synthesis, before attending a series of workshops.

Old members

Dr Philip Carter (right) with Dr Eric Sidebottom

It is always a pleasure to see former members of the department when they are visiting Oxford. **Dr Philip Carter**, photographed in Oxford last December, is a fomer visiting Fellow, and is now Professor of Microbiology and Immunology at North Carolina State University.

Jason Cyster (DPhil 1989-92) has been awarded 2005 American Association of Immunologists Biosciences Investigator Award for outstanding, early-career research contributions to the field of immunology. Dr Cyster is now at UCSF, San Francisco, California.

Professor Geoffrey Smith, now at Imperial College London, is the recipient of the 2005 Feldburg Foundation Prize in recognition of his research with poxviruses.

Discoveries

Amin Moghaddam and **Quentin Sattentau** have a patent (P28613GB) joint with Imperial College that has just gone public. It concerns a method for modifying an antigen to alter the Th1/Th2 bias of the immune response, by adding reactive carbonyl groups to the antigen or eliminating carbonyls by reduction. It has applications for a diverse range of things

including vaccine efficacy and reducing vaccine side effects, and has implications for allergies such as peanut allergy. For more information, contact Dr Goslik Schepers at Isis Innovation, Oxford University's technology transfer centre.

Grants

Twenty-five years after James Porterfield worked on Dengue fever in the Dunn School, **Professor Siamon Gordon**, **Dr Joanna Miller** and **Dr Ben de Wet** have been awarded over $700,000 from the Pediatric Dengue Fever Initiative to study how the dengue fever group of viruses infect human cells. Dengue is endemic in more than 100 countries and here are more than 50 million cases of dengue infection each year. The group hope that their investigation into how infection by the virus occurs, they will contribute to effort to prevent infection.

Obituaries

Leslie Alan Falk (known as Leslie Alan Epstein during his years in Oxford) died in Vermont in November 2004. He was a DPhil student at the Dunn School from 1937 – 40, where he worked closely with Ernst Chain and others in the penicillin team. Upon his return to the US, he was active in community medicine and the civil rights movement.

Philippe Shubik, who did his D. Phil under Isaac Berenblum and developed the two stage theory of carcinogenesis here in mid 1940s, died in December 2004. He had been Director of the Eppley Institute of Cancer Research in Nebraska, and latterly founder and President of The Toxicology Forum, based in Oxford.

On a botanical note...

The arching symmetry of the staircases leading to the front door of the Sir William Dunn School of Pathology frame two planting beds each of which display a magnificent growth of Melianthus major. This is a South African plant that is only half hardy/tender in the UK and often grown as a greenhouse specimen. The plants outside the Dunn School must represent one of the best displays in the UK and have the benefit of a protected, south facing aspect. Even so the luxurious foliage normally succumbs to the frosts of December or January and re-grows in the Spring. This year, however the foliage has survived and has produced its dramatic brick-red flowering spikes – a small sign of global warming in South Parks Road?

This choice of plant is perhaps rather fitting for its site given its South African origins and local use. Sir William Dunn was a Scot who made his fortune in South Africa and it was his bequest which funded the building of the Sir William Dunn School of Pathology in South Parks Road. The School has many current research links with both South Africa and other sub-saharan African countries. Also, in South Africa Melianthus major or Kruidjie-roer-my-nie, which means herb-touch-me-not, is common in the south-western Cape and, although toxic when taken internally, it is used medicinally by the local people to make poultices that are applied directly to wounds.

Keith Gull

From top: Georges Dreyer, Paul Fildes, Bill Joklik, Des Kay

Virology at the Dunn School

In November 2004, Dunn School alumnus Malik Peiris came to give a well-attended departmental seminar. Malik, who did his D. Phil under James Porterfield in 1977, is now the Head of Clinical Virology at the University of Hong Kong, and his accomplishment in uncovering the SARS coronavirus and ongoing work on influenza have given him a dizzying schedule for the last couple of years. He recalls his time in the Dunn School as being 'really crazy', and he has retained the connection, through collaborations with Siamon Gordon on bird flu interaction with macrophages, and George Brownlee on the influenza virus. His visit, which also saw the return of James Porterfield to hear his former student, prompted William James to review the standing of virology at the Dunn School.

Oxford has no Departments labeled 'Microbiology' or 'Virology' (nor, for that matter 'Immunology'). In spite of this apparent deficit (or is it, perhaps, because of it?) Oxford has consistently been a world leader in these disciplines. The Sir William Dunn School of Pathology has made substantial contributions in Virology since the earliest days, and continues to do so. **Georges Dreyer** himself, the first Professor of Pathology at Oxford, published an important study in 1933 on the biology of the viruses of bacteria (bacteriophages).[1]

Howard Florey, the second Professor of Pathology, invited his old friend, **Paul Fildes** [2] to set up a 'Virus Research Unit' at the Dunn School, when he retired from the MRC in 1948. As well as making significant contributions himself, Sir Paul was responsible for training at least two eminent virologists, Bill Joklik and Des Kay. **Wolfgang (Bill) K Joklik** joined Fildes' Unit in 1949, as an Australian National University Scholar. During his graduate work on bacteriophages T1 and T2, he was able to show in 1952 that there really is no infectious virus, even in the cytoplasm, during the "eclipse phase" of the virus life cycle, which follows cellular infection. A similar finding had recently been made in bacteriophage T4 by Doerman (1951), and simultaneously for phage T5 by Desmond Kay (see below), showing that this was a general property of virus replication. After his D. Phil, Joklik went on to work in New York's Albert Einstein College of Medicine on Vaccinia virus. Amongst other things, he was able to demonstrate that at least part of the 'interferon effect' was the prevention of translation of virus mRNA though inhibition of assembly of polysomes. From 1968-92 he was head of Duke University's Department of Microbiology and Immunology, where he became a world authority on reoviruses. He published the standard text *Principles of animal virology* in 1980, and became a pre-eminent figure in American virology. Bill's exact contemporary in Fildes' Virology Unit was **Des Kay**. From the very start, he worked on bacteriophage T5, and continued with this fascinating virus up to his retirement from the Dunn School over 40 years later. He was the acknowledged world authority on electron microscopy, and wrote the definitive techniques book of the 1960s.

Henry Harris and John Watkins famously used *Sendai* virus to fuse cells from different species for the first time. Although not a virologist himself. Henry Harris recruited three leading virologists to the Dunn School in the late 1970s: James Porterfield, George Brownlee and Michael Fenwick.

By the time **James Porterfield** was appointed to the Readership in Bacteriology at the Dunn School, he was already considered to be the World authority on arboviruses – an enormous group of viruses transmitted by mosquitoes and ticks and of great medical importance,

1. *Eric Sidebottom has written about Georges Dreyer as part of his researches into the history of the Dunn School. Email eric.sidebottom@path.ox.ac.uk if you would like to know more.*
2. *Sir Paul Fildes, O.B.E., M.A., M.B., B.Ch., Sc.D., F.R.S. 10 February 1882–5 February 1971*

particularly in tropical countries. He had pioneered new methods of cultivating and serotyping these viruses during the late 1950s and 1960s and, as a consequence, was able to unravel the intricacies of their classification. The viruses on which James was such an authority – Batai, Dengue, Yellow Fever, Bunyamwera, West Nile, O'nyong-nyong and so on – are all now considered actual or potential 'emerging infections', while the rarity of experts like James poses a real danger for the future. While at the Dunn School, James turned his attention to aspects of cellular virology relating to the pathogenesis of these virus infections, particularly the phenomenon of antibody-dependent enhancement (ADE). This is the observation that weak antibody responses can paradoxically exacerbate the symptoms of virus infections such as Rabies and Dengue, and poses a significant challenge to the development of vaccines against these and other viruses.

James recruited and trained two graduate students, Malik Pieris and Jane Cardosa, to help him in this task, together with Siamon Gordon. The first, **Malik Pieris** was able to demonstrate ADE in a tissue culture system and show that the phenomenon was mediated by opsonization of virus through the Fc receptors on macrophages. Famously, Malik led the University of Hong Kong team that was the first to isolate the SARS Coronavirus. The second, **Jane Cardosa,** demonstrated that ADE could also be mediated by interaction of opsonized virus with complement receptors. She now runs the Virology department in Sarawak, Malaysia.

George Brownlee succeeded Edward Abraham as the Professor of Chemical Pathology in 1980. He had already made his name at the MRC's Laboratory of Molecular Biology in Cambridge by sequencing 5S rRNA, characterizing the immunoglobulin light chain mRNA and identifying polyadenylation signals. In Oxford, he continued to have wide interests, but a major one was the molecular biology of influenza virus. He had pioneered the use of nucleic acid sequencing to characterize the viral haemaglutinin gene of flu while in Cambridge, and he was the first to sequence the neuraminidase gene, showing that it had an unusual membrane topology and paving the way for the only current drugs effective against H5N1 'avian' flu. He has since exploited these molecular techniques to analyse the immune responses to influenza virus and, among other things, conclusively demonstrated the non-native form of cytotoxic T cell antigens. **Michael Fenwick** joined the Dunn School from Bernard Roizman's group in Chicago in 1979, and continued to make significant contributions to our understanding of the mechanisms by which Herpes Simplex virus shuts down the synthesis of its host cell's proteins.

On the retirement of James Porterfield, **Geoffrey L Smith** was appointed to the increasingly anachronistically entitled Readership in Bacteriology. Geoff had been jointly responsible for developing vaccinia virus as a vector for recombinant DNA while working in Bernie Moss's group. While in the Dunn School, Geoff undertook a systematic survey of the non-essential genes of vaccinia virus, in order to understand their role in viral pathogenesis. He discovered that vaccinia had picked up numerous immunomodulatory genes from its host that enabled it to escape some of the harmful effects of the immune system. Geoff's lab also studied vaccinia virus morphogenesis and identified and characterized several of the genes encoding proteins in the envelope of the extracellular enveloped form of the virus. His group showed that vaccinia virus uses microtubules to transport incoming and outgoing virions within the cell. Geoff moved to Imperial College in 2000, where he continues to thrive, but still enjoys giving lectures to final-year medical students in the Dunn School.

What of the present and future of virology at the Dunn School? **William James** joined the Porterfield group in 1984, and has been working on the interactions between HIV-1 and its host cell receptors. His group is pioneering ways of using artificial nucleic acid ligands, called aptamers to analyse and inhibit these processes. **Quentin Sattentau** was recruited from Imperial College in 2001. Already well-known for his work on neutralization of HIV-1 by antibody and the function of HIV-1 envelope glycoprotein, he is currently working on the 'infectious synapse' formed between infected

From top: James Porterfield, Jane Cardosa, Geoff Smith, George Brownlee

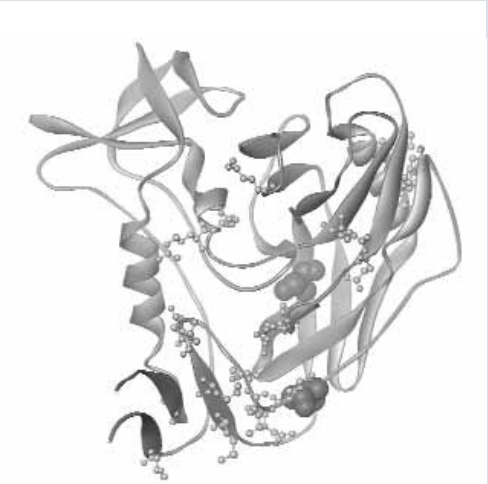
Some recent papers from the virology groups include:
1. Vreede, F.T., T.E. Jung, and G.G. Brownlee, Model suggesting that replication of influenza virus is regulated by stabilization of replicative intermediates. J *Virol*, 2004. **78**(17): p. 9568-72.

2. Khati, M., M. Schuman, J. Ibrahim, Q. Sattentau, S. Gordon, and W. James, Neutralization of infectivity of diverse R5 clinical isolates of human immunodeficiency virus type 1 by gp120-binding 2'F-RNA aptamers. J *Virol*, 2003. **77**(23): p. 12692-8.

3. Jolly, C., K. Kashefi, M. Hollinshead, and Q.J. Sattentau, HIV-1 cell to cell transfer across an Env-induced, actin-dependent synapse. J *Exp Med*, 2004. **199**(2): p. 283-93.

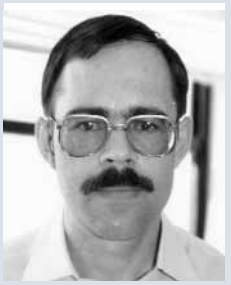
4. Fodor, E. and M. Smith, The PA subunit is required for efficient nuclear accumulation of the PB1 subunit of the influenza A virus RNA polymerase complex. J *Virol*, 2004. **78**(17): p. 9144-53.

5. Tahiri-Alaoui, A., A.C. Gill, P. Disterer, and W. James, Methionine 129 Variant of Human Prion Protein Oligomerizes More Rapidly than the Valine 129 Variant: Implications for disease susceptibility to Creutzfeld-Jakob disease. J. *Biol. Chem.*, 2004. **279**(30): p. 31390-31397.



and uninfected cells and is developing approaches to antiviral microbicides. **Joanna Miller** joined Siamon Gordon's group and together with **Ben de Wet** has been awarded a grant by the Pediatric Dengue Vaccine Initiative to investigate the cellular receptors for dengue virus on human monocytes and macrophages. **Ervin Fodor**, a former student of George Brownlee, was attracted back from the United States with an MRC Senior Research Fellowship to work on influenza virus replication. He developed an important new method for reconstructing influenza virus from cloned DNA which is now the foundation for the rapid production of vaccine in response to the emergence of new strains. His main research interests now are the interaction of influenza virus polymerase with components of the host cell transcription complex. Professor Brownlee is as active and original as ever, and continues to startle the world of virology with his elegant experiments on influenza virus transcription and replication.

Albert Beyers Travelling Scholarship



This fellowship was set up by colleagues of Albert Beyers in response to his tragic death at the age of 44 in 2000. Albert was an exceptional scientist who trained in Medicine at the University of Stellenbosch before taking the prestigious Nuffield Trust fellowship to work with Alan Williams and colleagues at the Sir William Dunn School of Pathology, University of Oxford in 1988, completing his D.Phil. in 1991.

At a time of great change in South Africa, Albert and Louise wanted to be there and despite the uncertainly, went to work in Cape Town in 1992. In 1994 Albert took up the first South African Wellcome Trust Senior Fellowship. He had built up a reputation for high quality research in immunology and tuberculosis when he died in 2000. In order to recognize his achievements, a travelling fellowship was set up, funded by his former Oxford colleagues to provide short term visits for South African immunologists to promote awareness of immunology and establish links for young South African biomedical scientists. The award gives the successful candidate two weeks in a UK laboratory to acquire specific skills in the field of immunology. These have involved visits to a number of institutes in the UK including the Universities of Edinburgh, Oxford, Southampton, Warwick and The Hospital of Chelsea & Westminster in London. The award is administered jointly by the South African Medical Research Council and the Sir William Dunn School of Pathology. Further contributions to enable this fellowship to continue would be particularly welcome and may be sent to the Sir William Dunn School of Pathology.

Albert Beyers Scholars

2001; Helen Steel (MRC & University of Pretoria) and Lee-Anne Stanton (Stellenbosch University). **2002**; Carminita Frost (University of Port Elizabeth) and Debra Meyer (Rand Afrikaans University). **2003**; Wendy Burgers (UCT Med School). Jo-Ann Passmore (University of Cape Town), **2004**; Noxolo Mkwetshana-Kuse (University of Port Elizabeth); Annie Joubert (University of Pretoria).

You, Me and HIV

A campaign to help combat the spread of HIV/AIDS through educating children across sub-Saharan Africa about how the virus is contracted was launched in Cape Town, South Africa on 31 March 2005.

The 'You, Me and HIV' project is the brainchild of South African born Oxford scientist, Professor Siamon Gordon, GlaxoSmithKline Professor of Cellular Pathology at the Sir William Dunn School of Pathology. Over 70,000 free copies of a children's book will be distributed to NGOs, schools and at camps over the coming months. Thanks to new funding from the Bill and Melinda Gates Foundation, copies of the book *You, Me and HIV: with knowledge we have hope*, will be available in English, Afrikaans and Zulu, and will be accompanied by a teachers guide.

The new project follows the successful 2002 pilot programme *Staying Alive: Fighting HIV/AIDS*, also devised by Professor Gordon (see Fusion, Michaelmas 2002). Social scientist Linzi Rabinowitz evaluated the use of *Staying Alive* in the community and her analysis informed the new book's approach.

The book, written by Professor Frances Balkwill of Queen Mary, University of London and illustrated by Mic Rolph, uses brightly coloured diagrams and cartoons to explain in a simple yet scientifically accurate way how HIV/AIDS can affect people of all ages, and what individuals can do to protect themselves against infection.

Professor Gordon comments: 'HIV now affects ten per cent of the population in South Africa, and while anti-retroviral treatments are slowly becoming available in some areas, much more needs to be done to inform and educate the population about the spread of the virus. I hope that *You, Me, & HIV* will play an important part in educating children about the facts of infection.'

The campaign has already won the support of the SA Department of Education and of high profile South Africans, including Supreme Court Justice Edwin Cameron and Zackie Achmat of the Treatment Action Campaign. It is hoped that future editions of the book will be available in other languages and countries, including China and India, where HIV infection rates are increasing.

You, Me, & HIV is published by Cold Spring Harbor Laboratory Press. For more information see www.you-me-and-hiv.org or contact Prof. Gordon at: christine.holt@path.ox.ac.uk.

Peter Medawar and Jim Gowans at the Dunn School

Sir James Gowans 're-circulated'

Eric Sidebottom

The Dunn School has reason to be particularly grateful to three Secretaries[1] of the Medical Research Council; first to Walter Morley Fletcher for persuading the Sir William Dunn Trustees in 1922 to give £100,000 to Oxford University to build a new School of Pathology; second to Edward Mellanby, who arrived in the nick of time in 1935 to insist that Howard Florey be appointed to the chair of Pathology and particularly to James Gowans for the outstanding research he did in the Dunn School *before* becoming Secretary in 1977.

Gowans does not hesitate to attribute his success to his early training in the Florey camp. He is a great admirer of Florey's leadership, his common sense, practical skills and ability to get things done. In 1953, in suggesting to Gowans that he should work on lymphocytes, Florey said 'lymphocytes had already blunted the wits of a number of his colleagues and he saw no reason why Gowans should be spared a similar fate'. The contemporary state of knowledge had been summarized by Arnold Rich as, 'the complete ignorance of this cell is one of the most humiliating and disgraceful gaps in all medical knowledge'.

In the next 10 years or so Gowans published a series of about 10 papers (half as the sole author, most of the others with a single co-author: summarised in *Immunology Today* (1996) 17, 288) which clearly explained the life history of lymphocytes and their basic role as the key players in immune responses. The gap had been firmly closed. When Gowans started work others had already shown that sufficient lymphocytes enter the blood from the thoracic duct to replace the total blood stock about 10 times a day in the rat. But what happened to them was a complete mystery. Gowans' key contribution (a genuine breakthrough!) was to re-infuse lymphocytes labelled with 32P or tritiated compounds back into the blood and recover them quantitatively in the thoracic duct lymph. By this means the recirculation pathway was delineated in great detail and the life history and functions of the cells could be seriously investigated. Although the work on recirculation was done essentially by Gowans himself, the applications of that work to elucidating the functions of lymphocytes was shared with a number of students, postdocs and overseas visitors who, in increasing numbers, came to work with Gowans; housed, from 1963, in the MRC Cellular Immunology Unit. Prominent amongst these were: Vincent Marchesi, Douglas McGregor, Peter McCullagh, Julie Knight, Irv Weissman, Bill Ford, Jonathon Howard, Alan Williams and Don Mason. These, and others too numerous to mention, formed the 'Gowans camp'.

It is a great privilege and pleasure but a slightly humbling experience to talk to Jim Gowans these days. At 80 not only does he retain a great presence physically, but he brims over with enthusiasm for the unanswered questions of medical science. But his technique is unchallengeable. He has a network of experts that he consults in diverse areas of biomedical sciences. One can imagine him challenging them with direct questions such as 'why do we not know this, why has this experiment not been done'? He is also a bibliophile; on the shelves behind him in his study there is a magnificent collection of old scientific and natural history books and he is liable to pick out a treasure from amongst them to illustrate a point he is making.

Gowans left the Dunn School and bench science to become Secretary of The Medical Research Council in1977, a post he held until 1987. He was knighted in 1982. In 1989 until his retirement in 1993 he was Director-General of the Human Frontier Science Programme in Strasbourg. As befits a man who made one of the most important advances in 20th Century immunology, Sir James Gowans has won many prizes and holds numerous honours, honorary degrees and honorary fellowships but he is unlikely to mention these, much preferring to talk about future science, the mountains of Snowdonia or his family.

1 *Through grade inflation the 'Secretary' of the MRC is now known as the 'Chief Executive'*

Research Notes

Termination by Torpedo:

Most human genes encode for proteins and are transcribed by RNA Polymerase II (RNAPII). RNAPII must initiate and terminate transcription accurately. In a study recently published in Nature (25 November 2004)[1], Steven West, Natalia Gromak and Nick Proudfoot gained an exiting new insight into the process of RNAPII transcriptional termination, using the human beta-globin gene as a model. The RNA transcribed from close to the site of transcriptional termination was previously found to be cleaved co-transcriptionally. In this recent study it was demonstrated that the RNAPII-associated product of this cleavage is recognized by an exoribonuclease (Xrn2) that chews the RNA from the 5' to 3' direction acting like a molecular torpedo. Thus, the RNA is degraded by this enzyme which catches up with RNAPII causing its dissociation from the DNA template. Interestingly a similar mechanism of transcriptional termination has been shown to exist in yeast, highlighting the evolutionary conservation of this process.

In the same issue of *Nature*, the groups of Sasha Akoulitchev, Nick Proudfoot and William James at the Dunn School[2], showed that the end of transcription could be regulated by the RNA molecule itself, acting as an enzyme.

Taken together, these studies add to the growing body of evidence that RNA is more than just a 'middle man' between DNA and proteins, but in fact acts as an enzyme, catalyzing specific chemical reactions or playing a role in gene regulation.

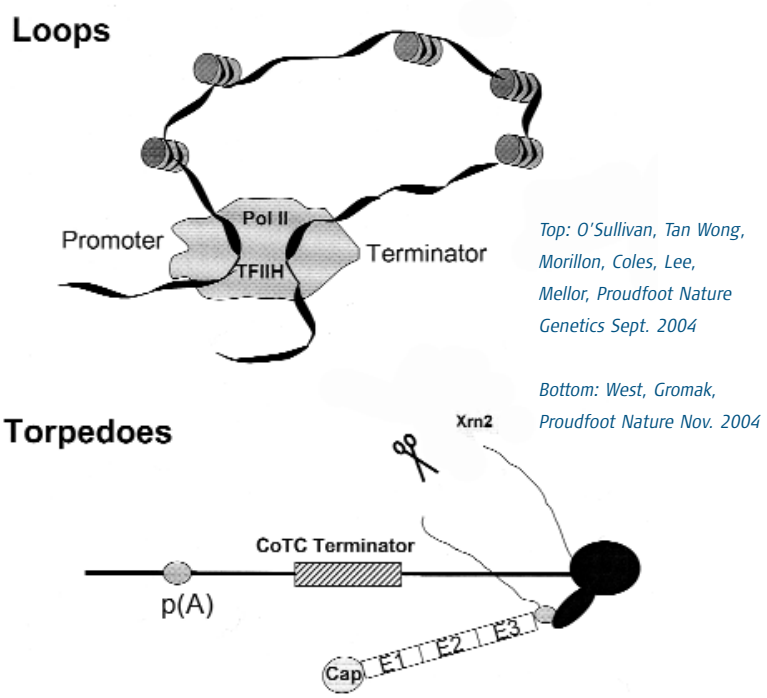
Gene Loops

Nick Proudfoot's work on yeast has also yielded interesting results on the structure of the DNA of active yeast genes.[3] His group have found that contrary to the linear structure generally drawn in textbooks, the DNA is in fact looped around (see figure). Control proteins are shared between the start and end points of the gene, and the looping appears to be essential to the activation of the gene. It is predicted that many eukaryotic genes will employ a similar looping strategy, as the loops permit the end of the gene to be defined before the costly process of gene transcription commences at the beginning of the gene.

1) West, S, Gromak, N, and Proudfoot, NJ (2004). Human 5'->3' exonuclease XRN2 promotes transcriptional termination from sites of co-transcriptional cleavage. *Nature*, 432, 522-525.

2) Teixeira, A, Tahiri-Alaoui, A, West, S *et al.* (2004). Autocatalytic RNA cleavage in the human [beta]-globin pre-mRNA promotes transcription termination. *Nature*, 432, 526-529.

3) O'Sullivan, JM, Tan-Wong, S-M, Morillon, S, *et al.* (2004). Gene loops juxtapose promoters and terminators in yeast. *Nature Genetics*, 35, 1014-18.



Top: O'Sullivan, Tan Wong, Morillon, Coles, Lee, Mellor, Proudfoot Nature Genetics Sept. 2004

Bottom: West, Gromak, Proudfoot Nature Nov. 2004

Graduate Student Symposium

The second of this annual series of symposia was held on 2 July 2004, this time including posters from both first and second year D.Phil students. Once again, the prizes were sponsored by Serotec and TolerRx, for which we are most grateful.

The first-year poster prize went to Dominika Misztela for *The roles of CD80 and CD86 in T-Cell Activation*; the second-year poster prize was awarded to Alison Paterson for *Antigen presentation for tolerance*; and the third-year presentation prize was won by Antu Dey for his talk on *Structural characterisation of RNA aptamers against HIV-1BA-LGP120.*

The next symposium will be on 1 July 2005.

Overcoming antibiotic resistance

It seems appropriate that the Dunn School, which did so much pioneering work on the early generations of antibiotics, should play a role in developing new-generation, broad-spectrum antibiotics. Professor Jeff Errington, FRS, Chair of Microbiology at the Dunn School, has for many years been investigating aspects of microbial genetics, the cell cycle, and cell morphogenesis. His research has also led to the establishment of spin-out company, Prolysis, which is developing a portfolio of novel antibacterial agents.

Prolysis was founded in 1998 (as MicroGenics), aimed at exploiting fundamental work on bacterial cell and molecular biology in the Errington lab at the Dunn School. Most modern antibiotics belong to a handful of classes, based on target activity. However, genetics and genomics had demonstrated that a much greater number of potential protein targets exist (>200). Ideal antibiotic targets comprise proteins that are: (1) essential for bacterial viability, so that chemical compounds that inactivate them will be toxic; (2) widespread among bacteria, so that the compounds will have the potential to have broad spectrum activity against many bacteria; (3) absent from human cells, so that the compounds will be selective for bacteria. The Errington lab had worked on basic aspects of bacterial cell and molecular biology for many years, without any particular commercial objective. In the mid 1990's it became clear that the pharmaceutical companies were moving towards a general target-led approach to drug discovery. The major bottleneck to target-led discovery lay in understanding the biology of the target, so that compounds acting specifically on the target could be found among the huge chemical collections that drug companies had amassed. Jeff realized that his basic research could be exploited in this way.

After several attempts to license methods of screening for new antibiotic targets to big pharma it emerged that exploitation depended on demonstration of proof of principle, and the only route to this lay down the spin-out route. Prolysis was founded in 1998 as a vehicle to develop screening systems for commercial use, based on the original assay ideas. Unfortunately, reorganizations throughout the pharma industry at that time resulted in a global reduction in big companies that could act as clients for Prolysis. The assay ideas were nevertheless developed into robust, commercially applicable systems. In 2002, Prolysis was refinanced, primarily by the Boston-based investment company, East Hill Management. The refinancing has allowed the company to develop its screening technology across a range of targets and, in collaboration with chemistry company Evotec OAI (itself based on a previous Oxford spin out) to identify compounds active against a series of novel antibiotic targets. The most advanced project concerns a series of compounds that prevent cell division. These CDI (cell division inhibition) compounds now kill a range of Gram-positive and Gram-negative pathogens. Further work is needed to develop this series of compounds to the point where they are active enough for the clinic. Nevertheless, the future seems bright for Prolysis, given the range of compounds they now have in early development and the re-emerging interest in antibiotic therapy among big pharma, while Jeff's lab continues its basic science research on cell division.

The Mould in Dr Florey's Coat

Eric Lax, the author of *The Mould in Dr Florey's Coat*, gave an entertaining and well-attended public lecture on the writing of his book on 13 September. It was a particular pleasure that so many former members of the department were able to come to the lecture and to tea beforehand.

Norman Heatley

Norman Heatley's life was commemorated by many friends and former colleagues at a moving ceremony held at the Dunn School on 18 September. Norman's wife, Mercy, and elder daughter Rose, talked about his childhood and enduring fascination with invention, while Eric Lax remembered Norman's kindness and hospitality. Eric Sidebottom gave an historical overview of the Dunn School in and before Norman's time, and Sir Henry Harris, who was unable to attend, wrote about Norman's contribution to the development of penicillin in a paper which was read eloquently by Simon Hunt.

The Norman Heatley Memorial Fund received a significant boost from the sale of a penicillin vessel and vial of the original penicillin at Christies in November, raising nearly £20,000 which was donated to the Fund by Dr Heatley's family.

Fishing for Understanding

Dr Elizabeth Patton has come to the Dunn School with a mission: to show how a tiny fish can provide a model for numerous human diseases, and offer hope in the search for new treatments. Following her arrival at the Dunn School in September 2004 on an MRC Career Development Fellowship, she is in the process of establishing the first zebrafish research facility here, as part of her investigations into the cell cycle as related to cancer.

Prior to coming to the Dunn School last year, Elizabeth was a Human Frontiers Postdoctoral Fellow in Leonard Zon's lab at the Howard Hughes Medical Institute, Harvard Children's Hospital, Harvard Medical School. In research conducted there and just published[1], she and her colleagues created the first zebrafish model of melanoma. Melanoma is an epidemic cancer, with over 50,000 new cases and 7000 deaths per year in the US alone, and increasing incidence in the UK. Melanoma can sometimes develop from a mole, and an important question in cancer research is why some moles become cancerous and others do not. While previous studies had indicated that the BRAF gene is mutated in about 75% of melanomas and mole tissue samples, no one knew what role it played in the development of the cancer within the context of a living animal. By engineering zebrafish to express a mutated version of human BRAF, Zon, Patton and colleagues showed that BRAF expression induces dramatic black pigmentation in the skin of the fish—the equivalent of moles in the fish! – showing that, when activated, human BRAF mutations are sufficient for the formation of large ectopic moles. Their experiments also demonstrated that when the fish are also deficient for a cancer gene, p53, an aggressive melanoma develops in the fish. The zebrafish model of melanoma shows that, when activated, human BRAF mutations are sufficient for the formation of large ectopic moles. BRAF in itself is insufficient to cause cancer; particular genetic mutations, such as the p53 mutation are required for a melanoma to develop. Researchers in Zon's lab plan to use this model to examine, among other things, how the melanomas metastasize, and how other gene mutations may participate in the transformation of moles into malignant melanomas, with a view to developing pharmaceutical targets.

Elizabeth herself is planning to apply the techniques from the Zon lab to continue asking questions about cancer. Chris Norbury's group have identified the cell cycle and possible cancer gene, Int 6, gene as implicated in multi-drug resistance in yeast. Elizabeth is hoping to use zebrafish mutated to exclude this gene, supplied by Nancy Hopkins at MIT, to further investigate how this gene influences development, and how the proteins it makes are involved in cancer gene networks.

Other researchers at the Dunn School are keen to take advantage of this new resource. Professor Waldmann's lab have initiated a collaboration to look at the effect of regulatory T-cells in zebrafish, and various infectious diseases, including tuberculosis and bacterial infections, can also be studied at the genetic level.

The zebrafish genome has already been sequenced; with the continuing array of genomic tools, the power of this model can only increase further.

Zebrafish are proving an increasingly popular model for basic research. Small (3cm adult size), fast-developing vertebrates, they are easy to maintain, manipulate and observe in the lab. And an increasing number of mutants are now available to enable the analysis of gene regulation and function.

Image: The black pigmentation on the Zebrafish is induced by BRAF expression.

References

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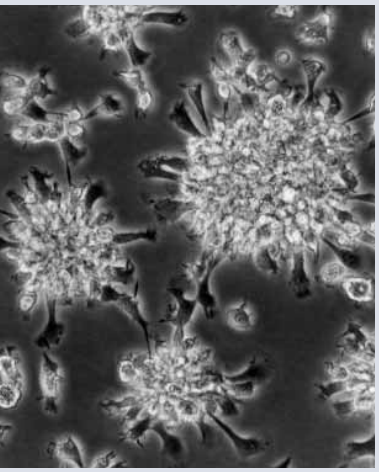

Embryonic Stem Cells and the Tithonian Dilemma

by Paul Fairchild

Man's dreams of outwitting the natural course of ageing may be traced to classical times. In Greek mythology, Tithonus was granted immortality by Zeus, but not the everlasting youthfulness he desired: instead, afflicted by Zeus' jealousy, Tithonus endured an eternity of the debilitation and dementia of old age. Although confined to the realms of legend, the moral of the Tithonian dilemma has a strangely contemporary feel, namely, that increased longevity provides no guarantee of greater quality of life.

The past century has witnessed an unprecedented increase in life expectancy in the western world due partly to medical advances, to which the discovery of penicillin has made a significant contribution. Should this current trend continue, the proportion of the population over 80 years of age will quadruple within the next 20 years, accompanied by an increased incidence of debilitating conditions such as diabetes and Parkinson's disease. Since the treatment of chronic and degenerative disease states already consumes 78% of the healthcare budget of the United States, the ageing nature of the population is set to place an unsustainable burden on limited healthcare resources.

Enter embryonic stem cells. Derived from blastocysts prior to implantation, ES cells capture a fleeting moment during human development which never recurs: the moment of pluripotency. As such, ES cells harbour the ability to differentiate into any somatic cell type, given the necessary conditions and environmental cues. By navigating the appropriate differentiation pathways, it has already proven possible to produce cell types as diverse as cardiomyocytes, dopaminergic neurons and pancreatic islets, capable of secreting insulin. The implications are far-reaching, since lines of ES cell may provide, on demand, the necessary tissues for cell replacement therapy, heralding a new era in regenerative medicine.

But while the potential of ES cells to meet the growing demand for tissues and 'spare parts' has been widely acclaimed, their translation to the clinic poses a number of challenges, not least of which is the prevention of their subsequent rejection by the patient's own immune system. Therapeutic cloning offers to circumvent rejection by creating ES cells genetically identical to the recipient. Yet somatic nuclear transfer faces formidable logistic hurdles and an ethical quagmire so deep as to inspire proposals for an outright ban by the United Nations. However, the very same pluripotency that makes ES cells unique may offer an alternative solution to the problem of rejection. By obtaining a ready source of hematopoietic cells from their differentiation in culture, it may prove feasible to reprogram the immune system of the patient to accept replacement tissues, prepared from the same parent cell line.

Work in our laboratory over the past few years has laid the foundations for just such an approach. In particular, we have devised protocols for the derivation of almost limitless numbers of dendritic cells (DC) from mouse ES cells, supplied by Richard Gardner's group in the Department of Zoology. The significance of DC lies in their ability to orchestrate the immune response, defining the all-important balance between tolerance and immunity. Work by Stephen Yates in our laboratory has provided compelling evidence that administration of DC alone is able to establish a robust form of tolerance to tissues derived from the same donor, provided the DC themselves are restrained from maturing. While Stephen's work has focused on the use of DC cultured from bone marrow precursors, whose spontaneous maturation is notoriously difficult to intercept, DC differentiated from ES cells are uniquely arrested at an immature stage of their life cycle, making them attractive candidates for tolerance induction. It is this prospect we are now actively pursuing in experimental models of allograft rejection. While for Tithonus these developments may prove rather too late, if successful, they may one day help treat a wide variety of chronic and degenerative diseases through the panacea of regenerative medicine.

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