fusion

THE NEWSLETTER OF THE SIR WILLIAM DUNN SCHOOL OF PATHOLOGY

ISSUE 7 · MICHAELMAS 2008

UNIVERSITY OF OXFORD

Editorial

Welcome to this 7th Edition of Fusion! It has been largely put together by Paul Fairchild and Eric Sidebottom; thanks to them and all the contributors for a really stimulating read.

Contributing to Fusion is something of a Rite of Passage, and this edition celebrates just about every phase conceivable in a scientifically illustrious career. To start at the beginning, we have a prize-winning essay by Kathy Liu, a graduate student with Paul Fairchild and Herman Waldmann, who would present her engineered stem cells as a fitting gift to China's first emperor, who sought the elixir of life (see page 11). The excitement of human embryonic stem cells – and now induced pluripotent stem cells (iPS) – has encouraged many to exaggerate their potential as cure-alls for ageing, but several groups in the Dunn School are making serious use of them for scientific purposes. The Oxford Stem Cell Institute, part of the James Martin School for the 21st Century, is based here, and its promising start is described on page 14. At the senior post-doc stage, Mick Dye describes his ground-breaking work on the eukaryotic transcription machinery on page 9. His elegant experiments in Nick Proudfoot's lab have produced a very satisfying account of how the process of mRNA splicing is organized around the actively transcribing RNA polymerase. Even more pleasingly, his artistic interpretation of the work has now made the front cover of *Molecular Cell* twice!

This edition marks the appointment of Steve Bell as Professor of Microbiology, in succession to Jeff Errington. Some readers may not have heard about the Archaea before, and others may wonder what they have to do with Pathology. However, as anyone who reads Steve's work quickly comes to realize, these microorganisms offer an amazingly powerful way of investigating the basic transcription and replication machinery that lies at the heart of human cells (see page 3). Steve is a world-leader in this field, and the buzz in his lab is palpable. Also senior newcomers to the department are Liz Robertson and Liz Bikoff. Liz Robertson is a Wellcome Trust Principal Research Fellow, who is famous for her early work with mouse embryonic stem cells. She has used this powerful technology over recent years to open up the field of developmental biology. The group have made particular contributions to our understanding of the transcriptional control of the early differentiation of mesoderm and endoderm, and the signalling pathways governing the patterning of the early body axis. We had hoped to persuade them to tell us about their work in this edition of Fusion but they have promised an article for the next edition. We were lucky to be able to attract Peter Cresswell last year as the Newton-Abraham Visiting Professor. He joined Neil Barclay's lab from Yale for a very hands-on period as a sabbatical bench worker, and he was a truly inspirational colleague. His advice to the young (page 8) is based on experience and example: (I paraphrase) "Select a good mentor; choose an interesting, difficult but tractable problem; work really hard; get lucky".

At the most senior level, we mark the retirement of several of our most valued, long-standing colleagues (see page 13). As is so often the case at the Dunn School, retirement just marks another phase in one's productive scientific life for at least one, Gordon MacPherson. He reminisces on 44 years at the Dunn School (on and off) that have been marked by his unstoppable rise to the heights of his profession, both as a world-expert on dendritic cells, and as the best Pathology teacher. Luckily for us, he will be returning next year as a part-time Departmental Lecturer, to continue to educate, stimulate and train our students.

My own rite of passage has been to serve the department as acting Head for a year, while Herman was officially on sabbatical. It has been a great privilege and a thoroughly enjoyable experience, thanks to Herman's willingness to be on hand for much-needed advice, and the great *esprit de corps* that has developed at the Dunn School over the years. As Herman prepares to return to the fray, I wish him all the best. With new building developments and major recruitments coming up in the next year (see the next *Fusion* for details), he has an exciting time ahead!

William James

Contents

Honours; Prizes; News

Congratulations are due to the following members of the Department.

Professor Herman Waldmann has been awarded:

1. The prestigious **2008 Thomas E. Starzl Prize in Surgery and Immunology.** He received the prize and gave a lecture in Pittsburgh in March 2008.
2. An **honorary doctorate (Doctor of Science) from the University of Cambridge.** This was conferred at a special Congregation held in the Senate House on 23rd June.
3. A **BTG Lifetime Achievement Award,** presented at the Scrip Awards on 4th December 2007 at the Park Lane Hilton, London.

Professor Keith Gull has been awarded an honorary DSc degree by the University of Kent.

Professor Liz Robertson was awarded the 2007 Pearl Meister Greengard Prize from Rockefeller University, and also the 2008 EG Conklin Medal from the International Society of Developmental Biologists.

Kevin Maloy has been appointed to a University Lecturership in Experimental Pathology from 1st October, 2008.

Helen Dawe (Gull lab) has been awarded the title of University Research Lecturer.

Ervin Fodor was awarded a Research Councils UK Academic Fellowship.

Janine Coombes (Powrie lab) and **Johanna Hoog** (Gull Lab) have both been awarded Sir Henry Wellcome Postdoctoral Fellowships. (These Fellowships are for the most promising newly qualified postdoctoral researchers to help them make an early start in developing their independent research careers. It provides an award of £250,000 to support the basic salary and research expenses.)

Susan Vaughan (Gull Lab) has been elected to a Research Fellowship at Wolfson College

David Greaves, David Vaux and **Paul Fairchild** are to be congratulated on receiving **Teaching Excellence Awards** from the Medical Sciences Division.

David Greaves has also featured prominently on the University Website recently for his work on cytokines involved in various inflammatory processes. This work could lead to the development of new anti-inflammatory drugs and is currently the subject of a patent application by Isis innovation.

Sylvain Lacombe (Gull lab) has been awarded the Henry Goodger Scholarship from the Medical Sciences Division.

Susan Lea's group has been developing something of a monopoly on awards in the Oxford University Research Staff Society Poster Competition. **Pietro Roversi** won this year's competion, **Steven Johnson** last year's (**Janet Deane** came 2nd) and the year before Steven came 2nd. Keep up the good work!

At this years Annual Graduate Symposium the following awards were made:

Best 1st year poster: **Erica Lacey**
Best 2nd year poster: **Claudia Brockmeyer**
Best 3rd year presentation was divided equally among three recipients: **Jenna Cash, Hashi Wijayatilake, Jan-Peter Daniels**

The **16th annual Norman Heatley** lecture was given on 29th November by **Professor Anthony Hyman,** Max Plank Institute of Molecular Cell Biology and Genetics, Dresden. Professor Hyman's talk was on the subject of "Boveri revisted".

A novel approach to the training of graduate students was taken recently by **Dr Marion Brown.** She writes:

As an addendum to my research techniques day I hijacked a successful theatrical performance which was part of a programme of engaging with the public conducted by the Museum of the History of Science. The rationale was twofold: firstly scientists need to learn how to contribute toward the public understanding of science and secondly, presentation is an important part of scientific training and I think lessons can be learned from the theatre.

Consequently, we were entertained by actors, including one of our students, Andrew Johnson, reading from Robert Hooke's "Micrographia" followed by excerpts from "The Virtuoso" by Thomas Shadwell. "The Virtuoso" was written in the late 17th century around the time the Royal Society was established. In the view of the Royal Society a Virtuoso was a serious experimental scientist but the caricature in the play suggests that in the popular mind at least, the Virtuoso or "new philosopher" was still a dilettante and a dabbler.

It was great fun and feedback from students and staff, including some of our own Virtuosi, indicated that they had grasped the points I was trying to make.

Research Funding

We are delighted to announce that the following laboratories have all been awarded research funding of more than £150,000 since the beginning of this year.

Fodor	MRC
Lea	Wellcome Trust
Bell	Wellcome Trust
Norbury	BBSRC
Saunders	Meningitis Research UK
Barclay	Wellcome Trust
Acuto	European Commission
Fairchild	James Martin 21st Century School

Introducing Stephen Bell

November 3rd, 1977 – the day our perception of life on Earth was fundamentally changed. We went to bed on the night of the 2nd secure in the knowledge that cellular organisms could be classified as either prokaryotes (cells without nuclei) or eukaryotes (cells with nuclei). The next morning, the New York Times and the Proceedings of the National Academy of Sciences revealed to the world that a whole new kingdom of life existed – the Archaea. This staggering discovery was made by Carl Woese at the University of Illinois in Urbana. He had been carrying out a painstaking analysis of the sequence of components of the ribosome – the cellular machinery for making proteins – and in doing so realised that the sequences grouped into three main groups or Domains. One Domain encompassed the Eukaryotes but the big surprise was that the "prokaryotic" group was actually comprised of two entirely distinct sub-groups. These are now called the Bacteria and the Archaea. Woese's proposal was, naturally, hugely controversial at the time but has been widely accepted in the intervening 30 years. An examination of Woese's famous tree of life (Figure 1) suggests that there is, in fact, a fractionally closer relationship between the Eukaryotes and the Archaea than there is between the Bacteria and these two lineages. It can be seen that bacteria branched off first, leaving a period of evolutionary history that was occupied by organisms that served as the common ancestral lineage from which Eukaryotes and Archaea arose.

As early as 1979 the similarity between Archaea and Eukaryotes was becoming apparent with Wolfram Zillig's pioneering analysis of the gene transcription machinery of *Sulfolobus acidocaldarius* – an archaeon that was isolated from a hot spring in Yellowstone National Park and grows at 80°C at pH 2. Zillig purified the RNA polymerase enzyme from *S. acidocaldarius* and found it to have 12 subunits – clearly more complex that the simple bacterial 4 subunit enzyme and reminiscent of the complex eukaryotic nuclear RNA polymerases. Indeed, Zillig went on to show that all the "extra" archaeal subunits had counterparts in eukaryotic RNA polymerase but not in bacteria. However, the RNA polymerase on its own was incapable of specific initiation and thus required accessory "general transcription factors" or GTFs. Subsequent work by Sohail Qureshi and me in Steve Jackson's lab in Cambridge, and independent studies by Michael Thomm's lab in Kiel, revealed that only two GTFs were required – termed TBP and TFB – and that these had clear counterparts in eukaryotic transcription by RNA polymerase II. However eukaryotic transcription is hugely more complex and requires an additional alphabet soup of factors (the TAFs, TFIIA, TFIIE, TFIIF and TFIIH). That archaeal transcription did not depend on all these additional 20 or so proteins meant that we had a simple model system with which we could begin to dissect the transcription machinery. But, beyond the basic mechanisms of transcription, we also wanted to understand how genes are switched on and off in the Archaea. To address this, we turned to the newly available archaeal genome sequences and there, to our surprise, we found that, instead of encoding eukaryotic-type regulators, they had counterparts of bacterial-type regulators. How then did these bacterial-type regulators impinge on the eukaryotic-type transcription machinery. This turned out to be fairly straightforward and I was able to dissect a couple of examples where the regulators repressed transcription by physically binding to the DNA and simply blocking access to the area where gene transcription started. Finally, we wanted to understand how the "chromatin" proteins that package *Sulfolobus's* millimetre of DNA into a cell with a diameter of 1 thousandth of a millimetre might influence transcription processes. This aspect of the work was a wonderful collaboration with a friend and colleague in St Andrews, Malcolm White. I had been intrigued by the presence of a gene for a protein called Sir2 in archaeal genomes. Sir2 is a deacetylase that plays some key roles in chromatin modification in eukaryotic cells. What was it doing in *Sulfolobus*?. To begin to address this, I purified the Sir2 protein from *Sulfolobus* cells and found a second protein had copurified in a complex with Sir2. At the same time Malcolm had purified a major *Sulfolobus* chromatin protein based on its ability to bind DNA. We both sent our proteins off to be sequenced and incredibly they turned out to be the same thing – a protein that we now call Alba. In our ensuing studies we found that Alba was in fact acetylated in archaeal cells and that Sir2 deacetylated it. Further, acetylation of Alba loosened its grip on DNA, providing a mechanism for modulating local chromatin structure – a process that my lab is still working on.

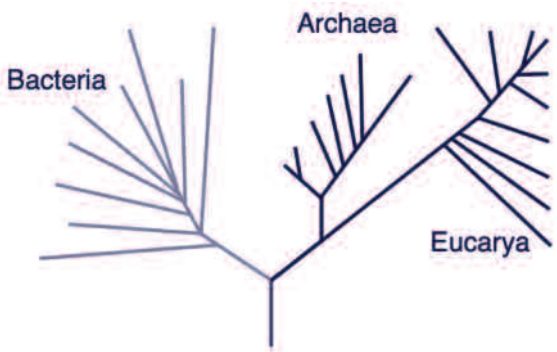


Figure 1. *Woese's famous tree of life*

About this time I had the chance to set up my own lab in the MRC Cancer Cell Unit in Cambridge. However, rather than continue my transcription work, Unit director, Ron Laskey was keen for me to switch topics to the process of DNA replication. The reason for this was that the genome sequences were telling us that the Archaea had a DNA replication apparatus that closely

resembles our own, but is very much a simplified version. Furthermore, the DNA replication machinery is inextricably enmeshed within the cell cycle apparatus in eukaryotes and this makes analysis of the basic functions of the key engines of DNA replication a formidable task. The hope was that Archaea would provide a simple, tractable model system with which to dissect the mechanistic basis of the conserved features of the replication apparatus. Fortunately, this seems to be the case! DNA replication has a number of key stages. A start site for replication must be assigned (the so-called origin of replication). The double helical DNA must be unwound to expose the templating bases at the heart of the helix. The melted region must be extended, and of course, the DNA must be copied. Our assault on the archaeal replication apparatus was aided by the fact that the proteins in *Sulfolobus* are heat stable – this makes purifying them reasonably straightforward. The proteins are also relatively easy to crystallise, allowing determination of their structure and thanks to a number of excellent collaborations, we now have structures of several components of the replication apparatus, greatly aiding our analysis of their function. The combination of biochemical and structural approaches has given us insight into the inner workings of the assemblies involved in unzipping DNA and in ensuring that DNA is copied accurately and in its entirety.

...it is estimated that there are 10^{28} Archaea in the oceans. This means that Archaea are the second most abundant form of life on the planet (after bacteria)...

Beyond the reductionist biochemical approach, we have a considerable interest in DNA replication in the cellular context. There is a pivotal difference in replication initiation between bacteria and eukaryotes – bacterial chromosomes have a single origin of replication, eukaryotes have thousands. As Archaea are "prokaryotes" with simple circular chromosomes – like bacteria – we naively assumed that, like bacteria, they would replicate their DNA from a single origin of replication. It was a thrilling surprise when my post-doc Nick Robinson revealed that in fact *Sulfolobus* had multiple replication origins: we now know from Nick's work, and that of Rolf Bernander in Uppsala, that *Sulfolobus* uses three replication origins. Furthermore, all three origins are used once and once only in each cell cycle – a situation reminiscent of eukaryotes – we are currently trying to work out how this coordinate regulation is effected. To address this we've developed new ways of synchronising cells and this in turn has opened the door to analyses of cell cycle control and novel approaches to unravelling the enigmatic aspects of archaeal cell division.

I think it is clear that hyperthermophilic Archaea have tremendous utility as a model for studies of the conserved features of the information processing machineries. They also have the fringe benefit that working on them also gives me the opportunity to go to conferences in Yellowstone National Park! However, although the hyperthermophiles are probably the most highly studied Archaea, there is a wide range of mesophilic archaeal species. In fact, at least one third of the human population have mesophilic Archaea in their digestive systems. Although no archaeal pathogens have yet been identified, model system studies have indicated a linkage between archaeal colonisation and obesity. Additionally, it is becoming increasingly apparent that Archaea are a dominant component of the biosphere – it is estimated that there are 10^{28} Archaea in the oceans. This means that Archaea are the second most abundant form of life on the planet (after bacteria). It is also becoming clear that Archaea are key players in globally important carbon and nitrogen cycles. Methanotrophic Archaea in marine sediments help reduce methane seep from natural sub-sea floor methane reservoirs. It is worth noting that, molecule for molecule, methane is a 25-fold more potent green house gas than CO_2. Archaea also predominate the soil-based ammonia oxidisers and, therefore, underpin a central step in nitrification. Finally, it has been found very recently that *Sulfolobus* and a number of its relatives, including the highly abundant oceanic Archaea, are capable of assimilating CO_2 into organic material by a novel biochemical pathway. The abundance of these Archaea suggests they may play an important role in global carbon cycling. Thus, Woese's remarkable discovery 30 years ago has paved the way for the development of new tools for understanding key cellular processes and also for gaining insights into the global mechanisms that make the planet a hospitable place for us to live.

Gordon MacPherson: A Retrospective Review

I became aware of the Dunn School in 1964 – at that time medical students took Pathology in the fourth year after three years focusing on anatomy, biochemistry and physiology. Our first lecture was, I think, Henry Harris's first as the new professor – we were given a historical introduction to experimental pathology with lots of fading photographs of the great and good. I soon learned that the quality of the lecturers varied enormously, and as the standard text was Florey's Pathology, written largely by the Dunn School lecturers, in some cases it was easier to learn from the books in one's room in college. We had microbiology lectures at 5 pm. At the end of one of them, a student in the front row remained asleep when all of us, and the lecturer, had departed. A friend happened to be passing an hour or so later and out of curiosity popped into the Dunn School. The student remained fast asleep. That is real pulling power. There were of course highlights – Van Heyningen telling us how to murder your wife with botulinum toxin, the saga of Ted Abrahams catching Weil's disease (Leptospirosis) after falling off his bicycle into the Cherwell, and a tall young immunologist by the name of Gowans exciting and confusing us at the same time with the mysteries of immunology (not much change there then). It was however this course which really stimulated me to want to learn about the science of disease.

After my clinical studies and house jobs I returned to the Dunn School to do a DPhil under the supervision of John French on megakaryocytes and platelet production – I was able to show that increased demand for platelets led to an increase in the numbers of endomitoses in individual megakaryocytes, leading to an increased number of platelets released by each cell, as well as to an increase in total numbers of cells. I had almost decided to go to the USA to do a post-doc but Henry Harris suggested I apply for the Florey Fellowship to Canberra. There I did my only post-doc – two years under the brusque, ovinocentric and oenological supervision of Bede Morris in Canberra, where I learned how to be sceptical about immunology – at around the same time two guys called Doherty and Zinkernagel were working across the corridor but in our group B and T were regarded as the first and last letters of a well-known Australian saying. I spent most of the time transplanting kidneys in sheep (my surgical skills at first were such that Bede thought I was the answer to the Australian sheep glut) and sticking tubes into sheep lymphatics. There I became aware of the irregular, veiled cells, at that time thought to be macrophages, that migrated in lymph draining skin, kidneys and liver and which have kept my interest and curiosity going over the last 35 years.

In 1971 I returned to the Dunn School, and apart from a sabbatical with Bob North at the Trudeau Institute in Saranac Lake, I have been here ever since. After a spell investigating the roles of macrophages in rat heart allograft rejection, I returned to lymph. Graham Mayrhofer, working with Jim Gowans (who had pioneered thoracic duct cannulation for the investigation of lymphocytes), showed that, following removal of the mesenteric lymph nodes in rats, large irregular cells appeared in thoracic duct lymph. I realised that this gave an opportunity to examine the sheep cells I had studied in Canberra in a rodent model, and this model has kept me going ever since. We still, as you will see, have a bit to do. I started by trying to show that these veiled cells were macrophages but they just would not do the right macrophagy things – they would not stick to glass or phagocytose particles. Chris Pugh, one of my first DPhil Students, was the first to characterise these cells. He quickly showed that they did not behave at all like macrophages, and at about the same time Ralph Steinman at the Rockefeller was starting his seminal investigations into a novel cell type in the mouse spleen – the dendritic cell. Siamon Gordon of course always has his nose to the ground and I think it was Siamon that put Ralph and me in touch, and the rest, as they say, is history.

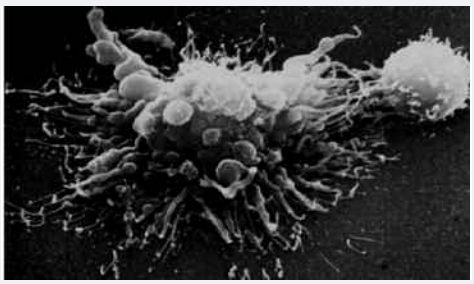


Figure 1 *Lymph dendritic cell talking to a lymphocyte*

DC are one of the hottest areas of immunology today – these cells are highly potent regulators of immune responses. T cells need to be told what to do and all the evidence suggests that it is DC that do the telling (Figure 1.) – they respond to signals in the periphery – via Toll-like and other receptors – and in lymph nodes determine the differentiation pathway of the T cells they activate – for $CD4^+$ T cells whether they become Th1 or Th2, regulatory T cells or are exterminated (tolerised). Thus, understanding how to regulate the properties of DC *in vivo* holds the potential for intelligent immunomodulation and immunotherapy. Over the years my lab has been focused on understanding the immuno-physiology of these migratory DC under steady state and perturbed conditions. Our approach permits us to collect DC that are in the process of migration in lymph draining the intestine – we can collect these DC with minimum manipulation, and these are the DC that are actually doing the work. This approach gives us real advantages in terms of the quality of the cells we collect, but has the real disadvantage that rats are not just big mice and we lack many of the reagents and genetically modified strains that are central to murine immunology.

So where are we now? Well, not so very far down the road. We have shown that there are at least three distinct subsets of DC migrating in intestinal lymph in the steady state – intriguingly one subset – the most potent immuno-stimulatory – is absent from liver lymph (Figure 2) – might this relate to the relative ease of liver transplantation? We have shown that one subset actively acquires apoptotic intestinal epithelial cells and transports them to T cell areas of lymph nodes – we think this steady state phenomenon is central to maintaining tolerance to self and food antigens and to commensal bacteria. Why DC are tolerogenic rather that stimulatory is not clear. It has been suggested recently that intestinal DC are constitutively suppressed by a factor secreted by epithelial cells – TSLP. However work by Simon Milling has shown conclusively that this is not the case – intestinal lymph DC are the most potent stimulators of naïve T cells that we have found and induce the secretion of mixed Th1/Th2 cytokines. So what is it that keeps them quiet? It is an old observation (first made possibly by Don Mason) that lymph plasma suppresses activation of allogeneic T cells in a mixed leukocyte reaction. We have recently confirmed this but the identity of the suppressing factor is unknown.

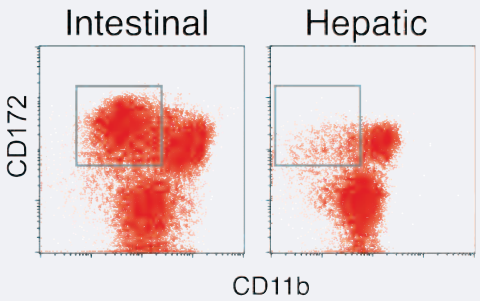


Figure 2. *3 subsets of dendritic cells migrating in steady-state lymph, identified by expression of CD172 (SIRP-α) and CD11b. The $CD172^{hi}CD11b^{lo}$ subset is virtually absent from hepatic lymph*

"Danger" and dendritic cells

A concept currently central to ideas on T cell activation is that DC respond to inflammatory stimuli in peripheral tissues by becoming "activated" and that this then regulates differentiation of naïve T cells. We have investigated this by using stimuli known to be involved in immune activation – signalling via Toll-like receptors and a known intestinal adjuvant – *E. coli* heat-labile toxin. It is difficult to summarise our results in a short space, but our main conclusions are that TLR stimulation *in vivo* induces TNF-α-dependent migration of large numbers of DC from the intestine, but that this is not due to a direct effect on DC – it involves primary activation of plasmacytoid DC – a quite distinct population of cells. The migrating DC show some signs of activation – in particular they upregulate expression of CD25 – the IL-2 receptor – but the significance of this is at present unknown. Once they enter the node, DC undergo a further activation, dependent on secretion of Type I interferon by plasmacytoid DC. These migratory DC also alter their positioning within the node – the more immuno-potent subset, normally excluded from the T cell area – now enters this area in large numbers. Perhaps this altered migration relates to the switch from tolerance to immunity. It is intriguing that the most potent stimulator of DC migration and activation that we have found – R848 – a TLR 7/8 agonist – has no adjuvant effect at all when given orally, mixed with ovalbumin. In marked contrast the *E. coli* toxin – a strong adjuvant for oral immune responses to ovalbumin – does very little to migrating DC – it does however increase CD25 expression and changes their migration within the node. We think that the ineffectiveness of R848 may represent "overcrowding" – the many extra DC arriving at the node that are not carrying the relevant antigen may prevent the few antigen-bearing DC from meeting specific T cells. This suggests that selective targeting – by physically conjugating antigen and adjuvant – may be more efficient than giving them separately.

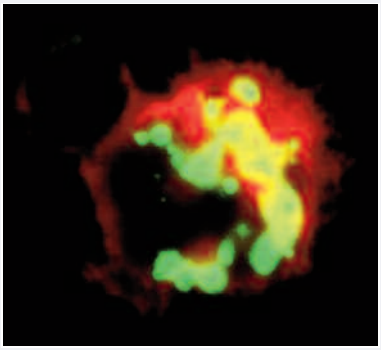


Figure 3. *CD172 (SIRP-α)-negative lymph dendritic cell labelled for MHC class II (red) and apoptotic DNA (green)*

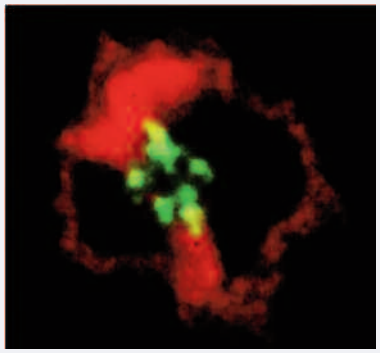


Figure 4. *Dendritic cell following incubation with fluorescent ovalbumin (green) and labelled for MHC class II (red). The ovalbumin does not co-localize with MHC class II and the FITC fluorescence is not quenched, suggesting a lack of endosomal acidification.*

We are, however, exited about another possibility for modulation of intestinal immune responses – a current DPhil student has shown that feeding rats a Schistosome-derived antigen causes the rapid release of cytokines into intestinal lymph, possibly from mast cells. The roles of these cytokines when they reach the node are at present unclear. I had speculated that DC might be able to endocytose cytokines, and transport them intact (see below) to nodes where they could be released to act on lymphocytes in the node. A first experiment suggests however that this is not the case – possibly my last blind alley, at least in research.

Dendritic cells and B lymphocytes

I was examining DC-lymphocyte interactions *in vitro* and as a control was incubating syngeneic cells together for short periods. I was surprised to find that large clusters formed with one or two DC surrounded by many lymphocytes. I was even more surprised to find that the clustering lymphocytes were naïve B cells. This led to a project in which we showed that DC, having endocytosed protein antigens, can retain them in an intact, unprocessed form for relatively long periods, can then release them to be recognised by B cells, and that the DC can give the B cells signals that influence antibody isotype switching. We think that this may be important in the early stages of an infection – when amounts of antigen are low, DC may be able to collect and focus antigen on B cells as well as T cells.

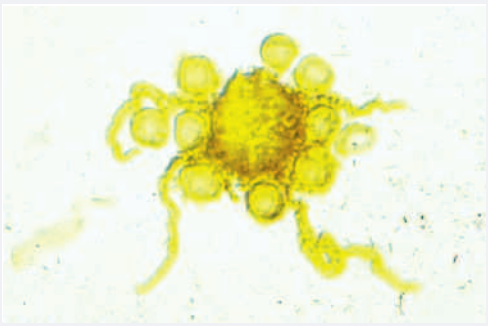


Figure 5. *Lymph dendritic cell clustering ten small B lymphocytes*

Prions

We all know that science develops through the logical generation of new hypotheses and their testing by experiment. Shelley (my wife) and I were having breakfast when there was a news item about BSE on the radio. Shelley (being an advocate) asked me "What do dendritic cells have to do with BSE?" I politely murmured "nothing". By the end of that day I had talked to the Edinburgh Neuropathogenesis Unit, within two weeks we had submitted a grant application and I should have framed one of the referee's reports. It just said "This is most important work. It must be funded". It was, and we showed that DCs can acquire prions given orally, and that they transport them largely undigested to the draining lymph nodes – the sites at which they accumulate/replicate before entering the nervous system. Currently, I have two post-docs working on scrapie – examining the roles of inflammation and complement on uptake and transport by DC and by exosomes.

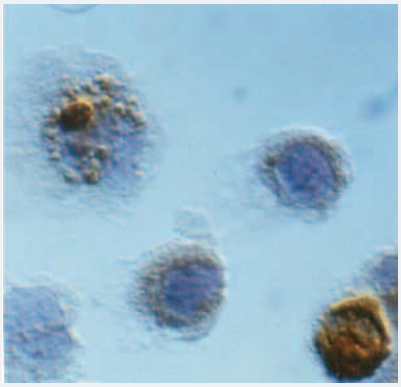


Figure 6. *Lymph dendritic cells from a rat that had been given intra-intestinal scrapie agent (PrP- prions). Several cells contain brown-labelled agent*

Teaching

The pathology course at the Dunn School has always been regarded as one of very high quality – focusing on the scientific basis of disease. I have been lecturing and demonstrating for more years than I like to remember. We still use many of the specimens and slides that were used in Florey's days – pathology does not change that much. However, changes in regulations mean that we are more limited in what we can do. One of the highlights of the practical course used to be the session where students took venous blood from each other. There were always one or two who fainted during the procedure and so there were always demonstrators poised, ready to catch. What we were not prepared for was for the person (one of my Oriel students) who was taking blood to keel over – she fell backwards off her stool and suffered a nasty blow to her head. We no longer do this – a great shame because doing things such as measuring the levels of anti-tetanus antibodies in student's blood was a dramatic illustration of immune memory.

As for most lecturers, I was horrendously nervous to start with – I actually read out my first lecture – awful. I began to realise that I could cope with most eventualities when, about 10 minutes into a 9 am lecture, a girl got up from the back of the theatre, came down all the steps (in the Dunn School theatre the entrance was at the front), walked up to me and said "Dr MacPherson – it's not that I am not enjoying your lecture – I'm going to be sick". Happily she made it out of the door.

Teaching does have its research benefits – more than once a smart question asked by a student during a tutorial has made me stop and think about our experiments and on occasion has actually led to a novel approach.

The future

When I retire in September it is almost inevitable that not only will thoracic duct cannulation cease in the Dunn School – the use of rats in experimental immunology will also cease. Thus will come to an end a major stream of experimental immunology in Oxford, a stream that was initiated by Jim Gowans and propagated by a succession of first class scientists – Don Mason, Alan Williams and Neil Barclay amongst them. All is not lost however. Simon Milling, who worked with me as a post-doc for nearly six years has moved to Glasgow and is translating the model to the frozen North. Indeed Chris Jenkins, who over the years has been responsible for most of the surgery, will be visiting Glasgow to help Simon set up the model. Given the resurgence of rat immunology and the application of molecular techniques – we have recently shown that there are major differences in patterns of gene expression between migrating DC subsets – the future is bright.

Thanks

I cannot possibly thank individually all the DPhil students and post-docs who have worked in my group. My research is, of course, totally dependent on these excellent colleagues, and also on the many collaborators I have worked with over the years. I would like, however, to end by singling out Chris Jenkins. Chris and I have been together longer than either of us would like to contemplate. Chris took to micro-surgery with remarkable aptitude and over the years has trained many in the arts of cannulation – including some in the USA. He has managed the lab, managed the workers in my lab, and most importantly, has managed to manage me. I owe him, and all my colleagues and friends in the Dunn School and elsewhere an enormous debt of gratitude.

Peter Cresswell

Peter Cresswell, currently based at Yale University, recently spent six months at the Dunn School as Newton-Abraham visiting Professor. He took time out of a busy schedule to reflect on his career to date and his experiences here in Oxford.

Could you tell us a little about your background and how you came to be interested in immunology as a discipline?
It was a complete accident. After getting a Chemistry degree I did an M.Sc. in Newcastle on Microbiological Chemistry and worked on bacterial lipids. While doing so, I met Arnold Sanderson, also a Newcastle graduate, and one of the first people to get interested in the nature of histocompatibility antigens. He recruited me to do a Ph.D. with him.

Of which of your many scientific achievements are you most proud?
That's tricky. There have been a few cool things: showing that the class II-invariant chain complex was a nonamer; establishing that HLA-DM accelerated CLIP dissociation from class II; and, more recently, showing that tapasin-ERp57 complexes facilitated peptide loading by class I molecules. I'm bound to offend some of my ex-students and postdocs because I didn't cite their work!

The best we can hope for is that things we discover actually become important elements in the sum total of human knowledge

What has been the focus of the research you have been doing while spending time here as the Newton Abraham visiting professor?
I was trying to develop a technique that would identify cell surface glycoproteins on lymphocytes with labile disulfide bonds. It was a nice project because Neil Barclay and I had independently come up with the idea that a structural modification following such a step might affect ligand-receptor interactions between T cells and antigen presenting cells. Also it was pretty successful.

How have you experienced Oxford, and the Dunn School in particular, during your stay here?
I had a great time. Walking to the lab across the park in the morning was so pleasant, at least in the summer, compared to getting in a car and driving. People were friendly and helpful, and I rediscovered the value of chatting informally to colleagues over a cup of tea or coffee in the morning or afternoon, or over lunch. We don't often do that in the USA.

What remains your greatest ambition in science and for what would you most like to be remembered?
I'd like to figure out exactly how peptides are loaded onto MHC class I molecules in the endoplasmic reticulum. It's an astonishingly complicated process involving the interactions of multiple components, many of them integrated into the membrane. As for being remembered, I guess being remembered at all would be nice. We have to recognize that the vast majority of scientists aren't! After Galileo, Newton, Einstein, Watson, Crick and a few others, how many scientists have the average person heard of? The best we can hope for is that things we discover actually become important elements in the sum total of human knowledge.

What would your advice be to graduate students contemplating a career in science?
If you want to make it in basic academic research you have to choose the best mentors doing the best work. Then you have to work really hard. When you start your independent career you have to choose an interesting, difficult, but nevertheless tractable problem. Unfortunately, at all of these stages there is an element of luck. Certainly in my career, luck played a part, and I think most biomedical scientists would have to admit it played a role in their careers too.

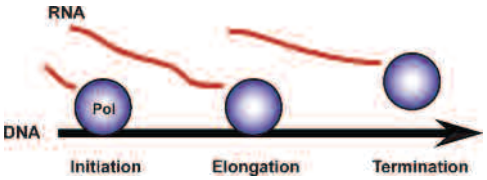
How does the research environment in the States compare with your experiences here in the UK?
It's probably more intense and competitive in the USA, or at least at Yale, but the pleasures are the same. Getting a good result and being the first person in the world to know even the smallest fact, based on an experiment you've designed and performed, these are what make it worthwhile on both sides of the Atlantic.

What will be your lasting memory of your sabbatical here at the Dunn School when you return to Yale?
The new friends I made and the old ones I reconnected with (I'd like to say thanks to them all), and the simple pleasure of doing experiments without being interrupted by a telephone ringing!

Transcription and RNA processing

Mick Dye

The first part of the Central Dogma of molecular biology (DNA-RNA-Protein), enunciated by Francis Crick in 1958, is the copying of DNA into RNA by a process called transcription. Transcription, which is catalysed by RNA polymerase, is initiated by its engagement with promoter sequences located at the beginning of a gene. Following the initial engagement, the enzyme complex then traverses the gene whilst producing the RNA transcript, in the transcription elongation phase. The process ends with transcriptional termination where RNA polymerase disengages from the DNA template and releases the RNA transcript.

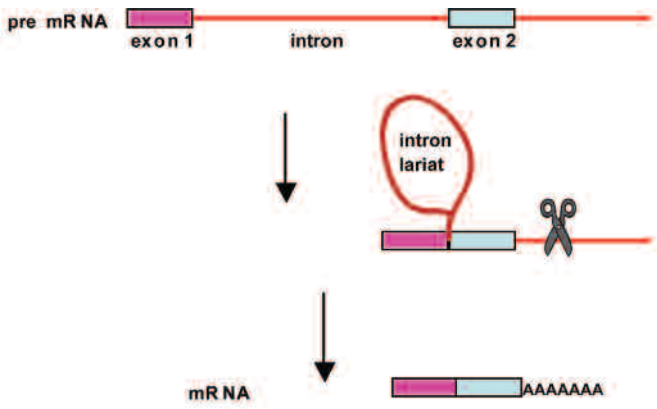


Transcription

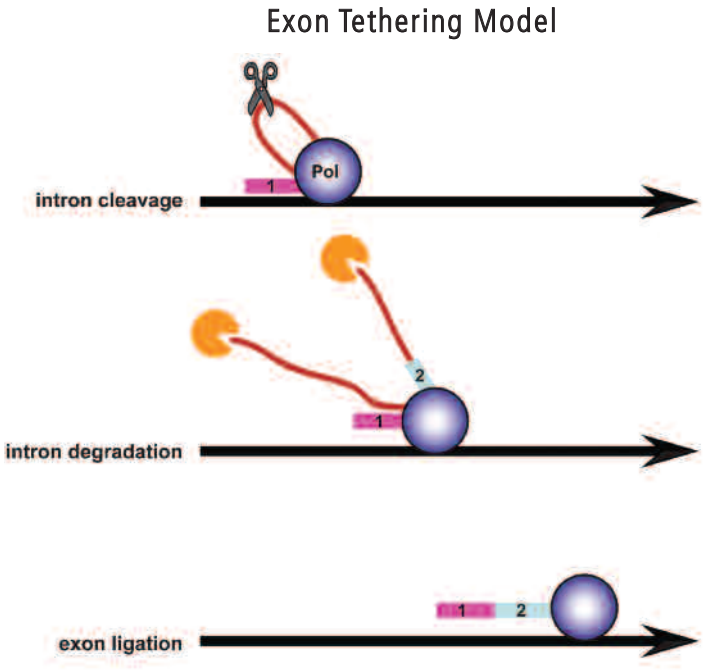
I first came to the Dunn School in January 1995 when I joined Prof. Nick Proudfoot's group as a graduate student. My remit was to study transcriptional termination by mammalian RNA polymerase II, the enzyme responsible for the transcription of all protein encoding genes. Work from the Proudfoot lab had already established that termination was dependent on processing of the RNA transcript (see below), however little else was known. During my D.Phil studies I identified dedicated terminator sequences in the human ε- and β-globin genes and developed a technique that enabled the selection of specific nascent RNA transcripts from living cells. Application of this technique to the analysis of nascent transcripts of the terminator sequences showed that they were subject to an extremely rapid cleavage activity *in vivo*. This finding indicated that this novel RNA processing activity, which we called Co-Transcriptional Cleavage (CoTC), was a prerequisite for RNA polymerase II termination. There was absolutely no precedent for this unexpected finding which, in the words of one of the reviewers of the paper, was 'either very important or an amazing artefact'. Shortly after the publication of this study in *Cell* in 2001, I left Prof. Proudfoot's lab in order to give special attention to my daughter Daphne, who was then five years old, due to the serious and distressing illness of her mother.

Prof. Proudfoot's lab continued to work on CoTC with the result that Steve West and Natasha Gromak showed, in a study published in *Nature*, that degradation of CoTC cleaved terminator transcripts, mediated by an endogenous 5'-3' RNA exonuclease, was essential for efficient RNA polymerase II termination. Given these findings, it was now inconceivable that CoTC could be nothing more than a strange artefact. Towards the end of 2004, with my daughter's welfare established, I returned to Prof. Proudfoots' lab in order to work on what I saw as the next chapter in the CoTC story. The idea behind this had developed in my mind since examining the effects of mutations of RNA processing signals on expression of the β-globin gene during my D.Phil studies, 6 years earlier. RNA polymerase II transcripts, known as pre-messenger RNAs (pre-mRNA) are processed by removal of internal non-coding sequences (intron splicing) and cleaved and polyadenylated at the terminal end to prepare them for translation into protein. In the traditional model of pre-mRNA processing, introns are spliced out in a multistep process which involves the formation of a loop of RNA, termed an intron lariat.

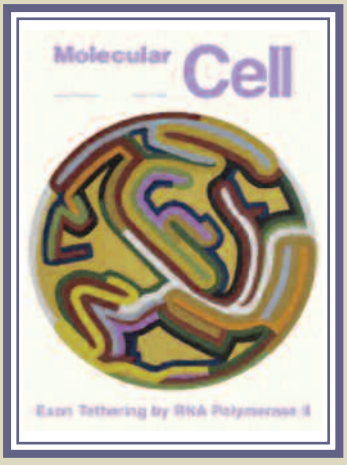
RNA processing



Although the average mammalian intron is about 3.5 kilobases in length, exceptionally long introns, some over 30 kilobases, are found in a number of genes with diverse cellular and developmental functions. The problem with the established model of intron splicing is that it is far from understood how the ends of the intron to be spliced out find each other, especially when they are positioned very far apart. This question has occupied molecular biologists for many years. In my alternative 'exon tethering' model there was no intron lariat, transcribed exons were transiently connected to RNA Pol II and taken along with it so that they were perfectly positioned to be connected on to subsequent exons as they emerged from the polymerase.



Evidence for this theory came from studies in which I had seen how intron transcripts could be cleaved by CoTC without affecting the normal joining of the exons flanking the cleaved intron sequence. This observation indicated that a continuous intron sequence was not required and indeed may not exist in many genes. Moreover, when checking the literature, I found that there is scant evidence for the existence of intron lariats *in vivo*. With the help of Natasha Gromak, I proved the exon tethering model and we published the findings in *Molecular Cell*. I quite enjoy painting and at the time of the exon tethering paper I was working on an abstract representation of nucleic acid interactions in the nucleus. Fortunately, the editors chose to use it for the cover of the issue containing our paper, thus giving the exon tethering theory a bit of publicity.

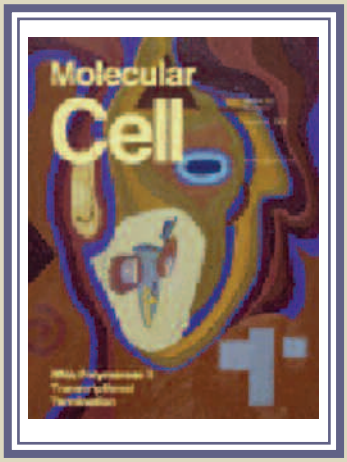


Molecular Cell, Cover 21(6)

2006 was very good year for me as shortly after the publication of the exon tethering paper I was awarded a University of Oxford, Medical Sciences Division, Divisional Research Prize for my work on transcription and RNA processing.

Pol II transcription termination

I have now returned to work on Pol II transcription termination. A graduate student, Eleanor White, and I are defining minimal terminator sequences which I hope will be of use for vector design in areas where gene transcription needs to be controlled. This could be especially pertinent in the area of gene therapy. We are also examining the sequence specificity of the CoTC activity. It appears that many non-coding transcripts are targets of CoTC. I have a theory that co-transcriptional degradation of non-coding RNA is a default mechanism in eukaryotes which clears the nucleus of 'junk' RNA transcripts, such as very long intron transcripts, as they are being made. It appears to me that this mechanism may have been co-opted to help in other transcriptional processes such as termination.



Molecular Cell, Cover 29(5)

I have recently worked with Steve West on a study in which we described new and interesting details of the RNA polymerase II termination process. Once the paper was accepted for publication, I produced a painting which the editors used for the cover of the issue containing our paper. I called this painting 'The Alchemist': it is an amateur's attempt to depict the magic and wonder I see in the subject I feel so privileged to study.

Kathy Lui, a DPhil student with Paul Fairchild and Herman Waldmann, was awarded the 2007 Peter Beaconsfield Prize in Physiological Sciences which rewards young researchers who are 'capable of escaping from the stereotype of narrow specialization, and who display a wider grasp of the significance and potential applicability of their research'. Here, we reproduce her winning essay —

Embryonic Stem Cells:
The best gift for the Emperor Qin Shi Huang to rescue scholars in the Qin Dynasty

When talking about the best landmark in China, everybody knows it is the Great Wall, the only man-made artefact on Earth that can be seen in space. Who built it? It was constructed by Qin Shi Huang, the first emperor of the unified China who ruled from 221–210 BC. However, this is not exactly how the Chinese remember him. With his torching of China's books and burying of scholars alive, Qin Shi Huang was notorious as the man who bound China with blood and tears. The execution of the scholars had been exposed when an alchemist fled to Japan. He was charged by Qin Shi Huang to seek a potion for longevity: in vengeance, the Emperor buried all the scholars of his ilk.

With current advances in contemporary medicine, the dream of longevity is no longer for nobles alone but also for the general public. Nevertheless, longer life expectancy has also fuelled a crisis: social security pension schemes around the world are facing a number of challenges, of which demographic ageing and healthcare expenses are the most commonly acknowledged. Chronic diseases, such as cardiovascular disease and diabetes, are among the most costly of all health problems. About 80% of the national healthcare budget of the US can be attributed to the treatment of chronic diseases. Treatment of Diabetes, the sixth leading cause of death in US, has already cost $132 billion in 2002 compared to $20 billion 20 years ago.

Despite the enormous therapeutic potential offered by embryonic stem (ES) cells for treating a variety of degenerative diseases, including Parkinson's disease, spinal-cord injury, diabetes, liver and heart failure, their rejection by the recipient's immune system remains a critical barrier to the success of regenerative medicine. Components of our immune system are especially good at defining their own territories: we have the defending soldiers (ie T lymphocytes) which attack any foreign immigrant (such as a graft); we have also some friends (e.g. regulatory T cells) which suppress activation of the immune system, preventing the soldiers from damaging our own cells, should they become caught in the cross-fire. In order to maintain the social order, we now know that we have the arbitrators (the dendritic cells) which instruct whether we should go to war or pursue peace instead. Therefore, by using various pharmacological agents, I am investigating ways of directing dendritic cells (DC) derived from ES cells (esDCs) to teach our immune system not to attack grafts derived from the same parent ES cells.

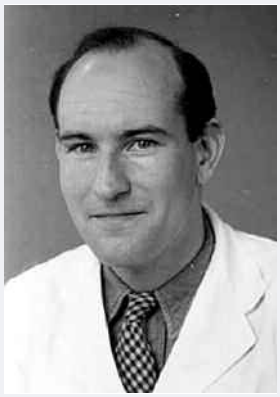
I have also genetically modified mouse ES cells to express a mayday signal able to recruit the friendly regulatory T cells (Treg), empowering the tissues derived from them to repel an immune attack. CCL-22, also known as macrophage-derived chemokine (MDC), is a chemokine produced constitutively by DC found in reactive lymph nodes, and also by macrophages, activated B cells and natural killer cells. Intriguingly, previous studies also illustrated the expression of CCL-22 in various tumor models, including bladder cancer, leukemia and lymphoma, pulmonary granuloma and ovarian carcinoma. However, the roles of intratumoral expression of CCL-22 are not fully elucidated. More recently, it has been clearly demonstrated that CCL-22 is important in homing of $CCR4^{+}$ Treg cells to suppress immune reactions in the peripheral sites. In an ovarian carcinoma study, an immune-privileged site is fostered in tumors as a result of recruitment of $FoxP3^{+}CD4^{+}CD25^{+}$ Treg cells by CCL-22-producing tumor cells and infiltrated macrophages, indicating an efficient suppression of anti-tumor responses directly within the tumor. The notion that efficient recruitment of Treg cells to effector sites is required to achieve tolerance was further strengthened in a study using a model of cardiac allotransplantation. Both CCL-22 and CCR4 were up-regulated in tolerized allografts and tolerance induction could not be achieved in $CCR4^{-/-}$ recipients. Since the chemokine CCL-22 is known to recruit Treg, we have stably expressed the gene in ES cells and investigated the potential protective effect *in vivo*. We showed that embryoid bodies (EB) differentiated from the transfected ES cells develop fully-differentiated structures after implantation under the kidney capsule, even across an MHC class I barrier, whereas controls showed significant necrosis, consistent with rejection. Moreover, EB expressing CCL-22 showed less infiltration with macrophages and T cells and a higher proportion of Treg. These findings suggested that CCL-22 may empower ES cell-derived tissues to repel an immunological attack. More work is underway to delineate the mechanisms by which CCL-22 fosters an immune privileged site for EB and whether the tissue can overcome greater MHC disparities.

History Corner

100 years ago (1908)

The first Oxford University Pathology Department with its own new building (NOT the Dunn School!) was up and running successfully. **James Ritchie**, the first Lecturer in Pathology had recently departed to Edinburgh and **Georges Dreyer**, a young anglophile Dane had been appointed to the newly created chair.

In 1907 and 1908 **Ernest Ainley-Walker** published two papers in the BMJ on 'rheumatism' but intriguingly they were on totally different subjects. The first (May 25th 1907) "On the micro-organism isolated from Acute Rheumatism (Rheumatic Fever), and its relation to other members of the Streptococcus group" outlined the case for and against the involvement of haemolytic streptococci in the aetiology of rheumatic fever. This was, of course, before the concept of autoimmunity had been put forward, and so a direct causal relationship was being sought. The second paper (Oct 10th 2008) was entitled "Bee stings and rheumatism". This attempted to address the popular belief (old wives tale?) that the poison of a bee sting is protective and/or curative against chronic rheumatism (rheumatoid arthritis). In this paper Ainley-Walker refers to an Austrian physician, Terc, who had treated over 700 rheumatoid patients with bee stings. Despite this experience no clear conclusion is reached and the author suggests that a trial of formic acid and the alkaloid in bee venom is needed to decide the issue.



40 years ago

It is nearly 40 years ago since the sudden, untimely and tragically early death (aged 49) of **Guy Newton**. Guy was Edward Abraham's right hand man in the work on the isolation, purification and characterisation of Cephalosporin C. Indeed, it has been said that Newton was to cephalosporin what Heatley was to penicillin – "the unsung hero". Although Newton is remembered in the Guy Newton Research Fund and various Newton-Abraham Fellowships, there is little in the scientific literature about his life and work. That deficit has now largely been repaired by a recent short but comprehensive and sympathetic biography of Guy by John Jones. John, archivist at Balliol, is engaged on writing a history of Organic chemistry in Oxford. During that work he could find little about Newton despite the importance of his research, and so he determined to discover more about the man, his work and his life. The result has just appeared in the *Journal of Peptide Chemistry* (vol 14, p545). It is available on line and is highly recommended to anyone interested in the history of the Dunn School.

Penicillin re-visited: visitors from the past

It always surprises me how many people contact us about the early days of penicillin. They are usually delighted when I say 'why don't you visit us and tell us about your experiences'. Two such recent visits were:

Pat Ingrams (89) and **Rosemary Powell (93)**, pictured in the 'holy of holies', the Professor's study. These two nurses worked with Howard and Ethel Florey on penicillin trials at an outlying unit of St Thomas's Hospital in 1942–3. Their patients were injured soldiers returned from war fronts in France. Apparently the needles used for injections were very large and the injections long and painful!

A group from Beecham, lead by George Rolinson, the chemist responsible for the synthesis of the 6-aminopenicillanic acid group, the basis of the semi-synthetic penicillins. George has recently published an historical article to celebrate the 50th anniversary of the discovery. His colleagues were Jean Ashwin, Ralph Batchelor, John Copeland, Nick Heightman and Bill Smith. After giving them a short talk and conducted tour of the Dunn School I was presented with a 6-APA tie and taken to lunch at the Trout!

Nearer to home, Dave Daw, who has been in the workshop since July 2000 delights in telling how his uncle was saved by penicillin in 1942. Dave writes: I can recall as a very small child my mother, while on her way to work in the large houses of North Oxford, stopping outside the Dunn School and saying a prayer for the people working in the building; "that's where God's work goes on" she used to say. I had no understanding of the reason for this until much later in my life when it was explained to me that within that building were the scientists who

had created the wonder drug that had saved the life of my mother's youngest brother during the war. My uncle Bill had been very seriously injured in N Africa in Aug 1942 and had been brought back to England for hospital treatment. On the way home his ship had been torpedoed and although he was saved he was seriously burned and close to death. He was taken to the Radcliffe Infirmary where, on admission, he was given the Last Rites. He was seen by Dr Fletcher (Charles Fletcher, 'our great Dr Fletcher' to my mother), who suggested using a new drug. With treatment Bill's condition improved dramatically and he was transferred to the new Army hospital 'The Churchill' in Lye Valley. Later he worked at the Morris Motors car factory. In hindsight, of course, we now know that he was treated with penicillin and he must have been one of the first of thousands of servicemen who benefitted from the brilliant work carried out in the Dunn School.

Retirements

The impending retirements of two of our most celebrated academic immunologists, Gordon Macpherson, who arrived in 1968 and Siamon Gordon in 1976, have been celebrated elsewhere in Fusion.

Steve Simmonds is the latest in a line of dedicated and extremely skilled technicians to retire (technically 'early') after spending the whole of his working life in the Dunn School. The official record is that he started on the 3rd Oct 1966 and retired on the 9th May this year. But some readers will have noticed that he has recently reappeared in a part time guise. (Some of you might think, like me, that he doesn't look old enough to retire anyway).

Steve came directly from Bicester Grammar School to the Dunn School where he was interviewed and admitted by Jim Gowans and the formidable administrator, Peggy Turner. He was assigned to work with Bill Ford in room 50 (now 214-20-06) and given a basic training in animal handling by Jim Kent. Soon Steve's surgical skills were evident and much in demand for experiments on lymphatic drainage, perfusion, etc. In those days, Steve reminisces, lymphocytes were either small, large or 'other'. Bill Ford moved to Edinburgh and was replaced by Don Mason for whom Steve worked until the latter's retirement and the official closure of the MRC Unit. During that time he remembers sharing a desk with a promising DPhil student, Fiona Powrie! Since Don's retirement he has worked for Neil Barclay and Marion Brown.

He has, almost inevitably, become a 'jack of all trades' in the Unit taking on all the major new immunological techniques such as FACS, Macs and BIAcore. He has given his own lab talks and Powerpoint presentations and has an impressive list of publications to his name, with an average 'impact factor' that many of our scientists would be proud of. Nevertheless one suspects that the greatest satisfaction in his work has derived from his surgical skills.

Steve's early memories include the delightfully eccentric DPhil student, Jonathan Howard and Susan Ellis, Gowan's personal assistant who was eventually swept off her feet (and off this Island) by the Australian post-doc Bruce Roser. Gowan's departure to be Secretary of the MRC in 1977 and Alan Williams appointment as head of the Unit led to a change of scientific direction but Steve has only happy memories of all the changes in personnel and research techniques that he has encountered through his 40+ years.

Outside work, Steve has also clearly had a contented time. He and his wife Mary have lived in the same house in Kidlington (extended three times) since their marriage in 1970. They have two grown up children, both successful professionals. Steve describes his hobbies as mainly gardening – he has a large garden and an allotment – and football. He is a Director of the Oxfordshire FA Council, having spent much time organising boys' football in the county.

We are delighted that *Fusion* has the opportunity to pay tribute to Steve and thank him for the lifetime of dedicated service that he has given to the Dunn School. We wish him a long, happy and healthy (semi) retirement.

Liz Darley has been quietly and very efficiently running the Histology service since her arrival in December 1990. She is one of the very few people who seem to have avoided having their official photograph taken during their time here and so *Fusion* regrets that it cannot show her off to readers! Liz retired at the end of Dec 2007. We thank her for her dedicated and skilled work and wish her a long and happy retirement.

There has been a revolution in the **Reception**. For what seems like many years the cheery faces of Syd or Dave have welcomed visitors and staff to the Department. **Syd Brown** has been with us since Dec 1996 and **Dave Phipps** since Nov 2002. They have both recently retired and we thank them for their unfailingly courteous and cheerful help.

Development news

We are delighted to announce that two major initiatives have recently reached fruition.

Jordan Raff has been appointed as the first César Milstein Professor of Cancer Cell Biology in The Sir William Dunn School of Pathology from 1st January 2009. The chair is named in honour of the man who discovered monoclonal antibodies. Milstein's discovery was built on the development of cell fusion carried out by Henry Harris and John Watkins, and has had a tremendous impact on many others who work in the Dunn School, including Alan Williams and Herman Waldmann.

Jordan read Biochemistry at Bristol University, and then took his Ph.D at Imperial College with David Glover. After four years with Bruce Alberts at the University of California, he returned to Cambridge and set up his own lab at the Wellcome Trust/CRC Institute (now the Cancer Research UK, Gurdon Institute); he is currently a Cancer Research UK Fellow there. Jordan's research focuses on the dissection of the centrosome, a major subcellular organelle first recognized by the early microscopists. All our textbooks tell us that this organelle is the organizer of the cell's microtubules – both during interphase (when it directs vesicular traffic and cell polarity) and mitosis (when it choreographs spindle movements). It has long been thought that derangements in the function of the centrioles that lie at the heart of the centrosome underlie the aneuploidy seen in many cancers. In 2006, Jordan published a paper in *Cell* with the astonishing title – 'Flies without centrioles'. He will continue to work on the inter-related signalling pathways that impinge on this important organelle when he comes to the Dunn School.

The first MSD-Norman Heatley student will be: George Song-Zhao from the University of British Columbia in Canada. His first degree was in Microbiology and Immunology and he will work in Kevin Maloy's group.

The Oxford Stem Cell Institute

Oxford has been at the centre of stem cell biology from its very inception – having hosted the work of pioneers such as Richard Gardner and John Gurdon – and currently boasts expertise in a broad range of technologies from adult to embryonic stem cells, and from nuclear reprogramming to tissue engineering. Nevertheless, laboratories actively involved in stem cell research are widely disseminated throughout the University, which has tended to hinder collaboration. In order to address these issues and promote Oxford as a centre of excellence in the stem cell field, the Oxford Stem Cell Institute (OSCI) will be launched in October, funded by a generous donation from the James Martin 21st Century School.

The OSCI will be coordinated by Paul Fairchild at the Sir William Dunn School of Pathology and Helen Mardon, based at the Nuffield Department of Obstetrics and Gynaecology, so as to help unite laboratories spread throughout the preclinical and clinical departments of the University. The purpose of the Institute will be to foster collaboration and synergy between groups by the organisation of events that will unite the stem cell community, and by the provision of seed funding to support innovative and collaborative projects between laboratories. In this way, it is envisaged that basic research in the stem cell field may provide a pipeline for the development of therapeutic strategies to address some of the major unmet medical needs of the 21st century. The OSCI will make its debut on the national and international stage next April when it will host the annual conference of the UK National Stem Cell Network (UKNSCN), anticipated to be the largest gathering of stem cell scientists that has so far been convened in the UK.

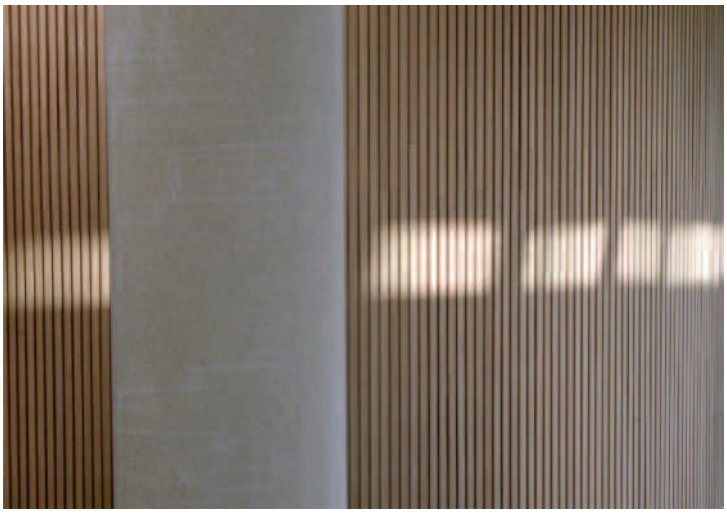
Paul Fairchild

Corrigendum and Apology: Wendy Brownsill

In Fusion 6 we listed the longevity of Dunn school staff BUT one of the longest serving and most deserving was omitted. Our sincere apologies to Wendy who first arrived in Aug 1963, shortly before the new Professor Henry Harris took up office!
She left in Jan 1976 for what might be described as family reasons!
She returned in March 1983 and is still enjoying her work in the lab and classroom.

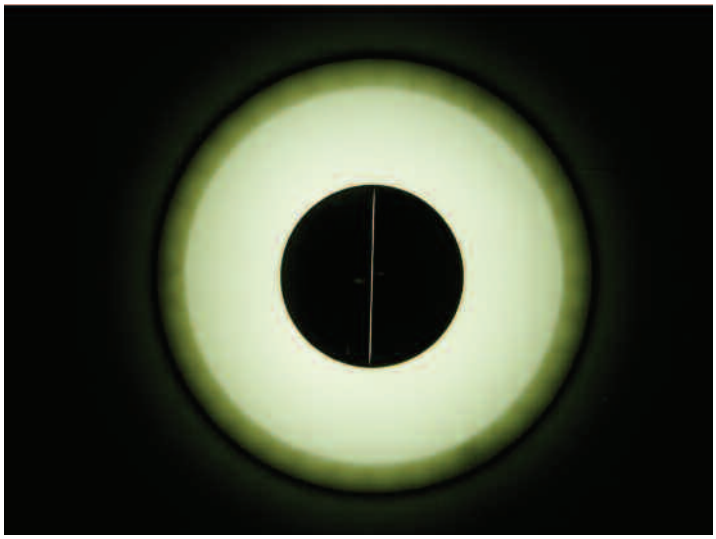
Photographic competition

Thanks are due to Hao Zhang and William James for their initiative in organising a Dunn School photographic competition. There were three categories and the winners were:



Architecture Category Winner: *Vertical lines by Peter Collingridge*

Portraiture Category Winner: *Night Shift by Duncan Howie*



Still Life Category Winner: *The Music of the Dunn School Spheres by Pietro Roversi*

Runners-up in the competition are displayed on the back page

UNIVERSITY OF OXFORD

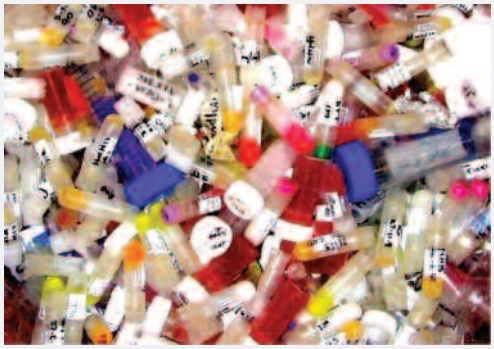
Photographic competition runners-up

THE SIR WILLIAM DUNN SCHOOL OF PATHOLOGY
is a department of the University of Oxford
website: www.path.ox.ac.uk

CONTACTS:
Professor Herman Waldmann, FRS
Head of Department
Sir William Dunn School of Pathology, South Parks Road Oxford OX1 3RE
herman.waldmann@path.ox.ac.uk

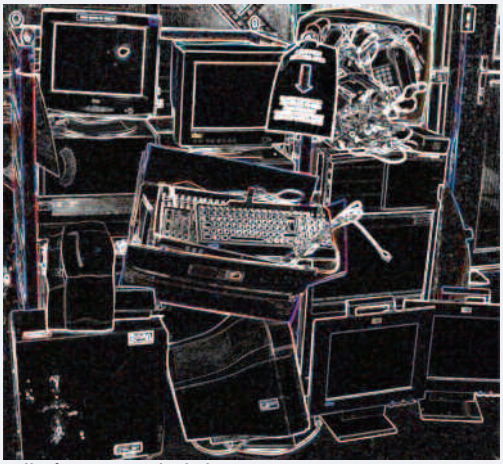
EDITORS
Dr Eric Sidebottom
Sir William Dunn School of Pathology, South Parks Road Oxford OX1 3RE
Tel: (44) (0)1865 285751
email: eric.sidebottom@path.ox.ac.uk

Dr Paul Fairchild
email: paul.fairchild@path.ox.ac.uk



Still Life Category Runner Up: *Lab Trash (by Carolina Arancibia)*

Judges' Recommendation: *Snowdunnia (by Elisabeth Coene)*



Still Life Category Third-place: *The Morgue (by Simon Hunt)*

Architecture Category Runner Up: *Vanishing Point (by Hugo Garcia Rueda)* — Ok, this is not the most cheerful picture of the Dunn School. But it's a kind of metaphor of the long way that scientists, thirsty for results and hungry for data, have to go to reach THE TRUTH … or a can of coke and a pack of crisps !!

Making a gift to the Dunn School

The Dunn School owes its existence to a philanthropic gift, from the Trustees of Sir William Dunn, and over the years has been the beneficiary of many acts of philanthropy, not least from those who have worked here. Any gift made to the Dunn School helps to further research here, whether it is made to support a specific initiative such as the ones described in this newsletter, or at the discretion of the Head of Department.

If you would like to make a gift to the Department this year, please use the gift form enclosed with this edition of Fusion. Please make sure that you have completed a gift aid form so that we can reclaim tax on your gift, and note that if you are a higher rate tax-payer, you can also set your gift against your tax liability for the year. All gifts made to the Dunn School from the USA are also fully tax-deductible, when made through the University's 'giving vehicle' there, the Americans for Oxford, Inc organization.

Hot from the press

It has recently been announced that the EPA Trust Funds have agreed to fund the major costs of a new research building to replace the existing Leslie Martin building. It is expected that work will start early next year.

Also many readers will have recently seen the news that the Collegiate University of Oxford has launched the largest appeal ever by a European University, for £1.25bn.

More about this in future editions.

Fusion is produced by the Medical Informatics Unit, NDCLS, University of Oxford. Telephone +44 (0)1865 222746.
Ref: Fusion0908/1000