fusion

THE NEWSLETTER OF THE SIR WILLIAM DUNN SCHOOL OF PATHOLOGY

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Editorial

This third volume of *Fusion* draws attention to the department's growing involvement in infection and immunity. The sad death of Norman Heatley, so soon after that of Edward Abraham, has deprived us of two of the key figures responsible with Florey for the clinical application of antibiotics. We are aware of the heritage they have left us, and intend to continue to play an important part in the battle against microbial diseases.

On a brighter note, the new Edward Abraham Research building was opened on 10 July last year by Nobel Laureate Tim Hunt who also gave the 2003 Heatley lecturer. It was a great pleasure to welcome back so many old members and friends of the Dunn School on what turned out to be a fine day. The Edward Abraham Building provides valuable space to allow the Dunn School of expand its research in Infection and Immunity. Members of the Dunn School (notably Jeff Errington, Nigel Saunders, and Keith Gull) have been major contributors to elucidating the sequence of *B.subtilis*, neisserial and trypanosome genomes. William James, Gordon Macpherson, and Quentin Sattentau are expanding our efforts to get to grips with the natural history of prion and HIV infections, while Fiona Powrie is developing our understanding of how our immune system interacts with gut flora both to shape the immune system, but also as a potential cause of inflammatory bowel disease. Ariel Blocker's research programme focuses on the mechanisms by which shigella bacteria cause disease; she has recently suggested a structural basis for the means by which a major shigella toxin exerts its biological effect on the host. We are hopeful that their efforts will lead to new knowledge and new generations of anti-microbial drugs, vaccines and other therapeutic strategies to limit the diseases caused by these and related microbes.

Allied to this expansion in microbial research this volume also draws attention to the development of platform technologies in gene arrays and proteomics that are having a major impact on the research of the department. We are grateful to Alexandre Akoulitchev, Nigel Saunders, and Neil Barclay for being so far-sighted in establishing these systems within the Dunn School.

Herman Waldmann, FRS, Head of Department

Opening of the Edward Abraham Building on 10 July 2003. From left to right: Sir Colin Lucas, the Vice-Chancellor; Professor Herman Waldmann; Sir Henry Harris; Nobel Laureate, Dr Tim Hunt

Contact microarray printers at the Dunn School have enabled population studies on the four key experimental strains of N.gonorrhoeae

Research in the new Edward Abraham Building

One of the most exciting aspects of the new Edward Abraham Building is that it has provided space for a number of new groups working on Infection and Immunity. One of these is The Bacterial Pathogenesis and Functional Genomics Group, led by Dr Nigel Saunders. This group uses state-of-the-art techniques from functional genomics to shed light on the mechanisms by which bacteria cause disease, in particular meningitis and gonorrhoea.

The over-arching theme of our work is founded upon identifying and understanding the key steps of bacterial interactions with their hosts which make them dangerous, and differentiate them from the many similar bacteria which live on their hosts without ever causing disease. This approach is one that is based upon consideration and awareness of the functions of the organism as a whole, and the nature of different host-interactions, rather than the exclusive pursuit of a limited set of predetermined candidate virulence genes. Ultimately, however, experiments focused on single genes, and combinations of genes, result from these studies.

We are seeking to identify the central mediators of the diseases studied, with the long-term goal of identifying new vaccine candidates and therapeutic drugs

This approach is made possible through the exploitation of complete genome sequences. Using a combination of different approaches we ask a number of questions relevant to how the pathogens cause disease, and then consider the results of each study in combination. This is necessary, because when working with a large number of genes even in single organisms (typically 2000) individual questions rarely give a good overall picture of how things work. A key component of this approach is to compare related organisms that are associated with different abilities to cause infection, which cause different types of infection, and unrelated species with similar systems controlling virulence to gain additional basic insights into the process of pathogenicity through these comparisons. Often, through seeing what is similar, and what is different, from these comparisons, the broad picture of how these processes really work is revealed.

The main organisms being studied are *Neisseria meningitidis* and *Neisseria gonorrhoeae*, two very closely related bacteria which cause very different infections (bacterial meningitis and gonorrhoea, respectively). The other organism we investigate in detail is *Helicobacter pylori*, which is the main cause of stomach ulcers and gastric cancer. Although they are very different, these species share common ways of controlling the genes involved in infection. At the same time, largely through collaborations, studies are ongoing on the other bacteria associated with bacterial meningitis, including *Haemophilus influenzae*, Group B Streptococcus, and *E. coli*. Through our work, we are seeking to identify the central mediators of the diseases studied, with the long-term goal of identifying new vaccine candidates and therapeutic drugs.

The tools required for this approach embrace the latest tools in functional genomics. Initially work was based upon developing and using tools to study the complete genome sequences, and the sequences are still used as a framework for the design and interpretation of experiments. More recently, we have specifically concentrated upon bacteria with altered expression of genes to study how different genes are controlled during experiments and infection. This includes work based upon microarrays, and we designed the first multi-strain multi-species microarray as part of an international consortium spanning the UK, the USA, and Australia, and now manufacture a revised version of this microarray (and others) within the recently established microarray facilities within the Dunn School. These tools are used to compare the genes that are present in different strains of bacteria, and how expression is controlled by measuring mRNA. Current efforts are focused on extending the use of new technologies to also measure protein expression, both directly and using antibody and protein microarrays.

For more information see the Saunders group web page at: www.path.ox.ac.uk

Nigel Saunders

Beyond The Genome: Understanding Sleeping Sickness in 2004

Professor Keith Gull, Wellcome Principal Research Fellow, previews exciting developments in trypanosome biology later this year, with research at the Dunn School playing an important role

Keith Gull

The Trypanosome Genome Project

The trypanosome genome project is part of the World Health Organization's new strategy for research on tropical diseases, including malaria, sleeping sickness, schistosomiasis and leishmaniasis. An independent global programme of scientific collaboration co-sponsored by the UN Development Programme, the World Bank and the WHO, it aims to help coordinate, support and influence global efforts to combat a portfolio of major diseases of the poor and disadvantaged. The strategy for 2000-2005 seeks to address two interacting forces in research: the *push* of scientific discoveries and technological breakthroughs; and the *pull* of disease control needs for new interventions, method and approaches for these parasitic diseases, which wreak such mortality and morbidity in the developing world.

The influence of the *pull* of the need for disease control for these parasitic diseases is constant. However, a huge boost to the *push* of new information on the parasites and its influence on research and development comes in the early part of 2004 as we see the completion of the genome project for *Trypanosoma brucei*, the causal agent of African trypanosomiasis or Sleeping Sickness. This parasite is responsible for over 300,000 new cases of Sleeping Sickness each year in sub-Saharan Africa, and 50,000 deaths. Sequencing of the 11 chromosomes of the 35 Mb genome has been performed by the Wellcome Trust Sanger Institute, Cambridge and The Institute for Genome Research (TIGR), USA. The full sequence of the first chromosomes were published last year, six years after the first grant was awarded to myself and Dr Sarah Melville of Cambridge. During the next few months a consortium of researchers throughout the world including ourselves will annotate the genome leading to publication of the full genome in *Nature* in the middle of 2004. This will be one of the key events in the history of research on this disease, providing unparalleled insights to the biology of this parasite. The hope is that (as has been the case with the malaria genome) this view of the genome will lead to new opportunities for diagnostics, drug and vaccine development.

Trypanosoma brucei *is responsible for over 300,000 new cases of sleeping sickness in sub-Saharan Africa each year*

Bonsai Genomics

There is, however, one key component of the trypanosome genome that would have been missing without research done in the Dunn School. The genome project has concentrated on the 11 megabase sized chromosomes of the parasite. A key feature of the African trypanosome is that it can undergo antigenic variation involving periodic switching of the major cell surface protein, the variable surface glycoprotein (VSG). To facilitate this important survival mechanism, there exists in *T. brucei* a highly specialized gene organization that includes a large number of minichromosomes. The minichromosomes are small (30–150 kb), linear and very numerous. A population of ~100 minichromosomes comprising ~10% of the

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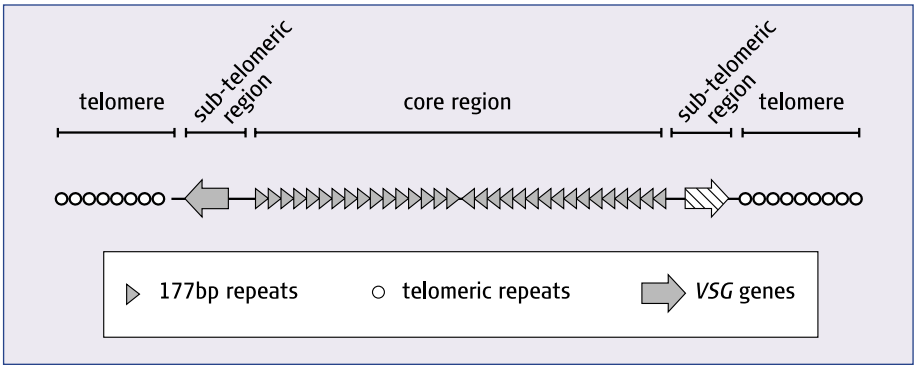


Fig. 1. Bill Wickstead's minichromosome analysis

Forthcoming Events

University of Oxford North American Reunion. This biennial meeting will be held at the Waldorf Astoria Hotel in New York on 16/17 April 2004, and is open to all Oxford alumni (for registration details please see the website: www.northamerica.ox.ac.uk). Professor Herman Waldmann, FRS, Head of the Sir William Dunn School of Pathology, will be giving one of the keynote seminars on Saturday 16 April and would be delighted to meet former members of the department.

The 14th Norman Heatley Lecture will take place on 17 June 2004. The speaker will be Dr Robert Tjian, Professor of Molecular Cell Biology at the University of California, Berkeley. Dr Tjian is renowned for his work on transcription factors and gene expression.

Dunn School alumnus Malik Peiris, will give a seminar here on 23 November, 4.30pm, on the pathogenesis of influenza and SARS.

nuclear DNA, is maintained by *T. brucei* as a means of expanding the number of available VSG genes. Such antigen genes from this repertoire of minichromosomes are the preferred genes for antigenic switching events early in the infection. Such switching events proceed by duplication and transfer of minichromosomal VSG genes into an active VSG expression site on a larger chromosome. Hence only one antigen gene is expressed per parasite but it can be switched in some parasites in the population so allowing this cohort to avoid the immune response and continue the infection.

For technical reasons, there was a danger that the structure and organization of this unique form of minichromosome, so central to understanding antigenic variation, would be missed out from the trypanosome genome project. However, this gap has now been closed by an analysis of these chromosomes by Bill Wickstead, a post-doc in the Gull Lab. Using a combination of sequencing and physical mapping Bill has produced fine-resolution maps of 17 complete minichromosomes. This revealed an unusual DNA structure likely to be shared by all minichromosomes and representing a 'stripped down' version of a chromosome. There is a large central core of 177 bp repeats. Around the core are variable length regions with a sole, silent VSG gene. The core region turns out to be a repetitive palindrome with a single inversion point common to all the chromosomes. This unexpected palindromic structure suggests a mechanism of genesis for these chromosomes and that the sequence inversion is one of the higher-order sequence motifs that confers chromosomal stability. Bill's 'bonsai genomics' project completes a vital part in our understanding of the genome of this parasite. Our hope is that this work in the Dunn School and the wider genome information forms part of the research push toward future clinical interventions into this devastating disease as envisaged by the WHO's new tropical disease research strategy.

Keith Gull, CBE FRS

News

Honours and Awards

Two members of the Dunn School were made Fellows of the Royal Society in 2003: Professor Jeff Errington and Professor Keith Gull, as was Professor Geoffrey Smith, now Professor of Virology at the Wright-Fleming Institute at Imperial College. Keith was also awarded the CBE in the 2004 New Year's Honours list.

The Academy of Medical Sciences awarded a Fellowship to Professor Siamon Gordon. Siamon Gordon was also the recipient of the Marie T. Bonazinga award of the Society of Leukocyte Biology, and was granted Honorary Membership of the American Association of Immunologists in 2003.

Professor Neil Barclay and Dr Fiona Powrie have given consecutive Eijkman lectures, in 2002 and 2003, at the University of Utrecht; both received the Eijkman medal for their contributions to immunology. The medal honours Christian Eijkman (1858-1930) was awarded the Nobel Prize for his discovery of vitamins.

Dr Rut Carballido-Lopez, who writes on p. 11, won the European Regional Prize of the prestigious Amersham Biosciences/*Science* Magazine prize for Young Scientists.

Congratulations also to: Dr Gordon Brown, awarded a Wellcome Trust Senior Research Fellowship; Dr Philip Taylor, for a Wellcome Trust Research Career Development Fellowship; Dr Michael Ginger, awarded a Royal Society Reseach Fellowship; Dr Alexandre Akoulitchev, appointed to the Monsanto Senior Fellowship at Exeter College; Dr Abdessamad Tahiri-Alaoui, appointed University Reasearch Lecturer; Namir Hassan, D.Phil student with Dr Marion Brown, on achieving a graduate award for outstanding achievements from Trinity College.

BioAnaLab, a spin-out company from the Therapeutic Antibody Centre, won the Best New Start-Up Laboratory at the *Laboratory News* Industry Awards in November 2003. BioAnaLab

was set up by Professor Geoff Hale and others from the Sir William Dunn School of Pathology and offers a contract testing service for the biopharmaceutical industry, in particular in the area of therapeutic monoclonal antibodies.

Brownlee-Abraham Professor of Molecular Biology

Nicholas Proudfoot has been named as the first Brownlee-Abraham Professor of Molecular Biology, and took up post in October 2003. This new Chair, held in association with Lincoln College, was made possible by the generosity of a number of donors, including the EPA Research Trust and BTG plc as well as several private individuals. BTG plc also sponsored a well-attended dinner to celebrate Nick's inaugural lecture on 12 February this year.

George Brownlee, Ian Harvey (BTG plc), Nick Proudfoot, and Herman Waldmann at the reception following Nick's lecture,

Graduate Student Day

The Department held its inaugural Graduate Students' Symposium on the 30th June, 2003. Modelled on a scientific conference and attended by the entire Department, this annual symposium provides training in vital communication skills as well as critical scientific feedback. A panel of judges evaluated all contributions and award a prize for the best poster to Laura Briggs ('Insight to flagellar protein function from studies with trypanosomes') and for the best oral presentation to Namir Hassan ('Regulation of the immune response through interactions of CD6). The conference was considered a great success by all participants, and we are grateful to TolerRx Inc and Serotec for sponsoring the prizes and to Amersham Health for sponsoring the lunch. This year's symposium will on Friday 2nd July.

Proteomics day

Proteomics was the topic of the Medical Sciences Division's fourth annual science day was held on 24 February. Dr Alexandre Akoulitchev of the Dunn School chaired a series of presentations, which gave an insight into the scope of work being done at Oxford using these technologies.

People

John F Watkins

John Frederick Watkins, who died in April 2003, was Reader in Bacteriology at the Sir William Dunn School of Pathology in the 1960s, before taking up the Chair of Medical Microbiology at Cardiff. He is perhaps best known for his collaboration on cell fusion with Henry Harris, leading to their seminal 1965 paper in *Nature*.

Judy Coughlin, who retired in December 2003

Judy joined the Dunn School in 1961 and worked for Professor Sir James Gowans in the MRC unit, from which the CIU evolved. She left in 1971 to work in the Zoology department before rejoining the Dunn School in 1987 to take up the position of classroom technician, which she held until her retirement last year.

Peggy Turner

Peggy Turner (née Smart), who died on 1st March 2004, joined the department as a junior secretary in Dec 1936 in Florey's early days and before the penicillin work.

Florey recognized and encouraged her talents and eventually promoted her to be Departmental Administrator, a post she filled with distinction under both Professor Florey and Professor Harris.

On retirement in December 1976 the University awarded her an Honorary MA.

Norman Heatley – A remarkable man

Norman George Heatley, OBE, DM. ***10 January 1911 – 5 January 2004***

Many of you will have read with sadness of the death of Norman Heatley in January this year. Eric Sidebottom writes about the life and work of the last survivor of the penicillin team at the Sir William Dunn School of Pathology.

Norman Heatley died on the 5th of January, less than one week short of his 93rd birthday. His passing can truly be described as the end of an era, since he was the last surviving scientific member of the team that developed penicillin as the 'miracle drug' in the early 1940s. He has often been described as the unsung hero of the penicillin story. Those who knew him will readily understand why. Heatley was the most delightful 'old fashioned gentleman'.

He was modest to a fault, courteous, kind, considerate and constantly trying to find ways to help colleagues and friends. He was a team player, rather than a leader of men.

Many myths surround the origins of penicillin: from the Oxford perspective the most important and difficult of these, particularly since it is what most schoolchildren are taught, is that Alexander Fleming not only 'discovered' penicillin (which he did, essentially by accident, in 1928) but that he gave the antibiotic ready to treat the grateful, waiting world. The truth is that Fleming and his colleagues actually found that the culture extract containing penicillin was unstable and the antibiotic was impossible to isolate in a pure state and so they effectively gave up research on it. Only when Florey and Chain decided to work on antibacterial substances in 1939 was serious research on penicillin resumed. When its importance became apparent in 1940, Fleming contacted Florey and visited Oxford to learn more about the 'breakthrough'. (At this time Chain is reputed to have said that he thought Fleming was already dead!) But St Mary's Hospital (this was pre-NHS of course) realized the enormous publicity value of their link with penicillin and Lords Moran and Beaverbrook were prominent in encouraging the press to publicize and exaggerate the contribution of Fleming and to play down the importance of the Oxford work. Florey himself must bear some responsibility for the distorted stories put out by the media because he consistently refused to speak to them and forbade his colleagues to do so. In a Florey Centenary Lecture given in 1998, Professor Sir Henry Harris (Florey's successor as Professor of Pathology at Oxford) succinctly summed up by saying: 'without Fleming, no Florey or Chain, without Chain no Florey, without Florey no Heatley, without Heatley no penicillin'.

'without Fleming, no Florey or Chain, without Chain no Florey, without Florey no Heatley, without Heatley no penicillin'

It is bordering on the bizarre that while Fleming apparently received 25 honorary degrees, 26 medals, 18 prizes, 13 decorations, the freedom of 15 cities and honorary membership of 89 scientific societies and academies, Heatley received one honorary degree (1990 Oxford – an Honorary Doctorate in Medicine, the first given to a non-medic in its 800-year history – and, in Heatley's view, 'an enormous privilege, since I am not medically qualified') and an OBE (1978). We might speculate that he missed out on the Nobel Prize given to Fleming, Florey and Chain, only because the rules of the Nobel committee restrict the number elected for an award to three. When it was suggested to him that he should have received a knighthood,

Above: Equipment used to extract penicillin at the Dunn School in 1939.
Left: Norman Heatley in the lab in 1940.

Heatley's characteristic response was to shrug his shoulders and say: 'Oh well...'.

But what he did get in large measure was the enormous satisfaction of knowing that he was a key part of the team that gave the world its first practical antibiotic; one that saved the limbs and lives of thousands of allied troops in WW II, and literally millions of patients all round the world since then. Few individuals have combined the talent, opportunity and good fortune to make such an impact on the world. As a result of the penicillin work Lord Nuffield endowed three Research Fellowships at Lincoln College. Heatley was elected to one of these and his close involvement with Lincoln College continued for the rest of his life, giving much pleasure to both parties.

Norman George Heatley was born on January 10th 1911 at Woodbridge in Suffolk. After graduating in Natural Sciences in 1933 at St John's College, Cambridge, he stayed on to do research for a PhD in Biochemistry. Soon afterwards he was invited to come to Oxford to work with Chain and Florey. Ernst Chain had found Fleming's 1929 article about penicillin and

'Penicillin girls' tending the Heatley-designed vessels for growing penicillin mould at the Dunn School in 1939/40.

urged Florey to investigate its properties further. With Chain, Heatley's role was to look at the growth, isolation and chemistry of the substances under study while Florey studied their biological properties. It soon emerged that penicillin was far more effective in fighting bacteria than the other anti-bacterial candidates but there was no simple way to measure its activity or to extract and purify it from the culture fluid. Heatley's genius for invention solved both these problems. He devised a new assay method that measured the activity of penicillin precisely, in what became known as 'Oxford units'. He also found appropriate conditions under which penicillin was stable and applied a multi-stage technique to isolate it from the culture fluid and concentrate it. The procedure was automated, using the now famous Heath Robinson set up of bath, milk churns, petrol cans and biscuit tin lids, etc., and yards of glass and rubber tubing. Despite its improvization the basic principles of the method are still used today to produce penicillin.

Heatley also played a key role with Florey in the first experiment that demonstrated penicillin's remarkable power in animals. At 11am on Saturday May 25th 1940, eight mice were injected with a lethal dose of virulent streptococci bacteria. One hour later four were given an injection of penicillin (two were given repeated injections). Heatley stayed in the laboratory until 3.30am the following morning by which time all the untreated mice were dead and all the treated mice lively. The experiment was repeated the next day with the same results. This was no statistical fluke! It was now clear that a trial of treatment in human patients was urgently needed. But a human is 3000 times larger than a mouse and the amount needed to treat humans would require large-scale production, which in wartime no commercial firm in Britain was able to undertake.

The Sir William Dunn School of Pathology was turned into a production factory utilizing several hundred Heatley designed ceramic 'bed-pans' for the growth of the penicillin cultures. These were looked after by six specially-recruited technicians, known as the 'penicillin girls'. After extraction and purification the dry powder produced turned out to be less than one per cent pure but was nevertheless deemed suitable for a clinical trial. The first patient to be treated was Albert Alexander, a virtually moribund policeman who received his first injection of penicillin at the Radcliffe Infirmary, Oxford, on 12th February 1941. After 5 days he had improved dramatically but unfortunately the penicillin had all been used and he slowly regressed and died on 15th March.

Other patients in the trial were 'cured' and overall it was clear that penicillin really was 'a miracle drug'. These results were published in the *Lancet* in August 1941. By now it was obvious that penicillin could be an effective treatment for infection and thereby make a very important contribution to the war effort, and to

The Sir William Dunn School of Pathology was turned into a production factory utilizing several hundred Heatley designed ceramic 'bed-pans' for the growth of the penicillin cultures.

the morale of injured troops. But increasing the yield of the batches of antibiotic proved impossible without industrial-scale production. Accordingly in late June 1941, Florey and Heatley flew to New York, to seek help from firms less restricted by wartime production than those in the UK. While Florey sought help from the 'top brass' in US research circles and the pharmaceutical industry, and indeed persuaded them to collaborate, Heatley worked with government scientists at the Northern Regional Research Laboratory at Peoria, Illinois. Improvements in the growth medium (corn steep liquor) and the use of a different strain of penicillin (isolated from a mouldy melon) increased yields twenty-fold. By late 1943 mass production of the drug had begun in America using a deep-tank fermentation process which was much more effective than the two-dimensional fermentation in thousands of bottles or flasks undertaken previously.

After the excitement of penicillin the rest of Heatley's career could have seemed something of an anticlimax but his genius for introducing new methods and refining and miniaturizing existing ones remained and the results, many of them collaborations with a wide range of scientists, are described in the 60 plus scientific papers he wrote or co-authored.

In 1992, an annual Norman Heatley lecture was established at the Dunn School by funds donated by Robert Marston, a former Rhodes Scholar and Heatley student who became Director of the US National Institutes of Health and President of Florida University, and by Johnson & Johnson; the two most recent lectures were given by the Nobel prizewinners Tim Hunt and Sydney Brenner.

Outside his work Heatley was a quintessential family man; a proud and immensely involved father, an affectionate husband, an accomplished house-husband, an excellent host. His practical brilliance was matched by his down-to-earth, sometimes impish, good humour. He was an excellent raconteur and hence very good company. His home in Old Marston has, for over 50 years, been a welcoming haven for generations of students and scientists working in Oxford.

A new book telling the story behind the discovery of penicillin and why it took so long to develop the drug is published this year. *The Mold* (*Mould* in the UK) *in Dr Florey's Coat* by Eric Lax is published by Little Brown in the UK and Henry Holt in the US.

A memorial service is planned for September this year. Details will be posted on the Dunn School's website and will be sent to old members.

To commemorate the immense contribution made by Norman Heatley's persistence and ingeniuty, a Norman Heatley Memorial Fund has been set up to support the lecture series and a Research Fellowship at the Sir William Dunn School of Pathology and Lincoln College. Some information is included in this issue of *Fusion*; if you would like more information on either the service or the fund, please contact Susan Harrison at 01865 285751 or susan.harrison@devoff.ox.ac.uk

Above: Norman Heatley with Dr Tim Hunt at the opening of the Edward Abraham Buidling in July 2003.

Left: Charles Fletcher, who treated the first penicillin patients, with Norman Heatley in 1991.

Thank You

We are very grateful to the estate of the late Dr Desmond Kay for a very generous bequest to establish the Desmond and June Kay Fund at the Sir William Dunn School of Pathology.

Thanks also to the Sir Samuel Scott of Yews Trust for a donation towards the work of the Therapeutic Antibody Centre.

Introducing Quentin Sattentau

Quentin Sattentau has come to the Sir William Dunn School of Pathology from Imperial College London. He is the new Lecturer in Molecular Biology. Our staff reporter David R. Greaves asks the questions.

Quentin, when did you first become interested in viruses?
I was interested in science from a fairly early age – see photograph! I enjoyed biology because it involved a lot of drawing; art was one of my favourite subjects at school. I remember reading a library book on *'Microbes'* when I was 15 and that got me interested in microbiology, which I went on to read at Bristol University. The best part of the course at Bristol was the third year experimental project in which I studied herpes simplex virus latency.

Where did you do your PhD?
I continued working on herpes viruses in a clinical virology lab at the Royal London Hospital in Whitechapel. In addition to studying virology I also had to teach myself quite a lot of immunology, which was very useful when I started studying HIV/AIDS.

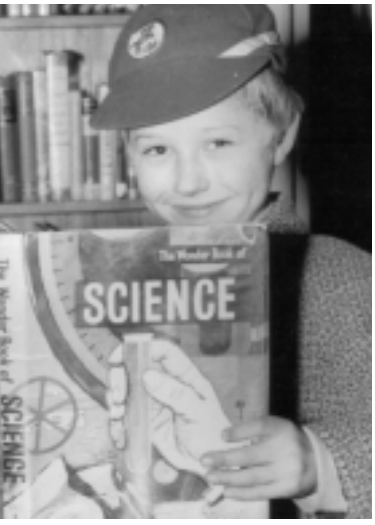
How did you get started in AIDS research?
I had the good fortune to do my first postdoc in Peter Beverly's department at University College London, collaborating closely with Robin Weiss, who has been a great role model for me and many other virologists. In 1985 AIDS offered a whole new disease and a brand new virus to study. Robin's work identifying CD4 as the HIV receptor had just been published and it was a very exciting time. The laboratory I worked in, however, was not the greatest; we did our category 3 work in a tiny Portacabin on top of a sexually transmitted diseases clinic in Charlotte Street.

You worked in New York and then moved to France?
That's right. In 1990 the MRC AIDS Directed Programme paid for me to spend 18 months in Dick Axel's lab in Columbia University which was a wild experience and I was exposed to a lot of exciting science. After New York I took up a tenured position at the Institute of Immunology in Marseilles. I stayed there for seven years. After a very enjoyable sabbatical in the Dunn School I was appointed to a Readership in Infectious Diseases at Imperial College London at St. Mary's Hospital.

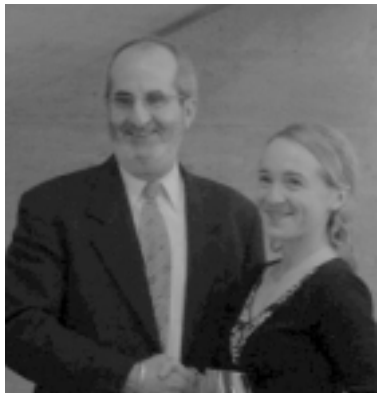
Which is the piece of work you are most proud of?
As well as our ongoing HIV work I am very excited about our current research on carbomyl groups and their effect on the immune response. I think that this work has relevance to areas as diverse as vaccine design, allergy and autoimmunity.

What do you think the big challenges are in HIV research at the moment?
Well obviously we need a vaccine, and as soon as possible. Unfortunately, despite some excellent science and a lot of hard work, the HIV vaccine field isn't moving forward as fast as we would hope and in my opinion we are a long way from developing a protective vaccine. On a more positive note, the microbicide field is moving ahead to phase-III clinical trials. Although this is not rocket science, it stands to save many lives, particularly in developing countries.

What interests do you have outside of lab work?
As you know only too well David, keeping a happy balance between work and family is a constant challenge and can drive one completely bonkers. Any extra time is spent training for this year's London marathon in April, which is madness but fun in a weird sort of way.



Shaping bacteria



Rut receiving her prize from Andrew Carr, CEO, Amersham Biosciences

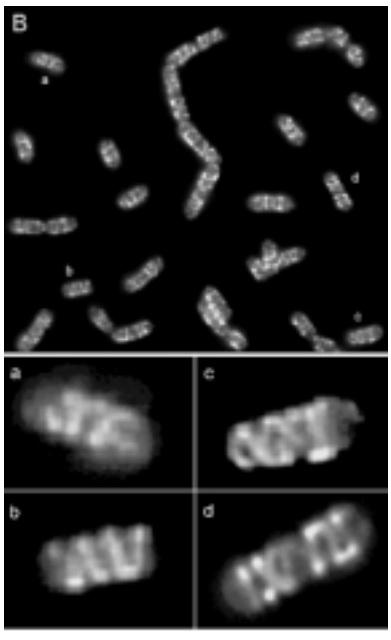
Rut Carballido-Lopez was the 2003 European Regional winner of the prestigious Amersham-*Science* prize for an essay based on her D. Phil research in Professor Jeff Errington's group at the Sir William Dunn School of Pathology. Rut's award-winning essay, 'Shaping Bacteria: The Actin-Like Prokaryotic Cytoskeleton,' takes us through the discovery and the characterization of the bacterial ancestor of actin (MreB), which has revealed the prokaryotic origin of the cytoskeleton and revolutionized our view of bacterial cell architecture. Rut's outstanding research qualities have been recognized by the award of three other major prizes. She received the Young Microbiologist of the Year Award from the Society of General Microbiology (SGM) in 2001, and won the prestigious Promega Young Life Scientist of the Year Award in 2002, in competition with top young scientists from all areas of the biological sciences. Last year, she was joint winner and first UK recipient of the Nat Sternberg Thesis Prize for the best doctoral thesis in prokaryotic molecular genetics.

In this article, Rut writes about the work that led to this garland of awards.

A fundamental question in cell biology is how cell shape is determined. Eukaryotic cells have a cytoskeleton of filamentous proteins for shape and movement, whereas bacteria were believed to have only a tough cell wall for support. Even powerful electron microscopes had failed to turn up any distinct internal structure, and the dogma espoused by most general textbooks of cell biology was that prokaryotes don't have a cytoskeleton. Wrong. Our work in Jeff's lab showed that bacteria do possess a cytoskeleton-like structure that is the determinant of cell shape.

My Ph.D. research provided the characterization of *mbl* (for mreB-like), a gene required for morphogenesis in *Bacillus subtilis*. Sub-cellular localization revealed that Mbl protein forms helical filamentous structures ('cables'), which lie close to the surface and run the length of the cell. The filamentous nature of these structures was suggestive of a polymerization event and, along with the limited sequence similarity of Mbl to eukaryotic actins and its distribution in different bacterial species with non-spherical cell shape, raised the possibility that MreB proteins had a cytoskeletal, actin-like in bacterial cell shape determination. The question was addressed from a variety of approaches including genetic, biochemical and cytological studies. Cross-linking and sedimentation assays were developed with both *B. subtilis* cell extracts and purified recombinant protein. These demonstrated that Mbl can self-assemble into high molecular weight complexes. Filamentous ordered structures were observed by electron microscopy. Mbl self-assembly was shown to be reversible, a common property of cytoskeletal proteins. Like actin, the protein was shown to bind and hydrolyse ATP. These results strongly suggested that the filaments observed in the cells are indeed formed by an actin-like polymerisation. Time-lapse imaging and fluorescence recovery after photobleaching (FRAP) methods were used to examine the dynamics of a GFP-Mbl fusion protein *in vivo*. Mbl filaments were shown to be stable but not rigid and to undergo dynamic changes during cell growth. FRAP analysis showed that the Mbl cables are continuously remodelled. Turnover occurs along their length, with no obvious polarity and a recovery half-time of 7-10 min, similar to that of actin filaments.

Taken together, these findings provided strong evidence that Mbl is a cytoskeletal element homologous to eukaryotic actin, and have important implications for ideas of bacterial evolution, growth and cell wall structure. The current model based in our findings, is that the machinery involved in the cell wall biosynthesis is directed by these internal, dynamic, actin-like filamentous structures. The next few years promise to be an exciting period during which important aspects of the structure, function and regulation of the bacterial cytoskeleton will be resolved.



Subcellular localization of Mbl. Helical localization of GFP-Mbl in live cells of Bacillus subtilis. Cells were grown to mid-exponential phase in the presence of 1% xylose and immobilized on an agarose-coated microscope slide.

Fiona Powrie

Gut Reactions

Fiona Powrie is a Wellcome Senior Research Fellow at the Sir William Dunn School of Pathology. Her research focuses on mechanisms of natural tolerance and the role of the mucosal immune system. The results of the disease models developed in this work suggest clinical approaches for IBD, colitis and Crohn's disease. Her group, along with 19 European partners, has recently been awarded a prestigious European Union Framework 6 grant to harness mechanisms of tolerance in the thymus for the treatment of autoimmune and allergic disease.

It is estimated that 300-500 different species of bacteria colonise the gastrointestinal tract in humans. In general this is a symbiotic relationship with benefits for both host and bacteria. However in patients with inflammatory bowel disease (IBD) these normally harmless resident bacteria can provoke an inappropriate inflammatory response. Crohn's disease and ulcerative colitis represent the two main forms of IBD. Although these diseases have different clinical and pathological features both involve chronic relapsing inflammation of the gastrointestinal tract. As with many chronic immune–mediated diseases, current therapies involve non-specific immune suppressive drugs that can have harmful side-effects.

Studies on IBD suggest disease develops as a consequence of complex interactions between genetic and environmental factors making it difficult to dissect the role of individual factors in causing the disease. In the last decade a number of models of chronic intestinal inflammation in rodents have been described, that resemble aspects of the pathology found in humans with IBD. These have provided excellent tools to study how genetic factors influence the host immune response and epithelial barrier function within the intestine. The sophisticated mouse genetics that are now available has meant that strains of mice can be generated that lack or over-express particular molecules. Using this technology it has been found that IBD can develop as a consequence of altered barrier function, deletion of regulatory cytokines such as IL-2 or IL-10, or over-expression of inflammatory cytokines such as IL-7 and TNF-α.

The incidence of disease that develops as a consequence of any one particular mutation is also affected by the other genes expressed in the host. Taken together these studies indicate that different genetic lesions can produce similar immune diseases and that the penetrance of major susceptibility genes is modulated by other genes present in the host. In the vast majority of models, intestinal inflammation develops when there is a sustained chronic immune response towards normally harmless gut bacteria. No IBD specific bacterial pathogen has been identified and it seems more likely that different bacteria may be involved depending on the particular model. Immune pathology is a consequence of disregulated T cell response and in many models there is evidence of differential activation of T-helper 1 type cells. These cells secrete high levels of TNF-α and IFN-γ and neutralization of these cytokines prevents disease. This is particularly relevant to Crohn's disease which also involves a Th1 cell response and has been shown to be responsive to anti-TNF-α therapies.

A theme that has emerged from a number of the animal models is that development of intestinal pathology is a balance between inflammatory responses and regulatory mechanisms. Studies from this lab and others have identified specialist populations of T cells, termed regulatory T cells, which prevent pathological immune responses. Our recent studies have shown that regulatory T cells not only prevent IBD but can also cure it in animals. Although the relevance of these immune-regulatory T cells in human IBD has yet to be established, patients who lack a transcription factor required for the development of these cells suffer from a number of inflammatory diseases some of which can resemble IBD.

Animal models of IBD have provided great insight into the factors that govern the development and regulation of intestinal inflammation. They provide excellent vehicles with which to test novel therapies for disease but they also allow dissection of the mechanism by which inflammatory responses are normally controlled. Regulatory T cells are one of the host mechanisms to limit immune pathology and it is hoped that a greater understanding of their functions may provide more specific therapies for IBD and for other chronic inflammatory diseases.

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