fusion

THE NEWSLETTER OF THE SIR WILLIAM DUNN SCHOOL OF PATHOLOGY

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Editorial

Welcome to the first edition of *fusion*! This is both an exciting and a challenging time for the Sir William Dunn School of Pathology. The past few years have seen much building work both on the new EPA building and on the Medical Sciences Teaching Block, situated behind the Dunn School and accessed by a walkway from the School.

This physical expansion of the department is necessary to enable the Dunn School to maintain its international leadership in research on mechanisms and treatments for disease in the face of increasing competition for research funding.

In this country the most common causes of morbidity and mortality are related to cancer and to cardiovascular and immunological diseases. The historic development of antibiotics in this department has, over the past 50 years, reduced the consequences of bacterial infection, although microbial resistance to the current generation of antibiotics will mean that unless new drugs are found bacterial diseases will again constitute a major problem. Outside the western world parasitic diseases and AIDS constitute an immense problem.

The challenge for the Department is to maintain strong scientific excellence while positioning itself to improve health in those major disease areas. In the areas of immunology and chemical pathology we have some of the strongest scientific groupings in the UK, soon to be strengthened even further by a recently endowed Chair in molecular biology. We now wish to expand our strong foundations in other areas of pathology, in particular in the areas of molecular microbiology and in cell and cancer biology. To that end, the Department is fortunate to have been able to create a Chair and a lectureship in microbiology. A further lectureship is currently being filled. We are delighted to welcome Professor Keith Gull, a world authority on protozoal diseases, to provide leadership in molecular microbiology. In addition, new research fellowships have allowed diversification of our effort in bacterial diseases. In the areas of cell and cancer biology recent appointments to a Chair and lectureship in cell biology will provide that added impetus. Our next goal is to raise funds for a Chair in cancer cell biology to continue the Department's long-standing expertise in that area. The area of cardiovascular disease is evolving around the crucial role of macrophages in determining lipid accumulation in blood vessels, and clearly remains a priority for the Dunn School.

The successful completion of the new E P Abraham building and the overwhelming endorsement of the Department's research with the award of a 5* rating in the recent RAE exercise provide both opportunities and challenges. Chief among the opportunities is our ability to attract the best scientists and their groups to the Dunn School. Among the challenges in the current financial climate is the need to find new resources to enable D. Phil students and young, independent post-doctoral research fellows – the scientists of the future – to study here, while also maintaining the services and fabric of the Department as a whole. The year ahead will see the start of a fundraising campaign to generate new income to support our goals in research and infrastructure, and I hope you will lend your support to this new effort.

Herman Waldmann

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How haemophilia B patients benefit

George Brownlee, Professor of Chemical Pathology, explains how he and his group were instrumental in developing the current treatment of choice for haemophilia B

'Dear Mr Brownlee
I am a haemophilia patient and I live in Turkey. I request information from you about your research on gene therapy for haemophilia B. Every haemophilia B patient in our city is looking for treatment not dependent on fresh frozen plasma or purified factor IX.
Yours sincerely, etc.'

'Dear Sir,
Gene therapy for haemophilia B is still being developed through clinical trials in Philadelphia, USA. It may take many years to develop an effective and safe form of gene therapy, although I believe it will be possible some day. However for the moment you and the other patients in your city should try and obtain recombinant factor IX from your doctor. It is now the drug of choice for treatment of haemophilia B patients. Recombinant factor IX is made in the laboratory under sterile conditions. It is not isolated from people and it is much safer than fresh plasma, or factor IX that is prepared by pooling blood derived from many different blood donors, because it is not contaminated by viruses –such as the AIDS virus or viruses causing hepatitis or neurological diseases, that still may be present in blood-derived products.
Yours faithfully,
George G. Brownlee

Recombinant factor IX is still an expensive drug, which is of major concern in countries that lack a free health care system.

Haemophilia B is an inherited bleeding disorder affecting one in 30,000 males. Like haemophilia A, it is caused by a defect of an X-linked gene. Hence it affects men but not women. If untreated, it leads to severe crippling and is life-threatening. Famously, the British royal family was affected by haemophilia. Queen Victoria was a 'carrier' of a defective gene, although it is not known whether this was haemophilia A or B. She transmitted it to one of her sons, who contracted the disease, and to two of her daughters who were also carriers, and responsible for taking the disease to other European royals, including the son of Tsar Nicholas II of Russia.

The factor IX gene was first cloned in my laboratory in 1982 when the technology for cloning and expressing genes was a demanding research project that few were prepared to undertake because of technical difficulties. The work was done by Andy Choo, Jaspar Rees, and Keith Gould. Three years later in 1985, Don Anson and Ian Jones with the help of Francesco Giannelli and Joyce Huddleson and I reported the production of recombinant factor IX, which was active in a clotting assay, in cells in tissue culture.

Rights to the factor IX technology were acquired by the British company BTG plc, who filed patents on the UK discovery and took the technology to the market place, by licensing it non-exclusively to several companies. Our laboratory's discoveries provided the scientific background which enabled one of these companies, Genetics Institute, under licence by BTG, eventually to devise a large-scale production process for recombinant factor IX. However, it took many years to reach that point. Only in 1997 in the USA and in 1999 in Europe did the drug (beneFIX™) become available for patients.

Recombinant factor IX, as I mentioned in my reply to the patient who wrote from Turkey, is now the drug of choice because of the continuing concerns about viral contamination of blood-derived products. However, recombinant factor IX is still an expensive drug, which is of major concern in countries that lack a free health care system. I suspect that this was why I was asked by the patient from Turkey about gene therapy which might turn out be a cheaper option because, in principle, medical intervention would be less frequent.

George G. Brownlee

Introducing Keith Gull

Keith Gull is joining us at the Dunn School from the University of Manchester where he is currently Research Dean in the School of Biological Sciences. Our own cub reporter David R. Greaves (DRG) interviewed Keith (KG) for the first edition of *fusion*.

DRG: *Having grown up in Yorkshire, you went to read microbiology at Queen Elizabeth College, University of London. What factors influenced that decision?*

KG: I hadn't really considered going to University even while studying for my 'A'-levels until a trainee teacher visited our school and started teaching us about microbiology. Looking back on it now I think this is one of several happy 'collisions' which have played an important part in shaping my career in science.

DRG: *What was it that you particularly enjoyed about your time as an undergraduate at QEC?*

KG: It was a very exciting time for me. The microbiology course at QEC was one of the first truly integrative microbiology courses in the country. We looked at every aspect of microbial biology; biochemistry, metabolism, genetics, ecology, not just the usual very dry bacterial taxonomy practicals.

The other great thing was we were a very small class and we all got on very well. Five of my year group went on to be Professors of Microbiology. My bench partner was Richard Sykes who recently retired as CEO of GlaxoSmithKline to become the Dean of Imperial College, London and my best friend was the late Bob Holness who made important contributions to the study of the herpes viruses. And I met my wife there!

DRG: *In Manchester you were Founding Director of the Research and Graduate School in Biological Sciences in Manchester University. What do you think are the biggest challenges facing graduate students in 2002?*

KG: Obviously there is just so much more graduate students need to know nowadays. Today's graduate students are under a lot more pressure to discover something for themselves while needing to take on board extra research skills. In my day I guess a lot of graduate teaching was done by 'osmosis' rather than through additional coursework.

DRG: *If you were graduating with a PhD in molecular & cellular biology today, which areas of scientific research would you be attracted to study and why?*

KG: I think I would still be attracted to studying cell and molecular biology, particularly the study of information processing. We are coming to an appreciation that molecules do not act individually but rather as molecular complexes. I think that is a real challenge in the post-genomic era.

DRG: *Keith, you have a long-standing interest in the molecular and cell biology of Trypanosoma brucei – the causative agent of sleeping sickness. Perhaps you could briefly introduce us to this fascinating protozoan parasite.*

KG: I have been studying the structure of this parasite for 15 years. Now with the genome sequence information we are at last in a position to start studying function. I think trypanosomes represent 'extreme biology', that is to say their biology is very unusual and they employ molecular biology of the highest order, RNA editing, trans-splicing, transposable genes, etc.

DRG: *Looking forward to your move to Oxford what are your personal and scientific goals over the next 5-10 years?*

KG: Having gone straight from my PhD to a Lectureship, a Professorial Chair and then Research Dean maybe this is my first postdoc! What I really want to do in the next 10 years is to develop new techniques to study how molecular machines are organized and how they are regulated. Genome sequencing will identify the molecular players – in essence I am interested in phenomena beyond the genome. What I find so attractive about the Dunn School is the mixed environment, the range of biology going on under one roof.

DRG: *Keith, you have a strong track record in the area of public understanding of science. Do you think this is something more scientists should be doing?*

KG: Absolutely. Public understanding of science is good for the scientist as well as the public. I really believe that you do better science by talking to a wider audience.

Keith Gull, newly arrived from the University of Manchester

The EPA Building at the Dunn School

By **William James**

Towards the end of the 1990s, it was becoming clear that the bit-by-bit expansion of the Dunn School over the decades had produced some unpleasant side-effects, as well as the undoubted benefits of more and better science.

Many laboratories were cramped and out-dated for modern science. Service areas were inadequate and unpleasant spaces in which to work. Most importantly, the existence of two almost-separate research buildings had led to the development of a fragmented culture which inhibited communication between groups. On top of this, it was clear that both scientific and financial pressures meant that we would need to expand substantially further in the new century, potentially exacerbating all these problems. Herman Waldmann asked me if I would undertake a thorough review of the challenge and steer the department through the necessary developments.

The first step was a 9 month period of analysis, in which a team of us investigated all service aspects of the department: measuring activity, asking users what they wanted to see, benchmarking against other research institutes and biotech companies, and finally making recommendations. This was an illuminating process. Certainly, we discovered plenty of previously unrecognized problems and inefficiencies in our own workings, but found that on many fronts, we were already doing rather better than 'the competition'. Our recommendations were accepted by the department and formed the basis of the brief which we eventually used to instruct the design team. Professor Waldmann bid for and won £5.5M from the EPA Trustees to fund the construction project, which was completed in early 2001.

The new EPA Building comprises a large, 3-storey laboratory and services block behind the original Dunn School building, which is linked to both the original building and the unlovely 1960s 'Leslie Martin' building by a dramatic steel-and-glass structure that houses an airy café (known as The Bridge) and serves as a link between all three buildings on all three floors. The Bridge café has proved to be a tremendous success, providing day-long coffee and snacks, breakfast and lunch. It provides a focus for interaction for the whole department, with many unplanned encounters between people from different research groups developing into productive discussions. When the weather is good, people can take their coffee onto the adjoining terrace and wander into the new garden, or make themselves comfortable in the adjoining Combination Room. A new Library, especially commissioned by the EPA trustees, is fully networked and has great views over the Parks but retains a sense of comfort and sobriety through the careful use of wood, leather and oriental carpets. On the second floor, we have three seminar rooms with digital projection facilities and a number of meeting rooms and offices. We were very aware of the environmental impact and running cost implications of excessive use of air-conditioning systems in many new buildings, so the architects and engineers devised a number of ways in which the 'public areas' could be kept cool by passive means. The whole south face of the building is shielded from excessive solar heat gain by a *brise soleil* – an array of cedar slats that provides shading while allowing high levels of visibility. They also used the 'stack effect' of double-height spaces to encourage stale, warm air to leave the building through automatically-opening windows. With very few exceptions, this approach has been remarkably successful, providing very pleasant conditions with minimum pollution or expense. On the ground floor there is a series of scientific

At the time of design, we had no idea of the identity of the future occupants and, although this was a challenge, it forced us to be open-minded and flexible.

service rooms, from the latest in DNA sequencing and surface plasmon resonance detectors, through centrifuges and cryopreservation to glass-washing, autoclaving, and stores. Each space is designed to provide ideal conditions for the service and the arrangement enables the staff to coordinate the delivery of goods and collection of laboratory waste in an efficient manner.

The north side of the building comprises four laboratory suites, designed to be suitable for work up to containment level 2, if required. Each suite has an open-plan main laboratory with benches and write-up desks for 16 scientists. The labs are air-conditioned, with extensive networking, epoxy bench surfaces and task lighting, as well as the usual services. Each suite also has a $10m^2$ office for a principal investigator, a service laboratory designed for up to three microbiological safety cabinets or other hoods, and shares a substantial instrument room with its neighbouring suite. The challenge was to design laboratories that would be flexible enough to accommodate scientists with interests ranging from pure biochemistry to working with human pathogens with minimal adaptation. At the time of design, we had no idea of the identity of the future occupants and, although this was a challenge, it forced us to be open-minded and flexible.

The domestic and service aspects of the EPA building have been fully occupied for a year and a half, and three out of four of the laboratory suites are now occupied. The feeling is that it's been quite a success, with a projected 50% expansion in staff numbers being accompanied by a growing cohesion and sense of lively community.

The entrance to the new EPA building showing the steel and glass cafe which provides a hub for the whole department

When cell biology met immunology

Gillian Griffiths is Professor of Experimental Pathology, and the holder of a Wellcome Trust Senior Research Fellowship. She came to the Sir William Dunn School of Pathology in 1997, and her research is concerned with the mechanisms of cytotoxic T cells.

I first started my own laboratory, aimed at understanding the cell biology of killer-lymphocytes, at an immunology institute in Switzerland. It seemed a bit perverse to try to learn cell biology in an immunology institute, but what became apparent was the strength of combining these two disciplines. Over this period the cell biology of immunology has become an increasingly popular area, and there are many good reasons for this. Many of the ways in which immune cell function can be measured experimentally involve enormously sensitive biological assays. For example the potency of cytotoxic T cells, which can destroy virally infected and tumorigenic cells *in vivo*, can be measured *in vitro* using assays which measure the release of proteins from the dead target cell. Many of these techniques are sensitive enough to measure the killing activity of a single cytotoxic cell. The proteins that appear on the surface of killer cells can also be monitored using a fluorescence activated cell sorter (FACS) which can detect very small fluctuations in protein levels. The opportunity to combine these tools of the immunologist with state-of-the-art microscopy has opened up many new avenues for research. An environment such as the Dunn School, which has both excellent imaging and FACS facilities, as well as all of the facilities required for a wide range of immunological approaches, provides an ideal environment for cell biology and immunology to meet.

Many of the ways in which immune cell function can be measured experimentally involve enormously sensitive biological assays.

My laboratory is currently studying genetic diseases which disrupt cytotoxic cell killing, such as Chediak-Higashi Syndrome (CHS). We now know that killing is mediated by the release of proteins from specialized secretory granules which move along microtubules to the point of contact with the target, known as the immunological synapse. The granules release their contents at the immunological synapse, as shown using the electron microscope (Figure 1). By looking at cytotoxic cells from genetic diseases in which defined proteins are missing, it is possible to identify where each of these proteins is required. Figure 2 illustrates the different stages required for the granules to move and secrete their contents, and some of the proteins identified (in parentheses) using this combined immunological and cell biological approach. Over the next few years our aim is to fill in this diagram and identify the different components of the machinery required for these lymphocytes to function as effective killers.

Gillian Griffiths

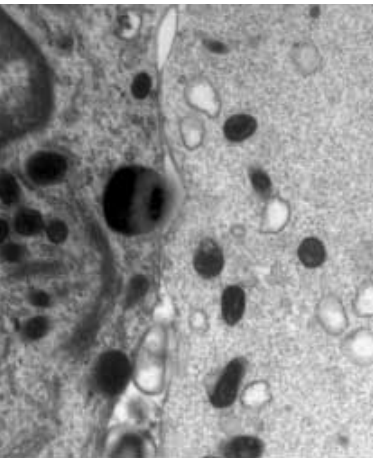
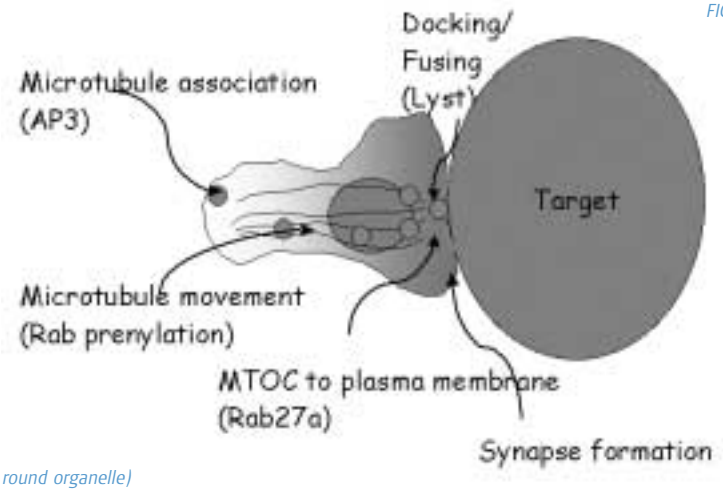


FIGURE 1
A cytotoxic T cell (left) releases granule (dark round organelle) towards target cell (lighter appearance) which will be killed

FIGURE 2



See Stinchcombe, J., Bossi, G., Booth, S., and Griffiths, G.M. (2001) Immunology **15** *751-761*

Gunther Blobel gives the Heatley Lecture

On the 30th of April 2002, the Nobel laureate, Gunther Blobel, MD PhD, gave the 10th Norman Heatley Lecture at the Dunn School.

Blobel received the Nobel Prize for Medicine or Physiology in 1999 for his discovery of the mechanism by which newly synthesized secretory and membrane proteins are targeted to the endoplasmic reticulum. In a wide-ranging and elegant talk, he described the decades of painstaking work, setbacks and frustrations that eventually led to the now-familiar model, in which translation of such proteins is first paused and then resumed following interactions of nascent signal peptides with first a ribonucleoprotein recognition particle and then the translocation channel (see *http://www.rockefeller.edu/pubinfo/proteintarget.html* for a movie of this process). Blobel doesn't rest on his laurels, though. He went on to describe the most recent investigations of his lab at the Rockefeller University, in New York, on the movement of proteins and RNAs into and out of the cell nucleus through the nuclear pore complex. These very challenging studies are beginning to elucidate the ways in which the complex, which is composed of approximately 100 different proteins, is able to regulate the two-way traffic of an enormous range of macromolecules.

The Norman Heatley Lectures are an annual event established in 1992 following a generous donation. Recent speakers have included Professor Peter Krammer (German Cancer Research Centre), and Professor Thierry Boon of the Ludwig Institute for Cancer Research.

Appointments and distinctions

We are pleased to welcome a number of new faces to the Dunn School this term. Keith Gull comes with a Welcome Trust Principal Investigator Award (see interview on p. 3). Professor Mark Greene of the University of Pennsylvania is the new Newton-Abraham Visiting Professor. His research focuses on cancer cell biology, as does that of Chris Norbury, who is joining the department as University Lecturer in Cell Biology from the Weatherall Institute of Molecular Medicine. Congratulations also to Gillian Griffiths on her recent appointment to a Readership and the award of Distinction to Professor and to David Greaves who was elected Reader in Molecular Pathology in the annual Distinctions exercise.

Prizes and awards

Congratulations to:

Rut Carballido-Lopez (Jeff Errington's group) has won the prestigious Promega Young Life scientist of the Year Award for 2002.

Another distinguished award, The Robert Feulgen Prize of the Society for histochemistry, was awarded to **Francisco Iborra** (Peter Cook's group) in September.

Frank Cordes, D.Phil student with Ariel Blocker, won the *Nature* poster prize at the ELSO meeting in June.

Luis Graca, Post-doc in the Therapeutic Immunology group, won first prize for a poster at the Oxford Immunology Day in June with his poster 'Regulatory T-cells are present in tolerated allografts'.

Rut receiving her prize – a unique glass trophy and cheque for £2000

Forthcoming events

NEWTON-ABRAHAM LECTURE

Professor Mark Greene of the University of Pennsylvania, this year's Newton-Abraham Visiting Professor, will give a lecture entitled *"The origin and reversal of cancer"* on 18 November 2002 at 4:30pm in the Medical Sciences Teaching Centre Lecture Theatre. The lecture will be followed by a reception in The Bridge. All welcome.

A full list of departmental seminars is available on the website http://www.path.ox.ac.uk

Fighting AIDS with books

Siamon Gordon would like to thank the following for the support they have given to this project: The Oppenheimer Trust, The Sir William Dunn School of Pathology, Cold Spring Harbor Laboratory Press, Christine Holt, and Martin Wilkins

Professor of Cellular Pathology, Siamon Gordon, spent much of this summer distributing 20,000 copies of a new book, *Staying Alive, Fighting HIV/AIDS (SAFA) in South Africa*.

More than three million people under 15 years of age are infected with the HIV virus, according to a recent report from UNAIDS. And it is reported that almost 60% of new infections each year are in under 15s – through perinatal infection, or infection from peers or adults. But other research from UNICEF shows that this vulnerable age group have little idea how HIV/AIDS is transmitted, or how to protect themselves from the disease. The aim of SAFA is to inform and empower these young people.

Siamon's involvement in the fight against HIV/AIDS began in 1999 when he ran a workshop on AIDS and Tuberculosis for sub-Saharan African scientists in Cape Town: 'As a South African born doctor, trained in immunology and researching basic aspects of cellular immunity at the Sir William Dunn School of Pathology in Oxford, I was in a privileged position to assess the current crisis in the country.... I believe that if young people have knowledge, they will seek to protect themselves.' After securing funds from an anonymous donor, the Oppenheimer Trust, and the publisher, Cold Spring Harbor Laboratory Press, Siamon recruited writer Fran Balkwill and illustrator Mic Rolph. Their text and illustrations are direct and often humorous, the result of detailed discussions with young people, their teachers, and health professionals in schools, squatter camps, and orphan villages around the country.

In August 2002, with copies of the book hot off the press, Siamon, the authors, publisher John Inglis and social worker Lindsey Rabinowitz visited South Africa to distribute the initial print run and assess the children's response to the book and its message. The response was overwhelming, and revealed the demand for what Kader Asmal, the Minister of Education, termed 'the social vaccination of education' in the absence of reliable medical treatment.

Siamon and his group visited both major cities and squatter camps and schools in rural

South African students reading Staying Alive, Fighting HIV/AIDS

Zululand. AIDS is rife, particularly in the poverty-riven squatter camps, and tragic cases of pregnancy and HIV in young children are not uncommon. However Siamon was struck by the level of grass-roots activity, which include the use of cabaret, traditional songs, memory boxes, and even an HIV-positive muppet planned for the forthcoming series of Takelani Sesame (the South African edition of the famous children's TV series) to raise awareness.

AIDS activists welcomed the book: 'Explaining to a 13-year-old how to prevent HIV is not just about understanding it is going to kill you, but how the virus works' said activist Mercy Makhalemele, who, together with her daughter, is HIV positive.

After three weeks touring the country, and collecting feedback questionnaires to inform subsequent editions of the book, the group returned home, exhausted but optimistic that people in South Africa want to make a difference, and that educational programmes such as Staying Alive, Fighting HIV/AIDS can play a major role in the battle against AIDS. Their only regret is that 20,000 copies of the book merely touched the surface, and Siamon's next goal is to raise money to print and distribute one million copies of the book in sub-Saharan Africa, as well as to investigate proposals to translate the book into other languages.

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