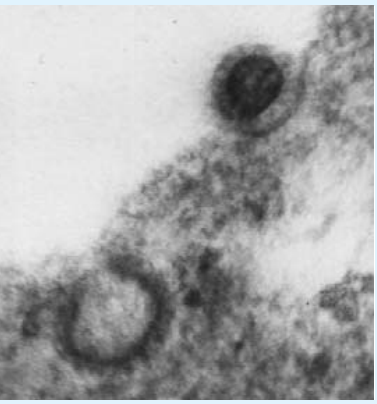
fusion 5



Influenza virus binding to infected cell via Haemagglutinin spikes on virus surface.

Bird flu vaccines and reverse genetics

Influenza is rightly perceived as a significant health risk, and the spread of H5N1 (bird flu) has provoked alarm as it spreads across the globe. The groups of Professor George Brownlee, FRS and Ervin Fodor have for the past decade been working on understanding the molecular mechanisms underlying the influenza virus replication and adaptation from one species to another. Here, post-doctoral researcher Dr Ruth Harvey explains their approach.

Influenza virus was first isolated in 1933, and it still remains a public health and economic problem today. Since its isolation there have been two major pandemics, 'Asian flu' in 1957 (H2N2 subtype) and 'Hong Kong' flu in 1968 (H3N2 subtype), estimated to have killed a total of 1.5 million people. But we should not forget the infamous 'Spanish flu' in 1918 (H1N1 subtype) that reportedly killed an estimated 20 to 40 million people. By contrast the current outbreak of 'Bird flu' has to date infected around 200 people with about 100 deaths since the first case in 1997.

The occurrence of influenza virus each year, and the recommendation for annual vaccination of at risk groups, such as the elderly or immunocompromised, is the result of antigenic drift – the ability of the virus, as with many RNA viruses, to mutate rapidly. There is however a form of more drastic genetic change, caused when segments of two viruses from different sources re-assort in a single cell. This is known as antigenic shift and essentially gives rise to a new sub-type of virus. Pandemics often follow such a shift.

The current vaccine used worldwide is a trivalent vaccine. Each year, the World Health Organisation (WHO) predicts the influenza strains, (A – H1 and H3 subtype and B) likely to circulate the following year based on epidemiological data collected worldwide. The three virus strains are grown in chicken's eggs and from these stocks a vaccine is prepared. The vaccine requires updating each year and so there is a very tight time frame for first deciding which strains to include and then producing the vaccines. This process means that there is always a chance that the viruses included in the vaccine will be out of date by the time the vaccine is administered, although the viruses are normally similar enough to give sufficient protection against any new antigenically drifted strains.

Two groups of drugs are used for the treatment of influenza. Amantadine/rimantadine block an ion channel activity required by the virus for the release of its RNA into the host cell, but resistance to this class of drugs is very common. The new neuraminidase inhibitors (such as Relenza and Tamiflu) block release of new virus particles from infected cells, but these drugs only work if administered in the first 72 hours after infection and there have also been reports of resistance starting to emerge. We still need more effective drugs or a better vaccine that would be effective against any strain of virus.

Influenza research at the Dunn School by George Brownlee, Ervin Fodor and others led to the development of the reverse genetics system that allows the construction of 'designer' viruses from potentially any combination of the virus genome segments. This is a huge step forward for the manufacture of vaccine strains, allowing vaccine candidates to be made that are, for example, antigenically relevant in a high growth background. This new reverse genetics system has been used to create a non-pathogenic seed vaccine against the H5N1 bird flu virus. The UK government plan now includes the manufacture of H5N1 vaccine from such a seed stock if pandemic bird flu occurs in the UK.

Currently both Prof Brownlee's group and Dr Fodor's group focus on fundamental work, attempting to elucidate the molecular mechanisms of transcription and replication of the influenza virus genomic RNA, the structure and function of the virus RNA polymerase, and the involvement of the polymerase in the adaptation of avian influenza to mammalian cells. This research should lead to a better understanding of how the virus works and why the function of the polymerase is so essential for the virus. Such an understanding may lead to new drugs targeted to viral or host proteins. Such drugs would complement those presently available, and increase our ability to combat the threat of any emerging influenza viruses, including bird flu.

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
email: herman.waldmann@path.ox.ac.uk

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

fusion

THE NEWSLETTER OF THE SIR WILLIAM DUNN SCHOOL OF PATHOLOGY

ISSUE 5 · MICHAELMAS 2006

Contents

Editorial

The department continues to thrive scientifically against a background of escalating costs and taxation for access to University services.

This is reflected in the expanson of 5 year programme grants which now total 11 on an annual basis. We are pleased to welcome Prof Oreste Acuto who has joined us from the Pasteur Institute, and provides for the community an expertise in cell signalling which will create many opportunities for understanding how interactions with ligands outside of cells can be transmitted to changes within. This area of research has broad relevance in areas of local research ranging from Immunology, Cancer Cell Biology to Cardiovascular Disease. The departure of Prof Jeffrey Errrington to head a major microbiology initiative at Newcastle University has inspired an energetic search to find new leadership in the area of Microbiology, and we hope that this appointment will be completed in the not-too distant future. Our hope is to use this appointment to provide a nidus for the resurgence of British microbiology, and this will certainly be facilitated by the very powerful immunology groupings within the department whose research efforts interface closely with microbial pathogenesis.

Our fundraising efforts for the Cesar Milstein Chair in Cancer Research have now taken us to the £2m mark, leaving us just £0.7m off our target. We are sorry to have lost our Development Officer Susan Harrison who has now taken on a significant role as Head of Development at Lincoln college. I am pleased however that she continues to help us complete the fundraising for this important Chair.

Not only do such endowed Chairs enable Oxford to attract star quality scientists, they also ease the pressure on departments such as ours by enabling the overheads that are raised on grants to provide support to the scientific infrastructure rather than be consumed by the salary costs. With the Milstein Chair the Dunn School will have five endowed Chairs and three externally funded senior appointments (Wellcome PRF, MRC Professorship and an MRC Senior Scientists). With the advent of Full Economic Costing, externally funded appointments and endowed postitions are likely to be the longer-term salvation of departments such as ours. Needless to say we will be seeking further endowed positions to maximize our financial viability.

Finally, our congratulations to William James and Quentin Sattentau for being awarded the Title of Distinction of Professor, and to Nigel Saunders and Shona Murphy to Readerships.

Herman Waldmann, FRS, Head of Department

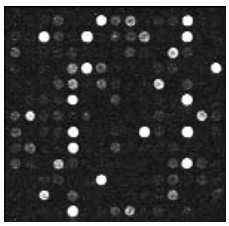
Siamon Gordon

News

Awards

Professor Herman Waldmann has been awarded the Mary Tyler Moore and Dr S. Robert Levine Excellence in Clinical Research Award by the Juvenile Diabetes Research Foundation (JRDF). The award, made jointly to Dr Lucienne Chatenoud, Prof J F Bach and Prof. Waldmann, recognizes the contribution made to the treatment of diabetes by the anti-CD3 antibody developed by Herman Waldmann and Geoff Hale at the Dunn School.

Another member of the Dunn School has been elected to the Royal Society. Professor Nicholas Proudfoot, Brownlee-Abraham Professor of Molecular Biology, was elected in May 2005, with the citation recognizing his pioneering work on polyadenylation and transcriptional termination which has had a major impact on current knowledge of the mechanism and control of mRNA processing.



Prizes

Marianna Papaspyridonos, from Dr David Greaves lab, was one of the finalists in the British Heart Foundation image competition feature on the BBC Health Website. She used DNA microarray technology to analyse gene activity in white blood cells from diseased blood vessels. Each spot in the image represents a single gene – the brightest are the most active

Grants

Two major grants to support work on microbicides in the department have been awarded over the past few months.

Dr William James has been awarded a programme grant by the US NIH to use the Envaptin technology originating in his laboratory to develop microbicides targeting multiple sexually transmitted infections. The award, totalling more than $3.5m, involves laboratories at the University of California, Los Angeles, and Leuven, Belgium in a concerted drive to take Envaptins from the laboratory to preclinical trials. The aim is to isolate Envaptins targeting Herpes Simplex virus Type 2 and Human Papilloma virus Type 16, to complement those targeting HIV, already isolated by William James, and to put them through a development program involving lead identification, medicinal chemistry refinement, formulation and ex vivo testing. The aim is to be able to offer a single preparation that will simultaneously protect against infection by multiple infectious agents.

Dr Quentin Sattentau's group is one of the recipients of The Bill and Melinda Gates Grand Challenges in Global Health Awards. Together with others in a consortium coordinated by Dr Robin Shattock at St George's Hospital, London, they have been awarded $19.5m over a five-

Graduate Student Symposium, 2005

The symposium was held on 2nd July and was attended by the Vice-Chancellor, Dr John Hood, for the first time. First and second year graduate students exhibited posters of their work, while third year students made presentations to the Department. Sponsorship for the day was provided by Serotec, TolerRx, Qiagen and Astellas.

The prizewinners are pictured with Dr John Hood (Vice-chancellor; extreme R), Professor Fiona Watt (CRUK and a former Dunn School graduate; 3rd from L) and Dr Chris Norbury (organiser; 2nd from R).

year period, to design and implement new forms of HIV vaccine delivery, with the specific aim of eliciting strong and persistent antibody-mediated immunity in mucosal sites.

Dr David Greaves, Reader in Molecular Pathology, has recently been awarded a five year programme grant by the British Heart Foundation to study the role of inflammation in cardiovascular disease.

Professor Jeff Errington, FRS, has moved to the University of Newcastle as Director of the Institute for Cell and Molecular Biosciences. Jeff has been at the Dunn School for more than 16 years, and we wish him great success in this new position.

"I told you so"

Henry Harris and George Klein are still discussing the importance of differentiation in cancer 36 years after the first Harris & Klein paper on suppression of Malignancy

Nature (1969) 223, 363-8. Suppression of malignancy by cell fusion. The first of 26 collaborative papers with Klein 1969-1980.

Photograph taken in Oct 2005 at a meeting on Cell Fusion & Cancer in Sweden.

Obituaries

Helen Muir, who died in November 2005 at the age of 85, started her career at the Dunn School, completing her D. Phil in 1947 and continuing as a post-doctoral fellow working on the synthesis of penicillin. Later, she moved to the Kennedy Institute for Rheumatology, where she developed her interest in osteoarthritis. She was made a Fellow of the Royal Society in 1977. Her obituary in the Guardian mentions her love of fast horses and fast cars, and she is remembered here as a striking and lively scientist.

Helen Muir

Jean Medawar, died May 3 2005, aged 92. Brought up in Cambridge, Jean went to Benenden school, in Kent, and won a scholarship to Somerville College, Oxford, to read zoology. After graduating she joined Florey's team in the Dunn School and took a BSc for work on the origin and development of lymphocytes.

While at Oxford, she met Peter Medawar, later Sir Peter, the Nobel laureate for medicine and director of the National Institute for Medical Research, and they married in 1937. They had 4 children who all survive. Jean, despite a very active career of her own, including Chairman of the Family Planning Association, cared for Peter after his calamitous stroke in 1969, helping him through 18 more exuberant and productive years.

Jean Medawar

Jonathan Austyn, Luisa Martinez-Pomares, Paul Crocker, Martin Stacey

Siamon Gordon Lab Reunion

David R. Greaves

On 21st September 2005 hundreds of immunologists converged on the Medical Sciences Teaching Centre in Oxford for the Society of Leukocyte Biology (SLB) meeting on Phagocytes and Innate Immunity. This meeting was preceded by a symposium to celebrate the contribution that Siamon Gordon has made to the study of innate immunity during his time at the Dunn School. The speakers and session chairmen were chosen to represent many of the key areas of research undertaken in Siamon's lab at the Dunn School from the late 1970s to the present day and included several current members of the Gordon laboratory.

Jonathan Austyn opened the meeting with recollections of the earliest days of the Gordon lab and the production and characterization of the first antibodies that specifically recognized tissue-resident macrophages that included the F4/80 monoclonal antibody. The cell surface receptor recognised by F4/80, Emr1, turned out to be a novel TM7 protein that is the first member of a family of related cell surface receptors that play important roles in leukocyte adhesion and regulation. Martin Stacey reviewed the history of the expanding gene EGF-TM7 family and talked about the continuing search for potential ligands for these receptors and reviewed recent findings from the Emr1 knockout mouse which suggests a role for F4/80 in peripheral tolerance in the eye and gut (Linn HH et al. *J Exp Med.* 2005; 201:1615-25).

Luisa Martinez-Pomares, who has recently taken up a lectureship at Nottingham University), presented an overview of the biology of another important macrophage cell surface receptor, the macrophage mannose receptor, which has been extensively studied in the Dunn School. The detailed analysis of the different ligands recognized by different domains of the mannose receptor continues to reveal new functions for macrophages in tissue homeostasis and immune function (Taylor et al. *Trends Immunol.* 2005; 26:104-110).

Annette Pluddemann, a current member of the Gordon Lab, reviewed the long history of research into macrophage scavenger receptors undertaken in the Dunn School before talking about her own recent research on the role of the SR-A receptor in the recognition of *Neisseria meningitidis* proteins. The SR-A cell surface receptor was originally identified through its role in uptake of modified LDL uptake and macrophage adhesion (Greaves & Gordon *J Lipid Res.* 2005; 46:11-20) and recent work in Siamon's laboratory continues to identify yet more physiologically relevant ligands for this most promiscuous of macrophage cell surface receptors.

Recent research in Siamon's laboratory has led to the discovery of an important new family of cell surface proteins that recognize conserved features of pathogens.

Speaking in the SLB main meeting Paul Crocker (University of Dundee) talked about his research on Siglec cell surface receptors, which are expressed by many cells of the innate immune system (reviewed in *Curr Opin Pharmacol.* 2005; 5:431-7). The prototypic member of this immunoglobulin super family of receptors, Sialoadhesin, was first characterized in Oxford when Paul Crocker and Stuart Muklow were working in Siamon's lab in

the Dunn School.

Recent research in Siamon's laboratory has led to the discovery of an important new family of cell surface proteins that recognize conserved features of pathogens. The prototypic member of this family is Dectin-1, the gene for which was cloned and characterized by Gordon Brown (*Nature*. 2001; 413:36-7). Phil Taylor talked about the wide range of pathogens recognized by Dectin-1 and presented recent data on how pathogen recognition by Dectin-1 leads to macrophage activation.

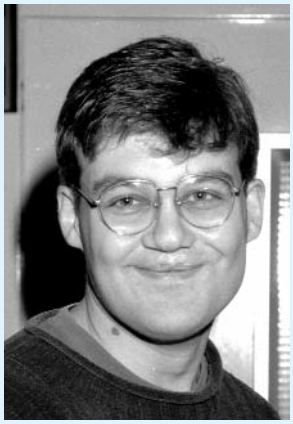
In addition to taking forward the cell biology of macrophages and their receptors other former members of the Gordon Lab have used molecular biology approaches to illuminate important aspects of macrophage biology. David Vaux (Oxford) presented new approaches to studying macrophage receptors using phage display and David Hume (University of Queensland, Brisbane, Australia) talked about his long-standing interest in the regulation of macrophage gene expression (*Curr Opin Immunol*. 2006; 18: 49-53). The main meeting also saw the return of a Gordon Lab sabbatical visitor, Prof. Christopher Glass (UC San Diego), who has made important contributions to our understanding of macrophage biology and transcriptional regulatory mechanisms. Another distinguished sabbatical visitor to the Gordon lab, Dr Thomas Schall CEO of ChemoCentryx Inc. (Mountain View, California) talked about chemokine receptors as a new therapeutic target in inflammatory disease and provided generous sponsorship for the meeting.

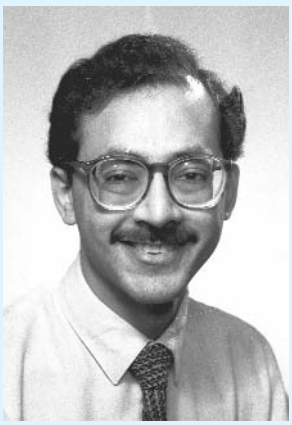
Many of the Gordon Lab alumni and alumnae have gone on to combine careers in clinical medicine with basic biomedical research.

Many of the Gordon Lab alumni and alumnae have gone on to combine careers in clinical medicine with basic biomedical research.

Clinician scientists were well represented at the meeting and included Alan Ezekowitz (Chief of Pediatrics at Mass. General Hospital) who continues to study macrophage phagocytosis (e.g. Kocks C et al. *Cell*. 2005; 123:335-46) and Lynn Morris (Head, AIDS Research Unit, National Institute for Communicable Diseases, Johannesburg, South Africa) who spoke about her important work on HIV/AIDS in South Africa. Wim de Villiers (Kentucky Medical Center, Lexington, KY) spoke about his continuing interest in macrophage scavenger receptors, while Satish Keshav (Consultant Gastroenterologist, Royal Free Hospital, London) talked about his work on inflammatory mechanisms in inflammatory bowel disease and Derralyn Hughes (University College Hospital, London) talked about the role of macrophages in lysosomal storage disorders, exemplified by her work on patients with Gaucher's Disease.

The Gordon Lab Reunion Symposium and the Society of Leukocyte Biology meeting served to remind us of Siamon's many important contributions to the study of innate immunity, not least of which is the international network of scientists and clinicians who continue to study the cells and molecules they first encountered under Siamon's tutelage here in





Phil Taylor, David Hume, Willem De Villiers, Satish Keshav

Hugh Rosen, Lynn Morris, Matthew Collin, Luis Montaner

the Dunn School.

Where are they now?

Name: Hugh Rosen D. Phil. Student and JRF 1984–1990
Current position: Professor of Immunology and Chair, Committee for Advanced Therapeutics, The Scripps Research Institute, San Diego
One thing you learned from Siamon: Integrative thinking. Siamon tried to teach me patience and perseverance but he did not quite succeed!

Name: Lynn Morris D. Phil Student and postdoc 1984–1989)
Current position: Head, AIDS Research Unit, National Institute for Communicable Diseases, Johannesburg, South Africa.
One thing you learned from Siamon: Always look at your cells....

Name: Matthew Collin (D. Phil student 1988–1992
Current position: Clinician scientist, haematology, Newcastle
One thing you learned from Siamon: Enthusiasm and generosity carry the day

Name: Peter Gough (D. Phil. Student 1994–99)
Current position: Investigator, GlaxoSmithKline, Philadelphia, USA
One thing you learned from Siamon: Treat your data like a new piece in a very big jigsaw – by constantly trying to fit the pieces together you'll end up making unexpected joins and have a very interesting new picture.

Name: Willem J.S. (Wim) de Villiers (D. Phil student 1992–95)
Current position: Professor and Chief, Division of Digestive Diseases and Nutrition, University of Kentucky Medical Center, Lexington, KY
One thing you learned from Siamon: Persistence and optimism. Bad experiments often have as much, if not more, educational value as good ones – if you don't try, you're sure to fail.

Name: Luis J. Montaner (D. Phil. Student 1991–95)
Current position: Director, HIV-1 Immunopathogenesis Laboratory Associate Professor, Immunology Program
One thing you learned from Siamon: Look at the big picture before judging on an incremental step.

Name: Luisa Martinez-Pomares (Postdoc 1994–2005)
Current position: Lecturer in Immunology/Microbiology, University of Nottingham
One thing you learned from Siamon: Be generous and trusting.

Name: Alan Ezekowitz (D. Phil. Student 1980–1984)
Current position: Charles Wilder Professor of Pediatrics, Harvard Medical School
Chief of Pediatrics Partners Healthcare System
Mass General Hospital for Children
Head of Laboratory of Developmental Immunology
One thing you learned from Siamon: How to write a paper

Name: Satish Keshav (D.Phil. Student and postdoc 1987–1996)
Current position: Senior Lecturer and Consultant Physician, Royal Free and University College Medical School, London
One thing I learned from Siamon: Cell biology is about cells, and the golden rule is "look before you lyse".

Name: David Vaux (D.Phil. Student and postdoc 1978–81)
Current position: Lecturer in Experimental Pathology, University of Oxford
One thing I learned from Siamon: "Stay broad, follow your intellectual curiosity and appreciate the beauty of your cells"

Research profile – David R. Greaves

David Greaves is Reader in Molecular Pathology, and combines his research into inflammation with undergraduate teaching on the BM course. He talked to Fusion about his scientific career.

I arrived at the Dunn School of Pathology in November 1993 having read Microbiology at Bristol University, studied for my PhD in Biophysics at King's College London and undertaken postdoctoral research at the Netherlands Cancer Institute in Amsterdam and the MRC labs in Mill Hill.

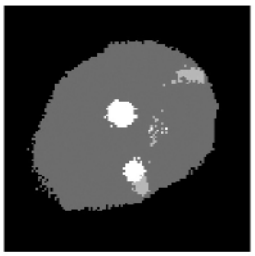
I had the good fortune to join the group of Siamon Gordon where I began to develop a deep appreciation for the biology of mononuclear phagocytes, a group of cells that includes monocytes and macrophages. Macrophages are found in virtually all tissues of the body where they are important for tissue homeostasis but they also play a central role in diseases characterised by chronic inflammation such as tuberculosis, rheumatoid arthritis and coronary artery disease.

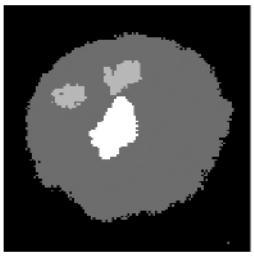
In the summer of 1995 I shared a bench with a sabbatical visitor from California, Tom Schall, who had just cloned the first cellular receptor for a family of potent monocyte chemoattractant proteins called CC chemokines. We now know that chemokines direct the recruitment of different leukocyte subsets into sites of infection and inflammation and they represent an important target for the development of a new generation of anti-inflammatory drugs.

My own contribution to the field of inflammation biology has been to show that chemokines are important for recruiting monocyte/macrophages into atherosclerotic lesions found in human coronary artery disease. In work funded by the British Heart Foundation we have shown that broad spectrum blockade of CC chemokine activity dramatically reduces macrophage recruitment into developing atherosclerotic lesions in arteries and vein grafts (Bursill et al. 2004 Circulation 110: 2460-6 and Ali et al. 2005 Circulation 112: I 235-41). We want to continue this work by engineering therapeutic chemokine binding proteins that could find application in the next generation of drug eluting stents used in coronary artery angioplasty.

Funded by a programme grant from the British Heart Foundation we are continuing our studies into the role inflammation plays in atherosclerosis. We are searching for new mediators of macrophage recruitment and activation that might represent new targets for the treatment of angina and myocardial infarction (heart attacks). We are using gene arrays to study macrophage activation in response to modified LDL and cytokines we know are expressed in arterial disease. We have identified two relatively new players in vascular inflammation, a C-type lectin expressed by macrophages in unstable atherosclerotic plaques in human arteries and an unusual chemokine called fractalkine/CX3CL1. In addition to studying the mediators that initiate and sustain inflammation in the artery wall I am very interested in studying endogenous mediators that are important in the resolution of chronic inflammation in vivo as this may give new insights into diseases characterised by continued monocyte recruitment and macrophage differentiation.

The Dunn School provides an excellent environment in which to pursue this research programme and we benefit enormously from many interactions with the wider cardiovascular research community in Oxford. Following a national competition Oxford University was awarded one of three BHF 4 year studentship schemes and as Academic Director of this programme I will oversee the graduate training programme for a cohort of up to 12 students over the next four years. I also contribute to undergraduate teaching through organising the BM General Pathology and Microbiology course and tutoring medical students at Hertford College. In addition to research, mentoring and teaching I also enjoy cooking, reading and cycling.





Research notes and findings

David Vaux is Lecturer in Experimental Pathology at the Dunn School and Lincoln College. His research is in the field of molecular cell biology. Here, he discusses a new project that has been generously funded by Tim and Kit Kemp through Lincoln College.

The development of particular cell types depends on expressing the correct pattern of genes at the right time. When this goes awry normal tissue function is lost and abnormal growth in the form of cancer may result.

Gene expression patterns depend on local DNA factors, diffusible DNA-binding factors and, for simple organisms anyway, the position of a gene within the nucleus. In recent work funded by a research grant from Tim and Kit Kemp, Dr Ashraf Malpas in my group has shown that similar position effects occur in mammalian cells. Working with a range of genetically engineered cells we first showed that defects in the nuclear lamina protein, lamin B1, result in an unstable nuclear periphery. In collaboration with Dr Nigel Saunders of the Microarray Facility in the department, Dr Malhas then showed that these cells have altered patterns of gene expression, including groups of over-expressed genes. Strikingly, one of these groups clustered on a chromosome that is normally tightly attached to the nuclear lamina (label at the edge of the normal nucleus in the top picture). This suggested that the altered gene expression might have been caused by detachment of the chromosome from the lamina, a prediction that was beautifully confirmed by imaging this chromosome in the mutant cells (bottom picture).

These results have implications for understanding both normal and abnormal control of gene expression and may offer important clues to understanding aging.

Dunn School joins European drive for new cancer therapies

Dr Gordon MacPherson's group is part of a European-wide network to explore the potential of dentritic cell therapy to cure cancer, in a consortium headed by Dunn School alumnus Professor Jon Austyn, now at the Nuffield Department of Surgery in Oxford.

Dendritic cells are specialised cells of the immune system that trigger and control many types of immune response. There is considerable interest in using them to treat cancer, HIV and many other diseases, and human trials in advanced cancer patients have already yielded promising results.

The DC-THERA is a €7.6m initiative established under the European Commission Sixth Framework Programme. Over the next five years, the 32 European research groups involved will collaborate in order to translate laboratory findings into clinical trials. In Dr MacPherson's group, the initiative will support work on understanding the roles of dendritic cells in the regulation of intestinal immune responses, with a view both to understanding intestinal diseases such as Crohn's disease and ulcerative coloitis, and improving the efficacy of vaccines against intestinal infections.

One main purpose of the network is to co-ordinate existing work – standardising disparate trials so that the data can be studied as a whole, and eliminating duplication. The other is to educate the next generation of European experts in the field.

'It's too early to say whether this could prove a treatment not just for cancer but also for a whole host of other widespread diseases, but the obvious potential is very, very exciting,' said Professor Austyn. 'If we get this right, the potential is enormous.'

Development News

As regular readers of *Fusion* will know, the Dunn School's development programme has been concentrating on supporting the department through the endowment of new posts, in particular a Chair of Molecular Cancer Biology, named in honour of César Milstein, and a fund to honour Norman Heatley. It is heartening to report that we are making good progress towards achieving both of these positions, of which more below. I would like to thank all those who have offered support for these, or more general Departmental needs.

The Norman Heatley Fund

Norman Heatley (1911–2004) was a pivotal member of the team which isolated and purified penicillin, and a sociable and much-loved member of the Department for most of his working life.

This fund for research in the basic biological sciences, which we are seeking to fully endow, got off to a good start when the Merck & Co. Foundation agreed to donate $500,000 towards its establishment. Merck & Co. played a pivotal role in the commercial development of penicillin in the 1940s, and indeed Heatley worked with scientists at the company's research headquarters in Rahway, New Jersey. It was a small sample of penicillin from there that was used to treat Mrs Anne Miller, the first patient in the USA successfully treated for streptococcus infection using penicillin. The fund has also benefited from many other donations from friends of Norman, and former colleagues. To complete this fund, the Department seeks a minimum of £130,000 – any help that former members can give, either directly or with suggestions for potential donors – would be greatly appreciated.

César Milstein Chair in Molecular Cancer Biology

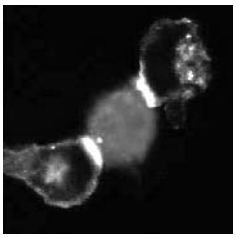
Named in honour of the co-inventor of monoclonal antibody technology, the Milstein Chair will ensure that the Dunn School is able to recruit a leading scientist in the field of molecular cancer biology, which will both complement work by other research groups in the Department and contribute to further therapeutic breakthroughs. Fundraising for this Chair has been coordinated by an Appeal Committee, of which Milstein's widow Celia is honorary President. Ably chaired by Dr Claudio Cuello (McGill), the Committee has raised over £2m of the £2.7m required to endow a Chair at Oxford. Generous donations have been received from the EPA Research Fund, the EPA Cephalosporin Fund, GSK Research, Genzyme, and many individuals who worked with Cesar over the years. One of the unexpected outcomes of the Appeal has been a renewed link with Argentina, through a post-doctoral fellowship linked to the Chair, to be funded by CONICET (the Argentine medical research agency) and an MRC-sponsored Fellowship for an Argentine scientist in the UK.

If you would like to know more about either of these initiatives, please contact Professor Waldmann – herman.waldmann@path.ox.ac.uk

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 on this page, 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.



An infected cell is examined by two T-cells simultaneously. The bright areas of the cell interfaces are areas where the T-cell receptors are gathering.

Size matters, to the immune system at least

A theory about the way in which the immune system identifies and responds to invasion has been confirmed in a Nature paper published last year (*Nature*, 436, 578-582). Dr Kaushik Chaudhury, Mr David Wiseman, Dr Marion Brown, Professor Anton van der Merwe, all from the Dunn School, and Dr Keith Gould from Imperial College London, show that a highly sensitive and specific immune response hinges on something as straightforward as large and small molecules jostling into size order.

Researchers have long wondered how exactly T-cell binding triggers an immune response. T-cells are kept in check by a constant battle at their surface between the small molecules that trigger the immune response and large, long molecules such as CD45s which prevent the immune response from being switched on. The spoilsport CD45 plays a crucial role: the immune system can attack as well as protect the body, and allergies and serious autoimmune illnesses are the results of the immune system being activated inappropriately. How, though, do T-cells overcome the inhibitory effect of CD45s when they *do* need to launch an attack on invaders?

The answer is now shown to be the kinetic segregation model, conceived at Oxford 10 years ago by Professors Anton van der Merwe and Simon Davies, and confirmed in the study published by Nature. The model proposes that, because both T-cell receptors and the telltale peptide MHCs are relatively small molecules, they can only come into contact and bind when the bulkier CD45s are out of the way – in which case the immune response can be activated without impediment.

The work was funded primarily by the Medical Research Council, while Dr Choudhuri was supported by the Wellcome Trust.
Mr Wiseman said: 'What we have shown is a whole new way that cells can control themselves. These are the earliest events in T-cell triggering, the key activation step in immune surveillance, and all it comes down to is whopping great molecules being shut out of close contacts zones, simply by virtue of their whopping greatness.'

NEW Faces

Alan Ezekowitz

It was a great pleasure to welcome Alan back to the Dunn School as the Newton-Abraham Visiting Professor in Medical, Biological and Chemical Sciences for 2005–6.

Alan was a DPhil student in Saimon Gordon's lab in the early 1980s (the photograph is from that time!). He made a big impact not only in the lab but also on the cricket field where he was a regular member of the University team and won a blue against Cambridge. Recently, Alan's laboratory research has focused on the role of innate immunity in host defense, using Drosophila as an experimental system and combining classical forward genetics with the characterization of cell lines to study phagocytosis. Using primary cells and cell lines, he has demonstrated that that this process in flies has marked similarities to the process that occurs in man and mice. After several years as Charles Wilder Professor of Pediatrics at the Massachusetts General Hospital, Alan has taken up a new senior post determining scientific policy at Merck.

Professor Oreste Acuto

He took up his post at the Dunn School on 1st March 2006. He is working in the laboratories recently converted from the old Lecture Theatre.

Oreste was previously Head of the Molecular Immunology Unit at the Institut Pasteur in Paris.

After obtaining a doctorate in Immunogenetics in Rome, he did post-doctoral work in the Biochemistry Department of the ETH in Zurich and in the Genetics Unit at the ISREC in Lausanne and then moved as an Assistant Professor to the Dana Farber Cancer Institute at Harvard Medical School in Boston. His involvement with the Dunn School goes back more than 20 years, when at Harvard University, he started to work on the T-cell antigen receptor at the same time as Alan Williams.

His current work revolves around the search for novel avenues in T cell signalling, the mechanisms by which the adaptive immune response is activated and regulated.

He writes:
We study the molecular mechanisms of T cell activation. The molecular information carried by antigen presenting cells and by cytokines is relayed to the T cell through a complex network of membrane receptors and intracellular signalling components able to decode positive (activator) and negative (regulatory and tolerising) signals. The outcome of these processes determines whether T cells become immediate effectors of the immune response or memory cells, or are tolerised. Our research is focused on understanding the role and regulation of key components on the signaling machinery. Moreover, we search for new signaling pathways by the use of mass spectrometry applied to intracellular protein complexes. Currently we are exploring new findings pointing at negative regulatory signals emanating from the earliest stages of T cell activation and at previously unexplored signalling pathways directing arginine methylation in T cells.

Oreste has a wife, who is also a research scientist, and a 14 year old daughter. They both will join him in Oxford later in the year.

Dr Susan Lea

She has recently been appointed to a Lectureship in Chemical Pathology. She recently moved into the laboratories vacated by Jeff Errington's group. Susan has been working in the Department of Biochemistry for 16 years and already has collaborations with several Dunn School laboratories, including those of Saimon Gordon, William James and Ariel Blocker.

The research of her group covers:
- Structural biology to aid understanding of host-pathogen interactions
- Innate immunity, especially the Complement system
- Pathogen evasion of host immunity, particularly serum dwelling spirochaetes

Susan writes:
An understanding of the way in which an invading pathogen interacts with its host at a molecular level is an essential aid to understanding the nature and extent of disease caused. My group aims to use a variety of techniques to probe the interactions that characterise different disease processes. Central to this approach is the use of X-ray crystallography to determine the structures of individual host or pathogen components with a view in the longer term to examining the atomic structure of important host-pathogen complexes. The major targets are protein based but we are also involved in projects where folded RNAs provide the structural target. To aid understanding of biochemical and structural data we use a variety of other biophysical techniques (including surface plasmon resonance) to further characterise the biological systems under study.