Front cover illustration:
Part of the structure of thyroxine-binding globulin showing the binding site for thyroxine (green), a hormone that controls cellular development as well as the rate of body metabolism. Verification of the binding site was achieved using the program Phaser developed in CIMR. (See also page 26, Randy Read).
The Wellcome Trust/MRC Building which houses the Cambridge Institute for Medical Research and the MRC Dunn Human Nutrition Unit.
The late summer of 2008 will mark the tenth anniversary of the first research groups moving into the Cambridge Institute for Medical Research (CIMR). Throughout the ten years we have tried to develop and maintain an institute that provides a unique interface between basic and clinical science and has as its major goal, the determination and understanding of the molecular mechanisms of disease. Over 40% of our Principal Investigators (PIs) are medically qualified and clinically active, a percentage that has remained constant since CIMR opened. CIMR is a cross-departmental institute, within the University of Cambridge Clinical School, but the departments represented have altered somewhat over the years. The Departments of Medicine, Medical Genetics, Clinical Biochemistry, Haematology and Pathology have always had a presence, but in recent years members of the Departments of Surgery and Clinical Neurosciences have joined the Institute. With the establishment and opening of the CRUK Cambridge Research Institute headed by Sir Bruce Ponder (a former CIMR PI), all remaining members of the Department of Oncology have now left our building. Similarly, PIs in the field of metabolic medicine from the Departments of Medicine and Clinical Biochemistry have moved out into the new Institute of Metabolic Science headed by Stephen O’Rahilly, who previously led a group in CIMR in addition to his group housed in the Department of Clinical Biochemistry. During 2008 we also expect Roger Pedersen to move into refurbished laboratories for stem cell medicine on the Forvie site. We hope to maintain close links with former PIs in Cambridge through such mechanisms as establishing some as affiliated PIs (who now include Stephen O’Rahilly, Sadaf Farooqi and Jennie Blackwell) and co-opting others as external members of our Management Committee.

Despite all the moves out, both within Cambridge and to other locations, we have continued to strengthen our scientific community. Amongst new PIs that we have recently welcomed are three Wellcome Trust Principal Research Fellows (PRFs): Gillian Griffiths from Oxford, Peter St George-Hyslop from Toronto and Chris Rudd who has brought part of his group from the Department of Pathology and will in the future operate at both locations. Added to our existing cohort of PRFs (David Clayton, Randy Read, Margaret Robinson and Linda Wicker), this now takes CIMR’s total to seven, 19% of the national total and certainly the most at any single location. Amongst our PIs we also have six Wellcome Trust or MRC Senior Clinical Research Fellows and four non-clinical Wellcome Trust or MRC Senior Research Fellows.

A very important milestone was reached in the recent period when CIMR was given a five year Strategic Award by the Wellcome Trust to support our core scientific facilities, to provide PhD studentships and allow us funds to attract young clinicians back into research. In our application to the Wellcome Trust we pointed out that within CIMR there are major ongoing strengths in medical genetics, immunology, structural biology applied to medicine, molecular cell biology and developmental/stem cell biology, which are brought to bear on a number of diseases. There are also major research themes that transcend individual research groups, namely misfolded proteins and disease, intracellular membrane traffic, autoimmune disease and haematopoietic stem cell biology. Within these themes the Institute’s present scientific goals include: (i) determination of the molecular mechanisms of intracellular protein aggregate formation and breakdown in health and disease, including the identification of novel therapeutic targets for protein conformational
diseases; (ii) identifying and characterising the molecular machinery of intracellular membrane traffic and determining how traffic pathways are coordinated, regulated and modified in health and disease; (iii) the identification of genes, proteins and pathways increasing susceptibility to, or protection from, autoimmune diseases; (iv) determining the transcriptional regulation of haematopoietic stem cells. A major objective for CIMR over the next five years is to understand protein localisation, function and metabolism in a range of diseases in which genetic studies have identified the causative genes. We argued to the Wellcome Trust that underpinning our core facilities is essential to achieve this objective and will provide added value to the considerable investment that the Wellcome Trust is already making to our scientific activities (currently about 60% of annual grant spend). In giving us a Strategic Award we believe that the Wellcome Trust has helped to ensure that CIMR is a flagship in the UK for interdisciplinary research at the interface between clinical and basic research.

There are many people whom I want to thank for their support of CIMR. These include the members of the International Scientific Advisory Board, chaired by Professor Nick Hastie, who always give us valuable advice and suggestions at their biennial visits and the Institute’s Strategy Committee, made up of Heads of Departments with staff in CIMR, chaired by the Regius Professor, Patrick Sissons. We remain very grateful to Professor Sir John Walker, the Director of the MRC Dunn Human Nutrition Unit housed in the Wellcome Trust/MRC Building, for access to the Dunn’s excellent proteomic facilities. In the foreword to the last Research Report in 2006 I thanked Sir Keith Peters and Martin Bobrow for their great contribution to the establishment of CIMR. This time I want to thank Jennie Blackwell. Jennie has recently left Cambridge to take up a Chair in Genetics and Health at the University of Western Australia in Perth. She was the first Director of CIMR, but her contribution to establishing our Institute started much earlier. Jennie came to Cambridge in 1991 as the Glaxo Professor of Molecular Parasitology first being based in the Department of Pathology and later the Department of Medicine. Almost immediately, Keith Peters identified Jennie as the person to articulate the rationale and objectives for the new Institute in an application to the Wellcome Trust. Jennie later described that period in her introduction to our first Research Report in 2000 where she wrote “Dreams of a modern research facility in Cambridge, where clinical and basic science could converge in the study of molecular mechanisms of disease, turned to reality in 1993 with a major capital award from the Wellcome Trust to the School of Clinical Medicine. At the same time the Medical Research Council was looking to re-house its Dunn Nutrition Unit in Cambridge. A joint project was conceived and, two years of planning and two years of building later, the new Wellcome Trust/MRC Building emerged on the Addenbrooke’s Hospital Site”. Jennie was the University’s main representative on the building project team for four years, led many applications for equipment grants and was one of a small group of senior scientists who selected our initial PIs. She established the management structure and appointed our first management and technical support teams. When we finally got into the building it was Jennie as our first Director who established a CIMR style and ethos underlying the way that the Institute functions. All of us at CIMR wish Jennie success in her new venture in Australia and we are very pleased that we will still see her from time to time because she will maintain some research activity here and is now an affiliated PI in CIMR as well as an Honorary Senior Visiting Fellow to the Department of Medicine.

Paul Luzio
January 2008
## CIMR Principal Investigators

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Investigator Status</th>
<th>Home Department</th>
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<tbody>
<tr>
<td>Folma Buss</td>
<td>Wellcome Trust Senior Research Fellow in Basic Biomedical Science</td>
<td>Clinical Biochemistry</td>
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<tr>
<td>David Clayton</td>
<td>JDRF/Wellcome Trust Principal Research Fellow and Personal Chair</td>
<td>Medical Genetics</td>
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<tr>
<td>Bertie Göttgens</td>
<td>University Reader</td>
<td>Haematology</td>
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<tr>
<td>Allison Green</td>
<td>Wellcome Trust Senior Research Fellow in Basic Biomedical Science</td>
<td>Pathology</td>
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<td>Tony Green</td>
<td>University Chair</td>
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<tr>
<td>Fiona Gribble</td>
<td>Wellcome Trust Senior Research Fellow in Clinical Sciences</td>
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<tr>
<td>Gillian Griffiths</td>
<td>Wellcome Trust Principal Research Fellow and Personal Chair</td>
<td>Medicine</td>
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<td>James Huntington</td>
<td>MRC Senior Research Fellow and University Reader</td>
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<td>Brian Huntly</td>
<td>MRC Senior Clinical Research Fellow</td>
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<td>Fiona Karet</td>
<td>Wellcome Trust Senior Research Fellow in Clinical Sciences and Personal Chair</td>
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<tr>
<td>Paul Lehner</td>
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<td>David Lomas</td>
<td>University Chair and Deputy Director CIMR</td>
<td>Medicine</td>
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<tr>
<td>Paul Luzio</td>
<td>Personal Chair and Director CIMR</td>
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<td>Katrin Ottersbach</td>
<td>Kay Kendall Leukaemia Fund Intermediate Fellow</td>
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<td>David Owen</td>
<td>Wellcome Trust Senior Research Fellow in Basic Biomedical Science and University Reader</td>
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<td>Andrew Peden</td>
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<td>Roger Pedersen</td>
<td>University Chair</td>
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<td>Lucy Raymond</td>
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<td>Randy Read</td>
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<td>Evan Reid</td>
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<td>Margaret Robinson</td>
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<td>David Rubinsztein</td>
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<td>Christopher Rudd</td>
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<td>Richard Sandford</td>
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<td>Matthew Seaman</td>
<td>Senior Research Associate (formerly MRC Senior Research Fellow)</td>
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<td>Symeon Siniossoglou</td>
<td>Senior Research Associate (formerly Wellcome Trust Career Development Fellow)</td>
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<td>Ken Smith</td>
<td>University Chair</td>
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<td>John Todd</td>
<td>University Chair and Director DIL</td>
<td>Medical Genetics</td>
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<td>John Trowsdale</td>
<td>University Chair</td>
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<tr>
<td>Linda Wicker</td>
<td>JDRF/Wellcome Trust Principal Research Fellow, Personal Chair and Deputy Director DIL</td>
<td>Medical Genetics</td>
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<tr>
<td>Geoff Woods</td>
<td>University Reader</td>
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<tr>
<td>John Yates</td>
<td>University Chair</td>
<td>Medical Genetics</td>
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Current Membership of the CIMR Strategy Committee:

Patrick Sissons (Chairman, Regius Professor of Physic), Andrew Bradley (Surgery), Alastair Compston (Clinical Neurosciences), Tim Cox (Medicine), John Danesh (IPH, Faculty Board), Tony Green (Haematology), David Lomas (Deputy Director, CIMR), Paul Luzio (Director, CIMR), Stephen O’Rahilly (Clinical Biochemistry), Bruce Ponder (CRUK CRI, Faculty Board), John Todd (Diabetes and Inflammation Laboratory), Andrew Wyllie (Pathology), John Yates (Medical Genetics)

Current Membership of the International Scientific Advisory Board:

Nick Hastie, Chairman (University of Edinburgh), Dennis Ausiello (Harvard University), John Dick (University of Toronto), Chris Haslett (University of Edinburgh), Louise Johnson (University of Oxford), Carl Nathan (Cornell University), Graham Warren (Max Perutz Laboratories, Austria)

Screening apparatus funded through a Wellcome Trust equipment grant
We are studying the role(s) of myosin motor proteins in intracellular transport of organelles and vesicles, and in cell migration and cytokinesis. In humans at least 40 different myosins operate to control and drive these complex range of motile and transport processes. Each myosin is composed of a motor domain that uses the energy released from ATP hydrolysis to drive along actin filament tracks around the cell and a tail domain that binds cargo and targets it to specific cellular locations. We have focused on myosin VI, which unlike all the other myosins so far characterised moves in the reverse direction along actin filaments and therefore has unique molecular properties and intracellular functions. We have localized myosin VI in membrane ruffles, at the Golgi complex, in clathrin coated pits and vesicles, at the centrosome and in the mid-body during cytokinesis and have shown that it is involved in a wide variety of intracellular processes such as endocytosis, secretion, maintenance of Golgi morphology, cell movement and cell division. The multiple roles of myosin VI in these membrane transport pathways are mediated by interaction of its specific C-terminal tail domain with a host of distinct binding partners which are currently one of our main areas of research. Mutations or the absence of myosin VI have been linked to such diverse pathological processes as deafness, cardiomyopathy, neurodegeneration and cancer. Our long term aim is therefore to establish the precise intracellular functions of myosin VI so as to allow us to develop therapeutic strategies to combat or alleviate these pathological disorders.

Myosin VI is recruited to cleavage furrow in early (A) and late (B) cytokinesis. (C) Cartoon illustrating the possible function of myosin VI in transporting vesicles into the cleavage furrow for the final abscission process.
Our aim is to develop and apply statistical methods in genetic epidemiology and, to a lesser extent, in other aspects of biostatistics. The main focus of this work is provided by the Diabetes and Inflammation Laboratory (DIL), although I have long-standing interests in studies into the genetic epidemiology of other complex diseases, including hypertension, and senile macular degeneration. Implementation and dissemination of analytical methods as an important part of our work.

A major commitment over the last two years has been the Wellcome Trust Case-Control Consortium (WTCCC). This is a genome-wide association (GWA) study in which 2,000 cases of each of 7 different diseases will be compared with two shared control groups, together comprising 3,000 subjects. Each subject was typed for ~500,000 SNPs. I co-chaired the analysis group and we have developed analysis software, which we have made freely available on the Internet. My group has also made a major contribution to the management of the huge quantities of data generated by this study. The main results of the study were published in early 2007.

The WTCCC has been remarkably successful in identifying new disease susceptibility loci, particularly for type 1 diabetes, and has generated much follow-on work. Fine mapping of causal variants remains a considerable challenge and refinement of methods for the design and analysis of fine mapping studies remains a high priority for my group. In addition the Type 1 Diabetes Consortium has funded a further genome-wide association study of 4,000 new cases and 2,500 new controls (all drawn from the existing DIL collections) and my group will be responsible for the analysis of the new data and for a combined analysis of the new data in conjunction with the existing WTCCC T1D data (2,000 cases and 3,000 controls). I also hope to provide advice and software for several proposed GWA association studies.
Transcriptional Control of Normal and Leukaemic Blood Stem / Progenitor Cells

Haemopoiesis has served as a model process for studying stem cell biology, and a close developmental link between the formation of embryonic blood and endothelial cells has long been recognised. However, the transcriptional networks that determine these early cell fate decisions are still poorly understood. The Göttgens laboratory is part of a consortium of Cambridge groups, largely in the CIMR, focusing on complementary aspects of normal and leukaemic stem cell biology. The specific focus of the Göttgens group is the combination of computational approaches with mouse experimental model systems for the analysis of transcriptional networks during the formation of embryonic blood and endothelial cells.

Recent work has employed both top-down and bottom-up approaches to identify and characterise key regulatory elements of blood stem cell transcriptional networks. A new suite of bioinformatics tools has been developed for genome-wide top-down computational identification of gene regulatory elements with predicted in vivo activity. In parallel, transgenic and molecular studies are performed to dissect the transcriptional regulation of LMO2, Ly1, SCL and endoglin, four key regulators of early blood development. The latter bottom-up studies continue to inform the design of bioinformatic search strategies to allow refinement of top-down computational approaches.

Identification of transcriptional hierarchies in normal cells will illuminate the molecular hierarchy of transcriptional programmes responsible for blood stem cell development. The importance of transcriptional control in both normal and leukaemic cells is underlined by the large number of transcription factor genes that are disrupted as part of the pathogenesis of haematological malignancies. Future work will address how transcriptional programmes are perturbed in specific subtypes of leukaemia and may thus open up new avenues for the development of targeted therapies.

Further details can be found at http://hscl.cimr.cam.ac.uk

A nascent HSC transcriptional network composed of 14 genes and 35 connections all of which have been verified by chromatin-immunoprecipitation and transgenic assays.
Deciphering Immunological Mechanisms to Control, or Promote, Autoimmune Diseases

The goal of our laboratory is to understand the mechanisms by which inflammation promotes autoimmune disease, particularly type 1 diabetes. Using a series of murine models either transgenic or knockout for key cytokines/co-stimulatory molecules, we examine the impact such events have on the ability of the immune system to generate CD4+Foxp3+ Treg cells, or autoaggressive CD8+ T cells.

We have established that CD154-CD40 interaction is critical for the thymic development of CD4+Foxp3+ Treg cells. Deficiency in either molecule reduces CD4+Foxp3+ Treg numbers by 50%. Bone marrow chimeric mice showed that CD40 signals derived from thymic epithelial cells (mTECs) or thymic dendritic cells (tDCs) promiscuously promote CD4+Foxp3+ Treg cell development. Further, CD154 requirement is restricted to developing CD4+Foxp3+ Treg cell and signals to induce its differentiation/expansion. In contrast to developing CD4+Foxp3+ Treg cells, CD40-CD154 signals are redundant in homeostatic maintenance of mature CD4+Foxp3+ Treg cells. Defining the molecular requirement for CD40-CD154 in CD4+Foxp3+ Treg biology is ongoing.

We also investigate how the suppressor cytokine TGFβ impedes diabetes development. Using a unique transgenic model where islet specific expression of TGFβ can be controlled by an on/off switch, we have defined a phase in the disease where a short pulse of TGFβ significantly delays diabetes progression. The mechanisms by which TGFβ controls the autoimmune response is subject to continued investigation.

We have shown that, surprisingly, B cells are central for promoting acceleration to diabetes in the presence of an inflammatory response. Impacting on end stage disease, B cells promote CD8+ T cells differentiate to CTL and survival within the islets. The mechanisms by which B cells manipulate CD8+ T cell responses are under investigation. Finally, we are using a series of congenic mice to establish if key genes that control diabetes are linked to immunological changes in the function of the B or CD8+ T cell compartment.

Interaction of Foxp3+ regulatory T cells (green) with thymic epithelial cells (red) in the thymic medulla.
Haematopoietic Stem Cells and Haematological Malignancies

Haematopoiesis represents the best studied adult stem cell system and continues to provide important paradigms for the mechanisms whereby normal stem cells are subverted to form malignancies. This laboratory is pursuing two complementary aspects of haematopoietic stem cell (HSC) biology.

1. Human myeloproliferative disorders (MPDs). These myeloid malignancies result from transformation of an HSC and are associated with expansion of one or more haematopoietic lineages. Patients are at risk of developing thrombosis, myelofibrosis and acute myeloid leukaemia. We are studying the molecular pathogenesis and management of the MPDs. Recent highlights include (i) the demonstration that an acquired V617F mutation of JAK2 is present in virtually all patients with polycythaemia vera (PV) and approximately half those with essential thrombocythaemia (ET) and idiopathic myelofibrosis; (ii) the demonstration that V617F-positive ET represents a forme fruste of PV; (iii) publication of the MRC PT1 study, the largest randomised clinical trial of any MPD yet performed; (iv) the identification of JAK2 exon 12 mutations associated with a distinct variant of PV.

2. Transcriptional regulation of haematopoietic stem cells. The stem cell leukaemia (SCL) gene encodes a bHLH transcription factor and was originally identified by virtue of its disruption in T-cell acute leukaemia. Loss and gain of function studies have shown that SCL is a pivotal regulator of haematopoiesis and that appropriate transcriptional regulation is critical for its biological functions. We are undertaking a systematic analysis of the transcriptional regulation of the SCL locus using genomic, transgenic, knockout, cellular and biochemical approaches. Recent achievements include (i) molecular characterisation of two HSC enhancers; (ii) characterisation of a novel enhancer which targets primitive erythropoiesis; (iii) description of the molecular basis for the emergence of an HSC enhancer during vertebrate evolution.

Leukaemic transformation of polycythaemia vera. Somatic mutation of JAK2 is present in chronic phase polycythaemia vera (PV) but unexpectedly absent from leukaemic blasts in most patients following development of acute myeloid leukaemia (AML).
Stimulus-secretion Coupling Mechanisms in Intestinal Neuroendocrine Cells

Hormones from entero-endocrine cells in the gastrointestinal tract play a role in the control of diverse processes such as appetite and insulin secretion, as well as coordinating local gut physiology. Two major “incretin” hormones, GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic peptide), are responsible for triggering up to half of the insulin that is released following a meal, and have therapeutic potential for the treatment of type 2 diabetes. GLP-1 based therapies have recently reached the marketplace as anti-diabetic agents, and other entero-endocrine hormones are under therapeutic evaluation for a range of clinical disorders.

The primary interest of our research group is to understand the mechanisms underlying secretion of the incretin hormones, with a view to identifying novel targets and pathways in entero-endocrine cells that could be exploited to modulate hormone release in vivo. We employ an approach based around the use electrophysiology and fluorescence imaging to study the events involved in stimulus detection and hormone secretion. Changes in plasma membrane potential, ionic currents, intracellular [Ca\textsuperscript{2+}] and GLP-1 release are monitored following application of a variety of nutrients, hormones and pharmacological agents. Populations of entero-endocrine cells can be identified and purified from transgenic mice exhibiting cell-specific expression of a fluorescent protein, opening the way to perform expression profiling and characterisation of primary entero-endocrine cells. Our hope is that understanding the stimulus-secretion coupling pathways in intestinal endocrine cells may pave the way for the development of alternative nutritional and pharmacological therapies for conditions such as type 2 diabetes, obesity and gastrointestinal disorders.

A second interest of our group is in understanding the electrophysiological mechanisms underlying pain perception in man. In collaboration with the group of Dr Geoff Woods, we have characterised the functional effects of mutations in a sodium channel gene that give rise to human conditions of altered pain perception. Work in this area has major implications for the future development of analgesic and anaesthetic agents.

GLP-1 secreting cells in intestinal tissue sections from transgenic mice are identifiable by their green fluorescence. Green: GFP; Red: glucagon; Blue: DAPI.
Cytotoxic T lymphocytes (CTL) and Natural Killer (NK) cells use polarized secretion to rapidly destroy virally infected and tumorigenic cells. Upon recognition of their targets, CTL and NK cells polarize their secretory apparatus towards the target, releasing the content of specialized secretory lysosomes into the immunological synapse formed between the two cells. We have shown that the mechanism of secretion used by CTL and NK cells is unusual, with the centrosome polarizing to a precise spot within the synapse, where signaling has taken place. Secretory lysosomes move along the microtubules towards the centrosome and are delivered to a specialized secretory domain as the centrosome contacts the plasma membrane.

We are now trying to understand the mechanisms that control polarized secretion from CTL and related immune cells. We are taking a number of approaches including the study of human genetic diseases, such as Hemophagocytic syndrome, in which CTL and NK cell function is disrupted. Using molecular, biochemical and morphological techniques we are able to ask where the secretory process is disrupted and identify the role of the proteins, which are disrupted in these genetic diseases, in secretion. We are also examining the roles of proteins which are known to be involved in cell polarity and asking whether these play a role in secretion from CTL and NK cells.

A CD8 (blue) cytotoxic T lymphocyte killing its target (right) with the centrosome (gamma tubulin, red) polarising to the point of T cell receptor signalling shown using an antibody to Ick (green).
Molecular Recognition in Haemostasis

Blood coagulation (haemostasis) is a complex process under tight regulatory control. Dysregulation leads to bleeding when the clotting response is insufficiently rapid and robust, and to thrombosis when coagulation is not limited. This ‘haemostatic balance’ is critical for human health, and understanding the regulatory mechanisms is crucial for the diagnosis, prevention and treatment of diseases such as haemophilia, deep vein thrombosis, pulmonary embolism, heart attack, and stroke. My lab studies the molecular events which maintain the haemostatic balance mainly by determining crystallographic structures of individual coagulation factors and of the multi-protein complexes they form. We have several projects running concurrently in the lab. The serpin project studies how the inhibitory activity of serpins is stimulated by heparin-like glycosaminoglycans. We have succeeded in defining the mode of action of therapeutic heparin by solving the structures of antithrombin and heparin cofactor II in recognition complexes with target haemostatic proteases, and have recently solved a similar structure of protein C inhibitor demonstrating how it carries out its procoagulant function. Another project in the lab focuses on determining the molecular basis of thrombin function. This has traditionally involved crystallographic studies of thrombin complexed to substrates, cofactors and inhibitors. We now have a productive NMR-based thrombin effort which promises to unveil the functional relevance of thrombin allostery and to map interactions with its molecular partners. The events which lead to thrombin formation are also studied. We are crystallising individual members of the haemostatic network of proteins and their complexes. In the long term, our efforts will define the principal molecular recognition events that govern haemostasis.

How antithrombin (AT, ribbon) is activated by heparin (ball-and-stick) to achieve rapid inhibition of target proteases (cyan) factor Xa and thrombin.


Molecular and Cellular Characterisation of Leukaemia Stem Cells

The aims of the Huntly group are to study mechanisms of leukaemogenesis and in particular to characterise leukaemia stem cells (LSC) at the molecular and cellular levels. Leukaemias and many other cancers have recently been demonstrated to be wholly dependent upon a small population of so-called cancer stem cells for their continued growth and propagation. These cells represent the most critical targets for treatment of leukaemia and a greater understanding of their biology and its interface with normal stem cell function is fundamental to improving treatment outcomes. The focus of the Huntly laboratory on this interface complements a local consortium of research groups (Profs Green and Warren and Drs Göttgens and Ottersbach) with interests in normal and leukaemic stem cells all based in the CIMR or on the Cambridge University Hospital campus. The Huntly group utilises functional assays and genomic techniques in complementary mouse models and human primary cells to study leukaemogenesis and LSC biology. We are particularly focusing on identifying novel and characterising known and novel self-renewal pathways downstream of leukaemia-associated fusion oncogenes such as MOZ-TIF2 and NUP98-HOXA9. In addition, we are aiming to identify genes which are required for LSC function but are dispensable for normal haematopoietic stem cell function. These genes would then be attractive candidates for therapeutic targeting of LSC. Another major interest of the group is the regulation of HOX genes in AML. We have recently described, along with collaborators, the association of the caudal-like CDX family members CDX4 and 2 with HOX gene regulation in AML and are further interrogating this association. Finally, we are characterising the LSC hierarchy and biology of the preleukaemic myeloproliferative disorders (MPD) using analysis of highly purified populations of stem and progenitor cells from MPD patients and a number of recently discovered mutations (such as the JAK2 V617F mutation) as clonal markers.

Leukaemia stem cells (LSC) as critical targets in disease eradication.

A) Current therapies do not eradicate LSC allowing disease relapse and resistance.

B) A greater knowledge of LSC biology will allow us to target this compartment and improve patient survival.
Molecular Physiology of Renal Tubular Homeostasis in Health and Disease

We aim to characterise molecular mechanisms governing human renal tubular homeostasis, with a major focus on acid-base balance and mechanisms underlying stone disease.

Acid-base regulation is the chief job of the α-intercalated cells (α-IC) in the distal nephron. Intact α-intercalated cell functions (secretion of protons in to the urine coupled to bicarbonate reclamation) are necessary for appropriate excretion of the net acid load of a normal diet, and for generation of adequate amounts of bicarbonate for buffering. However, neither the identity of all the transporters, pumps and channels responsible, nor the regulatory pathways involved, are yet well understood.

Adopting an initial genetic approach, we studied rare single-gene disorders (the distal renal tubular acidoses, dRTAs) where α-IC function is inadequate, imparting large quantitative effects on the kidney’s ability to maintain normal body fluid pH. dRTA is clinically defined by metabolic acidosis, rickets and calcium deposition in the kidney. The recessively inherited syndromes present with very severe changes at a young age and sensorineural hearing loss (SNHL) is often associated.

We described mutations in the basolateral anion exchanger gene AE1 in dominant dRTA, and discovered two genes (ATP6V1B1 and ATP6V0A4), encoding kidney-specific B1 and a4 subunits of the α-IC surface proton pump, where loss-of-function mutations cause recessive dRTA.

We discovered that proton pumps in the kidney contain four other organ-specific subunit isoforms (C2, G3, d2 and e2) and that G subunits interact physically with a-subunit isoforms.

Moving from genetic to functional studies, we demonstrated abnormal targeting of AE1 as a mechanism of dominant disease, and have demonstrated that the glycolytic enzyme PFK-1 is essential for normal proton pump function via a-subunit binding.

Our studies currently focus on characterizing the cellular behaviour of AE1, on further dissecting the proton pump and on identifying the molecular pathways responsible for various other tubulopathies.
The Regulation of Cell Surface Receptors by Viral and Cellular Ubiquitin E3 Ligases

The focus of my laboratory is to study the cellular regulation of MHC class I molecules and other immune receptors and how these are altered by invading pathogens. Receptor ubiquitination by E3 ligases has emerged as an important means of regulating receptor cell surface expression. We study both constitutive cell surface ubiquitination and ubiquitination induced by viral gene products. Both herpes and poxviruses have pirated ubiquitin E3 ligases from their vertebrate hosts. These viral E3 ligases ubiquitinate and downregulate critical receptors of the immune system. The cellular orthologues of the viral E3 ligases are the MARCH (Membrane Associated RING-CH gene products), whose function is poorly defined.

We are interested in (i) mechanisms used by viruses to evade immune recognition, particularly of the MHC class I antigen presentation pathway (ii) the role of ubiquitin in the regulation of cell surface receptor expression, including identification of ubiquitin E3 ligases, ubiquitin E2 conjugating enzymes and deubiquitinating enzymes involved in this process. We are particularly interested in lysine-63 mediated ubiquitin conjugation as a mechanism for receptor trafficking to an endolysosomal compartment (iii) The physiological role of the MARCH genes. We have developed a number of mouse models to identify the substrates of the MARCH proteins and to study the role of these novel E3 ligases in health and disease (iv) identification of the endosomal sorting machinery used by internalised, ubiquitinated cell surface receptors and (v) identification of receptors used by human and microbial heat shock proteins in dendritic cell signalling and activation.

Stable-isotope labelling by amino acids in cell culture (SILAC) followed by mass-spectrometry allows us to perform quantitative proteomic analysis of plasma membrane preparations. We can identify novel substrates of ubiquitin E3 ligases which regulate cell surface receptors. Dr Simon Hoer (CIMR) in collaboration with Dr Ari Admon, Haifa Technion, Israel.
The Serpinopathies and Alzheimer’s Disease: Disease Mechanisms and Therapeutic Interventions

One in twenty-five of the Northern European population carries the Z allele (342Glu→Lys) of α1-antitrypsin. Homozygotes for this mutation retain α1-antitrypsin within hepatocytes as inclusion bodies that are associated with neonatal hepatitis, juvenile cirrhosis and hepatocellular carcinoma. We have shown that Z α1-antitrypsin is retained within hepatocytes by a unique protein-protein interaction between the reactive centre loop of one molecule and β-sheet A of a second. The structure and significance of these loop-sheet polymers has been confirmed using biochemical, biophysical, crystallographic, and cell biology studies and with monoclonal antibodies and animal models of disease. We are now using in silico screening to identify compounds that can bind to, and prevent the polymerisation of, mutant α1-antitrypsin in vitro and in vivo. Alpha-1-antitrypsin is a member of the serine protease inhibitors or serpin superfamily of proteins. We have shown that mutants of another serpin, neuroserpin, also polymerise within neurones to cause an inclusion body dementia that we have called familial encephalopathy with neuroserpin inclusion bodies (FENIB). We have described 5 families with FENIB caused by 4 different mutations and have demonstrated a clear correlation between genotype and phenotype based on the rate of polymer formation. We are dissecting the mechanism of polymerisation of mutants of neuroserpin and determining how these cause neurotoxicity with biochemical, cell and Drosophila models of disease. Finally, we have demonstrated that neuroserpin is also important in the far more common dementia caused by Alzheimer’s disease. Indeed we have shown a specific interaction between the Alzheimer’s Aβ peptide and neuroserpin and have demonstrated that this interaction is neuroprotective in cell and Drosophila models of disease. Our long term goal is to understand the pathways of cell toxicity in serpin polymer mediated syndromes (the serpinopathies) and in Alzheimer’s disease and to develop novel therapeutic strategies.


Molecular Cell Biology of Post-Golgi Membrane Traffic Pathways

Secretion and endocytosis are fundamental processes occurring in all nucleated mammalian cells. We are currently focusing on how cells achieve sorting and delivery of endocytosed macromolecules to lysosomes. Lysosomes are small membrane bound organelles ~0.5 μm diameter, which are full of proteases and other hydrolytic enzymes as well as internal membranes. They function late in the endocytic pathway that takes up macromolecules from the cell surface, by fusing with endosomes, but also play a key role in phagocytosis, autophagocytosis and cell surface membrane repair, the latter by fusing with the plasma membrane. The late endosomes that fuse with lysosomes are observed as MVBs (multivesicular bodies) in the electron microscope and sorting of membrane proteins into the lumenal vesicles of these MVBs is mediated by ESCRT (endosomal sorting complex required for transport) proteins. A key protein in fusion events involving lysosomes is the membrane protein Vamp7. We are currently investigating at a biochemical and structural level, two binding partners of Vamp7, one of which is responsible for ensuring that Vamp7 is recovered from the cell surface following lysosome fusion with the plasma membrane and the other likely to be required for regulating lysosome-endosome fusion. We are also studying the role of different protein machineries including the ESCRT proteins in preparing endosomes for fusion with lysosomes and for sorting endocytosed cargoes in different ways. Our structural studies are in collaboration with David Owen and we also collaborate with Paul Lehner on the intracellular sorting of Class I MHC molecules following downregulation from the cell surface by viruses.

Immunoelectron micrograph showing endocytosed Class I MHC molecules (10nm gold) in a multivesicular body of a cultured human HeLa cell expressing a viral ubiquitin ligase.
Haematopoietic stem cells (HSCs) have been intensely studied for many decades as a model system for stem cell biology. Our work focuses on the emergence and regulation of the first HSCs in the mouse embryo in order to identify the basic mechanisms that control their generation from precursors and their initial expansion and dissemination to the different haematopoietic organs. Knowledge of these early regulatory pathways has proven to be invaluable for understanding how adult HSCs can be manipulated for clinical purposes and how interference with these processes may result in blood-related disorders. Our research therefore complements that of several groups on the Cambridge University Hospital site which also work on various aspects of normal and leukaemic stem cell biology.

Adult-type HSCs are first detected at day 10.5 during mouse development in a region of the embryo that comprises the developing aorta, gonads and mesonephros (AGM region). A day later these cells can also be detected in the yolk sac and the foetal liver. Our previous work has identified the placenta as another organ that harbours HSCs during development. In fact, stem cells in this organ by far outnumber those found in the AGM and yolk sac, thus making the placenta a very attractive tool for studying micro-environmental factors for HSC expansion.

We have also carried out a number of microarray experiments with the aim of identifying some of the key regulators in HSC generation in the AGM. This expression analysis involved comparison of (1) the region around the aorta before and after stem cell detection, (2) HSCs and their putative precursors and (3) different regions within the AGM that do or do not support HSCs. These studies resulted in a list of candidate genes which we are currently verifying by employing mouse knockout models and through other functional assays.

Schematic diagram of a mouse embryo (top). PL, placenta; YS, yolk sac; FL, foetal liver. Cross-section through the aorta (below). Putative HSC sources are: IAC, intra-aortic clusters; SAP, sub-aortic patches.
Molecular Mechanisms Involved in Transport Vesicle Coat Formation

Transmembrane proteins are moved between organelles in transport vesicles. Once cargo has been sorted into a forming vesicle, the vesicle buds from the donor membrane and is then transported to and fuses with the target membrane. Post-Golgi transport is mainly mediated by clathrin-coated vesicles (CCVs), whose coats are composed of an outer clathrin scaffold linked to the membrane by clathrin adaptors including AP complexes, GGAs, epsins and ARH. We use a combination of X-ray crystallography, biochemistry and cell biology to study the structure and function of components of vesicle coats.

Clathrin adaptors have folded domains that bind to membrane phospholipid headgroups and in some cases simultaneously bind to transmembrane cargo thereby selecting the cargo for incorporation into a CCV. The extended, flexible regions of the adaptors that connect the folded domains contain multiple short motifs, which bind to clathrin and the appendages of APs and GGAs. These latter interactions help to recruit lower abundance clathrin adaptors, such as the epsins and ARH, and non clathrin-binding accessory proteins into forming CCVs. Along with phosphorylation/dephosphorylation events, these interactions drive the assembly and disassembly of the CCVs coat. The folded domains of clathrin adaptors recognise short, transplantable, linear motifs that are found on the cytoplasmic portions of many cargoes such as YxxΦ and [DE]xxxLL (that bind AP complexes) and FxNPxY (that bind ARH) but also highly protein specific, fold-dependent, surface epitopes on a single cargo such as those found on SNARE proteins, which mediate the fusion of vesicles with their target membranes. Our current work focuses on the structure, interactions and regulation of AP complexes (collaborations with Phil Evans (LMB) and Stefan Honing (Cologne)) and how SNAREs and other non-motif containing cargo interact with CCV components (collaborations with Margaret Robinson and Paul Luzio).

The interaction between the endosomal SNARE vti1b Habc domain (green) and the clathrin adaptor epsinR ENTH domain (pink) is mediated by surface patches. Mutation of residues in the interaction interface inhibit binding in vitro and alter the trafficking of vti1b in vivo.

Funding:
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The cytoplasm of all eukaryotic cells contains a complex set of membrane bound organelles with a precisely defined protein and lipid composition. Proteins and lipids are transported between these organelles via small membrane bound transport vesicles, which bud from one compartment and fuse with another, thereby delivering their contents. The targeting and fusion of transport vesicles is regulated in part by the specific interactions of a family of molecules known as SNAREs. In mammalian cells there are at least 37 SNAREs, each one being localized to a different compartment and involved in a subset of transport pathways. Disruption or mis-localisation of SNAREs can lead to the incorrect targeting of proteins and lipids, thus it is essential SNAREs are delivered to the correct membrane. There are now 2 examples of human disorders caused by the loss of SNAREs, neurocutaneous syndrome (CEDNIK) and Familial hemophagocytic lymphohistiocytosis (FHL) type-4.

One of the main aims of my research is to try and understand how post-Golgi SNAREs are trafficked and how this relates to their function. To address this we are using several approaches.

1) We have developed a tagging system that allows us to follow the trafficking itinerary of post-Golgi VAMPs.
2) We are performing structure/function studies on the trafficking signals in the post-Golgi SNARE VAMP4.
3) We are characterising a VAMP4 gene-trap mouse.

Hela cells expressing VAMP-HA constructs were incubated in the presence of anti-HA antibodies for 3 hours at 37°C. As the constructs pass over the cell surface they bind anti-HA antibodies allowing the trafficking itinerary of the VAMPs to be studied.
The Genetic Basis of Learning Disability

The group aims to understand the molecular mechanisms underlying intellectual disability in humans and our main focus is on families affected with X linked disease. In collaboration with the Wellcome Trust Sanger Institute, we are using systematic searches for mutations through the whole of the X chromosome. We have established a large international collaboration iGOLD (International Genetics of Learning Disability Study) with genetics centres throughout the UK, Ireland, Australia, USA and Europe. We have so far identified 9 novel genes that causes X-linked mental retardation and a further gene that causes X-linked nystagmus.

We are continuing to identify novel genes that cause X-linked mental retardation in our cohort of 250 patients with intellectual disability. We are also determining the rare and common sequence variance of the X chromosome in these individuals that will provide data for the wider genetics community.

Future directions include determining whether duplications or deletions of regions of the X chromosome contribute significantly to X-linked mental retardation. We are also identifying genes that underlie specific areas of intellectual disability. In addition, we are developing assays of the disease genes we have identified to aid further understanding of the disease.


Genes on the X chromosome where mutations result in an X-linked mental retardation syndrome. Red dots indicate families where truncating mutations have been identified and green dots indicate families with pathological missense mutations.
Research in my group is in the field of protein crystallography. Crystallography is the primary method for determining the three-dimensional structure of a protein, which provides an essential framework for a detailed understanding of its biochemistry. We work both on extending the scope and power of the methods used in protein crystallography, and on applying those methods to determine the structures of proteins. In choosing what to study, we focus on proteins involved in pathogenesis and disease, the structures of which can be exploited in the development of new therapies.

We have a long-standing interest in the mechanism of action of bacterial toxins. Recently we succeeded in engineering pertussis toxin (produced by the bacterium that causes whooping cough) to act as its own substrate. Its structure gives the first view of enzyme-substrate interactions for a large family, including cholera and diphtheria toxins. Dr Aiwu Zhou leads work on members of the serpin family, which undergo an extraordinary conformational change on cleavage by proteases. The structure of thyroxine-binding globulin has revealed how this serpin exploits its conformational change to deliver the hormone thyroxine.

In crystallographic theory, we focus on the understanding of probability distributions relating the structure factors that arise from the diffraction experiment. A detailed understanding of these probability distributions underlies new developments in maximum likelihood methods, which we are implementing in our program Phaser. The current version of Phaser can solve structures by molecular replacement (i.e. using the known structures of related proteins), by using the information from single-wavelength anomalous diffraction (SAD), and by a combination of the two. It has been credited with solving a number of structures that had eluded other programs. Enhancements to use other sources of experimental information and to improve automation are currently under development.
The Molecular Cell Biology and Pathology of the Hereditary Spastic Paraplegias

Our research is focused on the hereditary spastic paraplegias, genetic conditions in which the corticospinal tract axons degenerate. HSPs selectively involve axons while sparing the neuronal cell bodies, so we study them to understand molecular mechanisms crucial for axonal maintenance and degeneration.

We want to understand both the normal functions of HSP proteins and how these functions are disrupted in the disease. An emerging theme in the HSPs is the involvement of many of the disease proteins in membrane traffic processes. Our work concentrates on understanding the functions of this particular subgroup of HSP proteins and is based on three main themes:

1. Understanding the functions of spastin and atlastin. These proteins are involved in processes at the interface between membrane traffic and microtubule regulation and we have shown that they are binding partners, strongly suggesting that they are functionally related. We are examining functional assays for selected membrane traffic pathways in cell models of spastin- and atlastin- HSP.

2. Understanding the role of spartin. Spartin is mutated in Troyer syndrome, a type of complicated HSP. We are exploring the role of spartin at endosomes using a variety of functional assays in cellular models.

3. Understanding the function of NIPA1. This project builds on data generated from fly models, and is carried out in collaboration with Dr Cahir O’Kane in the Department of Genetics. Its aim is to examine whether, like its fly homologue, mammalian NIPA1 is involved in Bone Morphogenic Protein (BMP) signaling. If so, we will determine how it regulates this signaling pathway and explore mechanisms by which disrupted BMP signaling could cause axonopathy.

HeLa cells expressing mutant spastin (red) and VSVG-GFP, a protein used to study secretory pathway traffic (green). Mutant spastin delays Endoplasmic Reticulum to Golgi (blue) traffic.
Proteins are transported between the various organelles of the cell by vesicles, which bud from one membrane and fuse with another. The formation of these vesicles and the selection of the right sort of cargo are dependent on coat proteins. Several types of coated vesicles have been described, the best characterised of which are the clathrin-coated vesicles (CCVs). The coats on CCVs consist primarily of two components: clathrin and adaptor protein (AP) complexes. Recently, we and others have shown that there are also “alternative” adaptors in addition to the AP complexes, and our working hypothesis is that for each trafficking pathway, there are a number of different adaptors, each of which is recruited independently onto the appropriate membrane. Once on the membrane, the various adaptors would work together to package different types of cargo into the newly forming vesicle.

To look for novel adaptors and other components of the CCV machinery, we have developed a comparative proteomics approach, in which we isolate CCVs from control HeLa cells and “mock CCVs” from clathrin-depleted cells, and then identify proteins that are present exclusively or primarily in the control fraction. One such alternative adaptor is epsinR, which we found originally as a binding partner for AP-1 and which we subsequently showed to be an adaptor for the SNARE protein vti1b. In collaboration with David Owen, we have recently established the structural basis for this interaction, revealing a new mode of cargo recognition which may be a paradigm for SNARE trafficking. Other ongoing studies in the laboratory include searching for new CCV sorting signals using a random tail library; screening a human genome-wide siRNA library for new CCV machinery; and investigating how the HIV-1-encoded protein Nef can exploit adaptor-mediated trafficking to evade the immune system of the host.

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The Pathogenesis of Diseases caused by Codon Reiteration Mutations (like Huntington’s Disease and Oculopharangeal Muscular Dystrophy)

We study diseases caused by codon reiteration mutations, like Huntington’s disease (HD) and oculopharyngeal muscular dystrophy (OPMD), which result from abnormally elongated polyglutamine and polyalanine codon stretches in the HD and PABPN1 genes, respectively. These diseases are associated with intracellular aggregate formation. We are addressing the following questions:

1. **What are the pathological changes that occur in HD and other codon reiteration diseases?**
   We study pathogenesis of these diseases using models of HD, OPMD and related diseases in cells, flies (in collaboration with Cahir O’Kane, Cambridge), zebrafish and mice.

2. **What are the genetic pathways that modify polyglutamine toxicity?**
   We are using genetic screens in mice (with Steve Brown, Harwell) and flies to identify modifiers of polyglutamine toxicity in HD models. Such pathways may give clues to potential therapeutic strategies.

3. **Can one attenuate polyglutamine toxicity by inducing autophagy?**
   The polyglutamine expansion confers a novel toxic function on huntingtin. Thus, it is important to understand how its levels are regulated. We have shown that mutant huntingtin fragments are autophagy substrates and that autophagy upregulation is protective against mutant huntingtin toxicity in fly and mouse models. Autophagy upregulation may have value to many diseases caused by intracytosolic aggregate-prone proteins. Currently, the only autophagy-inducing drug that is known to act effectively in mammalian brains is rapamycin. While it is designed for long-term use, it has significant side-effects and is not that well-tolerated. Thus, we have been trying to characterise novel autophagy genes and pathways, with the hope of identifying possibly safer ways of inducing autophagy.

4. **Are there common mechanisms causing pathology in different diseases associated with intracellular protein aggregation?**
   It is important to test if the different diseases associated with intracellular aggregate formation share common pathways, as this may inform the fundamental understanding of pathogenesis and aid prioritisation of therapeutic strategies.

Autophagosomes in cells treated with a chemical inducer of autophagy.

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T-cells play a central role in orchestrating the immune response against pathogens and tumours, and serves as a model for the study of aspects of cell biology. Activation is mediated by intracellular signals induced by the antigen-receptor (TcR/CD3) in combination with co-receptors such as CD4, CD8, CD28, CTLA-4, ICOS and PD-1. Our research is focused on the discovery of T-cell signalling pathways that couple surface receptors with downstream events such as adhesion, gene transcription and cytokine production. Our work has relevance to the development of novel approaches in the treatment of cancer and immune-based pathologies such as autoimmunity.

My laboratory was the first to discover that cell surface receptors interact with protein kinases with the identification of CD4 and CD8 binding to the src kinase p56
ttk. CD4 and CD8–p56
ntk are now accepted as the initiators of the tyrosine phosphorylation activation cascade in T–cells. These complexes regulate recruitment of the ZAP-70 kinase to the TCR complex leading to the phosphorylation of adaptor proteins that integrate signals. Our present work focuses on the structure-function regulation of adaptor signalling. We showed that adaptor SLP-76 is SUMOylated in a new process that regulates receptor micro-cluster formation and function. Further downstream, we identified novel adaptors ADAP and SKAP-55 that mediate ‘inside-out’ signalling for integrin (i.e. LFA-1)-mediated adhesion that is needed for migration and formation of conjugates with antigen-presenting cells (APCs). A SKAP-55 homologue SKAP-55-Related/Hom is ubiquitously expressed and may mediate adhesion in other cell types.

Co-receptors CD28, ICOS and CTLA-4, needed for a modifying signal, bind the lipid kinase phosphotidylinositol 3-kinase (PI 3K), while we showed that CTLA-4 has potent effects on motility and in reversing the stop-signal needed for T-cell-APC interactions. We are interested in unravelling the molecular basis of this response and its involvement in autoimmunity.

Also see www.path.cam.ac.uk/pages/rudd

Funding: The Wellcome Trust


Representation of signalling in T-cells induced by CD4/CD8-p56
ntk and the antigen-receptor complex. CD4/CD8-p56
ntk initiates activation, ADAP and SKAP-55 integrate signals for integrin adhesion.
Molecular Dissection of the Mechanisms of Neurological Disease

My laboratory focuses upon understanding the causes and molecular mechanisms of neurodegenerative diseases such as Alzheimer Disease, Parkinson Disease and Fronto-Temporal Dementia. We and others have shown that these diseases are frequently caused by the accumulation of neurotoxic proteins or protein fragments. We employ genetic, molecular biological, cell biological, and animal modeling strategies to: 1) identify disease-causing genes; and 2) to identify the molecular pathways by which these mutations or polymorphisms lead to neuronal death. In the case of Alzheimer Disease (AD), we have shown that several different proteins in the amyloid precursor protein (APP) processing pathway modulate the production of a proteolytic derivative of APP, termed Aβ peptide. The Aβ peptide self-assembles into neurotoxic oligomeric aggregates. Mutations in several genes in the APP processing pathway (including APP itself) appear to cause AD by: increasing the absolute amount of Aβ production (e.g. some mutations in APP); altering proteolysis of APP and increasing production of longer Aβ species such as Aβ42 that is prone to form neurotoxic aggregates (e.g. presenilin 1 and 2 mutations); increasing the sorting of APP into subcellular compartments where it is cleaved into Aβ (e.g. SORL1 variants); or modulating Aβ neurotoxicity/response to Aβ neurotoxicity (e.g. apolipoprotein E variants). We have shown that inhibiting the accumulation of neurotoxic Aβ oligomers can prevent and reverse both the AD-like neuropathology and the cognitive deficits in mouse models of AD. These anti-amyloid strategies include antibodies to Aβ and small drug-like molecules (e.g. scyllo-inositol) which inhibit the aggregation of Aβ into neurotoxic oligomers. Ongoing work will: 1) identify new AD susceptibility genes, some of which will likely be novel components in the APP processing pathway; 2) identify the key regulators of the activity of the APP processing pathway; and 3) identify the molecular structure of the known components of this pathway.

Diagram of amyloid precursor protein processing pathways that either generate neurotoxic amyloid β-peptide (endocytic) or preclude its formation (α-secretase of recycling pathways).


The Molecular Genetics of Common Renal and Hepatic Disorders

Many genetic diseases affect the specialised epithelium lining the tubular nephron and the intrahepatic bile ducts. My group has a particular interest in autosomal dominant polycystic kidney disease (ADPKD). This is a common condition affecting over 1:1000 people. Renal and hepatic cysts, which are derived from the specialised epithelial cells of the nephron and biliary tree, are the main clinical complication and cause organomegaly, pain, haemorrhage and renal failure. The molecular basis of ADPKD is mutation of \( \text{PKD1} \) and \( \text{PKD2} \). These genes encode proteins, polycystin-1 and polycystin-2 respectively, that regulate key functions of the primary cilium. Polycystin-1 and polycystin-2 form a mechanosensitive ion channel complex which responds to ciliary deflection by fluid flow. Our main research aim is to determine the mechanisms controlling the mechanosensitive properties and signalling functions of the polycysts. In particular we are characterising proteins that interact with extracellular and intracellular domains of polycystin-1 using \textit{in vitro} and \textit{in vivo} assays. \textit{In vivo} assays utilise mouse, zebrafish and drosophila models. Our ultimate goal is to define disease specific pathways that may be modulated to alter the clinical course of ADPKD in animal models and humans.

Genetic studies are also being carried out to identify genes involved in the pathogenesis of multiple biliary hamartomatosis and primary biliary cirrhosis, two further diseases of the intrahepatic bile ducts. Multiple biliary hamartomas are frequently seen in polycystic liver disease suggesting common genetic pathways in these two diseases.

Knock-down of a novel polycystin-1 interacting protein during zebrafish development causes a convergent extension phenotype with broadened somites (s) and shortened embryonic body axis.
Molecular Mechanisms of Endosome-to-Golgi Retrieval

Protein sorting and membrane trafficking in eukaryotic cells play essential roles in maintaining normal cellular homeostasis and are vital mechanisms that underlie diverse processes such as nutrient and macromolecule uptake, growth factor receptor downregulation, autophagy and synaptic transmission.

My lab is interested in the endosome-to-Golgi retrieval pathway that is required for the recycling of lysosome hydrolase receptors such as the cation-independent mannose 6-phosphate receptor (CIMPR). More recently this pathway has been implicated in the trafficking and processing of the amyloid precursor protein (APP) which, when cleaved by β-secretase enzymes, generates the pro-aggregatory neurotoxic Aβ peptide which is the causative agent in Alzheimer’s disease.

Our studies have focussed on a conserved protein complex called ‘retromer’ that is essential for the recycling of the CIMPR to the Golgi. Retromer comprises five proteins that assemble on the endosomal membrane and we have recently identified a retromer-interacting protein called EHD1 that functions to stabilise endosomal tubules thereby facilitating endosome-to-Golgi retrieval.

We are also interested in identifying the sorting motifs that direct proteins into the retromer-mediated endosome-to-Golgi pathway and have employed a reporter-protein approach along with site-directed mutagenesis to identify the conserved motif in the cytoplasmic tail of the CIMPR which is required for the interaction with retromer and the recycling of the CIMPR reporter protein (see Figure).

We are now expanding our search for retromer-interacting proteins and have interesting candidates to pursue and characterise and we are continuing our studies to identify membrane proteins (and their intrinsic sorting motifs) that are ‘cargo’ molecules for retromer. From these studies we will gain a greater understanding of the mechanisms that govern protein sorting and membrane trafficking between the endosome and the Golgi and will generate new insights into the cell biology of protein localisation diseases such as Alzheimer’s disease.

Identification of the endosome-to-Golgi retrieval motif in the cytoplasmic tail of the CIMPR. A CD8-CIMPR reporter protein is retrieved to the Golgi to colocalise with the marker protein TGN46 but when the retrieval motif (WLM) is mutated to alanines, the reporter protein fails to retrieve.
Phospholipids play important roles in organelle function and their carefully orchestrated production during development often underlies striking morphological changes in a variety of specialized cell types. Therefore it is not surprising that disruption of lipid metabolism and transport in humans can lead to a large number of disorders. Our aim is to understand the molecular mechanisms that coordinate phospholipid biosynthesis with nuclear membrane biogenesis and nuclear structure. Remodeling of the nuclear membrane is essential for the dynamic changes of nuclear architecture at the different stages of the cell cycle but the underlying mechanisms are still poorly understood.

We have recently identified a network of evolutionarily conserved genes in yeast that coordinate phospholipid biosynthesis with nuclear membrane growth. The main effector of this pathway is the Pah1p/Smp2p, a phosphatidic acid (PA) phosphatase that converts PA to diacylglycerol (DAG). We have shown that Smp2p is phosphorylated by the mitotic cyclin-Cdc28p/Cdk1 and dephosphorylated by the nuclear membrane bound phosphatase Nem1p-Spo7p. Loss of dephosphorylated Smp2p causes transcriptional upregulation of key endoplasmic reticulum enzymes involved in lipid biosynthesis concurrent with a massive expansion of the nucleus. Therefore Smp2p could link membrane production to changes in nuclear structure during the cell cycle. We are now using a combination of genetics and biochemistry to understand how quantitative and qualitative changes in lipids impact on nuclear structure and characterize the function of downstream effectors of Smp2p.

Mammals express three Smp2p homologues, Lipin 1, required for adipocyte differentiation and storage fat production, Lipin 2 and Lipin 3. The importance of Lipins in fat metabolism is underscored by the fact that, in mice, mutations in Lipin 1 cause lipodystrophy whereas its overexpression promotes diet-induced obesity. We are currently investigating the function of Lipins in lipid metabolism and nuclear structure in higher eukaryotes.

Upper panel: Transcription of key genes involved in phospholipid metabolism (INO1, INO2 and OPI3) is upregulated in smp2Δ and nem1Δ spo7Δ mutants. mRNA levels were quantified by RT-PCR. Lower panel: Nuclear membrane proliferation leads to nuclear expansion in smp2Δ cells. The nuclear morphology of wild-type (SMP2) and smp2Δ cells expressing the Sec63-GFP reporter was visualized by confocal microscopy.
Immune Regulation, Autoimmune Disease and Infection

We aim to discover how genetically determined variation in immune regulation balances the risks of autoimmune disease and infection. Initially focussing on the B cell, which remains a major interest, we investigate the function of inhibitory receptors such as CD22 and FcγRIIb, which act as "brakes" on the immune system. We have recently shown that FcγRIIb, which binds the Fc portion of IgG, is expressed on plasma cells, controlling their persistence and inducing apoptosis of both normal cells and malignant myeloma. While mice deficient in FcγRIIb are prone to autoimmunity, we have found that FcγRIIb balances bacterial clearance and the risk of septic shock, determining survival from bacterial infection.

We are investigating natural polymorphisms in FcγRIIb that are associated with autoimmune diseases such as systemic lupus erythematosus (SLE) in both mouse and man. Some reduce function and are common in Asia and Africa, where malaria is endemic. We have used mouse models of malaria, in vitro assays with cultured Plasmodium falciparum and human cells, and human genetics (in collaboration with the KEMRI/Wellcome Trust Unit in Kilifi, Kenya), and have shown that FcγRIIb deficiency can be protective against malaria, perhaps contributing to the evolution of predisposition to SLE in some ethnic groups. Further work on the interaction between malaria and autoimmunity is an ongoing priority.

We have established a programme in human autoimmunity, working with patients from the Addenbrooke’s vasculitis and SLE clinic (and led with Paul Lyons). By performing detailed laboratory studies (including transcriptomics and proteomics) in patients at presentation and after therapy we are finding new ways of targeting therapy to improve efficacy and reduce treatment toxicity, and are indentifying novel disease-associated pathways requiring further investigation. This programme has also provided a resource which allows us to interrogate mouse and human biology in an integrated fashion, increasing our capacity to probe immunity and disease.
Our aim is to discover the molecular basis for the autoimmune inflammatory disease type 1 (insulin-dependent) diabetes. We use an integrated combination of genetics, in large collections of type 1 diabetic families and case/control, statistics, genome informatics and data mining, and gene expression and functional studies. Our major effort now is to correlate susceptibility genotypes with biomarkers and phenotypes e.g. we have correlated plasma levels of the soluble form of the interleukin-2 receptor with the genotypes of the IL-2RA gene that are associated with type 1 diabetes susceptibility. This is a first step towards identifying disease precursors that could be used in the evaluation of future therapeutic studies. To achieve this we have helped build a local biobank of healthy volunteers in whom we can study the effects of disease-associated genotypes (The Cambridge BioResource: www.cambridgebioresource.org.uk). Our research efforts are part of the Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory, which includes the laboratories of Linda Wicker and David Clayton, as well as collaborations with the Department of Haematology, the Department of Paediatrics (David Dunger), the Wellcome Trust Sanger Institute and the MRC Epidemiology Unit.

Interaction of a human T regulatory cell and dendritic cell involving the type 1 diabetes susceptibility molecule, CTLA-4. Yellow=B7.1+CTLA4. Photograph reproduced with kind permission from Paul MacAry.
The Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory

The Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory (JDRF/WT DIL) is composed of three integrated laboratories: John Todd (human genetics and immunology), Linda Wicker (mouse modelling, human immunology) and David Clayton (statistics). In the last seven years under special programmatic funding we have discovered and defined several mouse and human susceptibility loci for type 1 diabetes. Now the challenge is to correlate the presence of susceptibility alleles with their functions to determine which genes and pathways are underlying the pathogenesis of type 1 diabetes. Our recent results have shown how important the interleukin-2 pathway is in autoimmune and type 1 diabetes, and we are exploring further these mechanisms. A key strategy is the collection of local healthy volunteers (The Cambridge BioResource) who are willing to donate blood samples, with which we can study immune cell populations and activities in relation to genotypes associated with susceptibility and resistance to type 1 diabetes and autoimmune disease. Also in the last three years, the JDRF/WT DIL has been centrally involved in the establishment of two major international consortia, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and JDRF funded Type 1 Diabetes Genetics Consortium (T1DGC) and the Wellcome Trust Case Control Consortium (WTCCC). Both collaborations are driving forward the genetic analyses of type 1 diabetes (and in the WTCCC, at least eight other diseases are being studied at the genome-wide level).

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Kara Rainbow  
Srilakshmi Raj  
Helen Schuilenburg  
Anna Simpson  
Debbie Smyth  
Helen Stevens  
Niall Taylor  
Jennie Yang

Cambridge BioResource
The Cambridge BioResource is a joint effort by the Departments of Medical Genetics, Paediatrics and Haematology (the Blood Transfusion Service) and the MRC Units, Epidemiology and Brain Science and Cognition.

Cambridge BioResource staff
Sarah Nutland  
Cambridge BioResource Co-ordinator  
Heather Lloyd-Jones  
Rachel Walker  
Maureen Wiesner


We study a key cluster of human genes, the human major histocompatibility complex (MHC). It encodes the most polymorphic proteins in the human genome and is associated with more diseases than any other region. Unravelling this complex of human loci, from sequence to function, will help to understand autoimmune diseases such as diabetes, multiple sclerosis and arthritis. In addition, it could lead to novel strategies for immunotherapy of cancer and transplantation. The class I and class II molecules encoded by the MHC play a pivotal role in alerting the rest of the immune system to disease by interacting with receptors on T cells. A major part of our work concerns these molecules. Other genes embedded in the MHC provide additional clues to mechanisms of immune recognition and we are studying the functions of some of them, including Myelin Oligodendrocyte Glycoprotein (MOG) and BTN.

Further information on the state of health of a cell is provided by interaction of MHC class I molecules with other receptors, on natural killer (NK) cells. Like some MHC genes, the NK receptors are part of extensive gene families. They are involved in activating, or inhibiting NK cells and some T cells. We are studying the organisation of the NK-receptor gene families, their polymorphism and association with disease, particularly in relation to interaction of the receptors with different MHC class I molecules.

Myelin Oligodendrocyte Glycoprotein (MOG) isoforms are expressed at different subcellular sites when expressed in MO3.13 oligodendrocyte cells. These confocal micrographs demonstrate that splice variation in the cytoplasmic domains of MOG affect its cellular localisation and transport.
Identification and Modulation of Molecular and Cellular Mechanisms in Autoimmune Disease

Our group is focused on understanding the molecular and cellular mechanisms mediating autoimmune syndromes such as type 1 diabetes (T1D) by identifying and characterizing the function of genes that contribute to disease susceptibility in both humans and in mice. The nonobese diabetic (NOD) mouse is an excellent model of T1D that mirrors many features of disease pathogenesis in human T1D. In both humans and mice, alleles at more than a dozen genes expressed in immune cells are known to alter T1D susceptibility. In addition, the genetic control of T1D in both species involves at least partially overlapping sets of genes and molecular pathways exemplified by variants affecting CTLA-4, a negative regulator of the immune system, IL-2, and a subunit of the IL-2 receptor (CD25). The IL-2 signalling pathway is critical for the function of FOXP3+CD25+CD4+ regulatory T cells, a T cell subset that dampens the immune response and that is less functional in T1D patients and NOD mice. In addition to other immune cell subsets that express CD25, IL-2, and CTLA-4, we are examining FOXP3+CD25+CD4+ regulatory T cells in the peripheral blood of T1D patients and healthy volunteers accessed through the Cambridge BioResource. Using multi-colour flow cytometry (see figure), the density of cell surface molecules associated with the function of regulatory T cells is correlated with gene variants that cause T1D susceptibility. Laboratory members are also examining immune cell subsets that upregulate CD25 after activation, rather than having constitutive expression as is the case for FOXP3+CD25+CD4+ regulatory T cells. The elucidation of the molecular consequences of the causative SNPs (single nucleotide polymorphisms) in the genes encoding CTLA-4, IL-2 and CD25 are also under investigation. For example, we have discovered that causative SNPs can modulate the levels of protein isoforms by altering mRNA splicing.

CD25+CD4+ regulatory T cells have constitutively high CD25 levels and low levels of CD127 (IL-7R alpha-chain). Most CD127int-medCD25hiCD4+ T cells express the FOXP3 transcription factor.

Funding:
The Wellcome Trust
Juvenile Diabetes Research Foundation
National Institutes of Health (USA)


*share senior authorship

The Study of Mendelian Disorders of Neurogenesis and Pain

We have two areas of research: first, to understand early human neurogenesis by the study of families with Primary Microcephaly; and second, to find the genes causing Mendelian disorders of pain perception.

Our predominant focus is MCPH, which appears to be a primary disorder of neurogenic mitosis. The MCPH brain is small but architecturally normal and the only phenotype is mental retardation— which can be mild to severe. The MCPH genes seem to act in the neuro-epithelium lining the interior of the brain, and from which the majority of neurones arise in foetal life. Our initial focus was to find the MCPH genes, now we are trying to find what these genes do and how perturbation of this process leads to a small human brain. As all MCPH genes to date centrosomal components we are studying their effects on mitosis, cytokinesis, cell polarity and the centriole and centrosome cycle and components using human cell systems, see Figure.

Another strand of our work is the evolution of the human brain and whether the MCPH genes have contributed to the recent threefold increase in human brain size (recent in evolutionary terms!).

We recently discovered that non-sense mutations in SCN9A, encoding a voltage gated membrane sodium channel, lead to an inability to feel any pain. Subsequently we have begun the study of a number of disorders where too much or too little pain is felt, or analgesics are ineffective. For each we will determine the causative gene and its function in normal nociception. This work has the clear potential to generate new analgesic targets.

Using similar methodologies we study a number of other Mendelian neurodevelopmental disorders. Whilst these conditions are rare, each will yield essential insights into normal neurodevelopment after we identify the causative gene and determination of its function(s).

Overexpression experiments showing that wildtype NDE1 co-localizes with gamma tubulin, a centrosomal marker (left). The mutated form of NDE1, which causes severe microcephaly, does not localize to the centrosome (see arrow in right image) and instead forms aggregates.
The above, and Michael Harbour overleaf, are all core staff funded as part of CIMR’s Wellcome Trust Strategic Award.
The MRC Dunn Human Nutrition Unit

The aims of the Dunn are to investigate problems of human nutrition that relate to Public Health and to advance basic understanding of human nutrition, particularly in the area of energy conversion. Our activities in the first area by Sheila Bingham’s group concern investigations of the influence of diet and common genetic variants on cancer risk, by intervention studies and by prospective epidemiology in the large EPIC cohorts in Norfolk and Europe. In the second area we have eight groups studying different aspects of the mitochondrion ranging from structural and functional studies of central respiratory enzymes (John Walker, Judy Hirst and Leo Sazanov) and transport proteins (Edmund Kunji), to cellular regulation of nutrient and energy turnover (Martin Brand), to studies of mtDNA replication in relation to mitochondrial disease (Ian Holt) and to aspects of apoptosis and generation of reactive oxygen species in relation to ageing (Michael Murphy). A bioinformatics group (Alan Robinson) is modelling structures of mitochondrial proteins of unknown function and metabolic flux pathways through the organelle. The goal is to develop models for the dynamics and control of the metabolic and bioenergetic pathways, particularly those associated with disease. A proteomics group (John Walker and Ian Fearnley) is using modern mass spectrometry to characterise proteins involved in respiration, in signalling in the mitochondrion and in mtDNA replication.

Currently, the Dunn has a staff of 107 including 42 PhD students.
**CIMR Affiliated Principal Investigators**

**Jennie Blackwell**
Chair in Genetics and Health
University of Western Australia
Telethon Institute for Child Health Research
PO Box 855
West Perth
Western Australia 6872
Australia

**Sadaf Farooqi**
Wellcome Trust Senior Research Fellow in Clinical Sciences
Institute of Metabolic Science
Metabolic Research Laboratories
University of Cambridge
Box 289, Level 4
Addenbrooke’s Hospital
Cambridge CB2 0QQ

**Stephen O’Rahilly**
Co-director of IMS & Director of IMS-MRL
Professor of Clinical Biochemistry & Medicine
Institute of Metabolic Science
Metabolic Research Laboratories
University of Cambridge
Box 289, Level 4
Addenbrooke’s Hospital
Cambridge CB2 0QQ
Genetic Susceptibility to Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is the leading cause of visual loss in the elderly and the commonest cause of blindness in Western populations. Development of AMD is influenced by both genetic and environmental factors. The aim of our research is to identify genes that influence susceptibility to AMD. This contributes to our understanding of disease pathogenesis and should lead to improvements in treatment. We have recruited 950 cases with end-stage AMD and 440 controls. All subjects have had retinal examined and photography to confirm their disease status and provided medical, lifestyle and family history information and DNA samples. We have carried out extensive association studies of single nucleotide polymorphisms in candidate susceptibility genes. Following the discovery that the polymorphism Tyr402His in the complement factor H gene is an important determinant of risk for AMD, we have particularly focused on the complement pathway. This has lead to our recent discovery that the common polymorphism Arg80Gly in the complement C3 gene is strongly associated with AMD. These data provide compelling evidence that C3, and the complement pathway are important in the pathogenesis of AMD. We are currently undertaking a genome wide association study aimed at identifying further AMD susceptibility genes.

John Yates will retire in 2008.
CHRISTMAS PARTY
2006
MONDAY 18TH DEC. 8PM ..... 

Tickets on sale for One Week Only!
(4th - 8th Dec)

Available from Level 7 lounge
between 12 and 1pm

£5 each, 1 per person + 1 guest ticket

Wellcome Trust / MRC Building
Addenbrooke's Hospital

CIMR/DUNN Presents:
MUSICAL ICONS

Fancy Dress Christmas Party
Monday 17th December 2007
7.30pm until Late
Tickets: £5 Staff/Guest

The Wellcome Trust/MRC Building's annual Christmas party posters
Principal Investigators who have moved on from CIMR since Research Report 2006

Moved on to:  
Contact at:  

**Krish Chatterjee**  
Professor of Endocrinology, Institute of Metabolic Science, Metabolic Research Laboratories, University of Cambridge, Box 289, Level 4, Addenbrooke’s Hospital, Cambridge, CB2 0QQ  
www.mrf.ims.cam.ac.uk

**Hisao Kondo**  
Professor, Department of Molecular Biology, Faculty of Medical Science, Kyushu University, Fukuoka 812-8582, Japan  
www.kyushu-u.ac.jp

**Kerstin Meyer**  
Cancer Research UK Cambridge Research Institute, Li Ka Shing Centre, Robinson Way, Cambridge, CB2 0RE  
www.cambridgecancer.org.uk

**Gillian Murphy**  
Group Leader, Proteases & Tumour Micro-environment, Cancer Research UK Cambridge Research Institute, Li Ka Shing Centre, Robinson Way, Cambridge, CB2 0RE  
www.cambridgecancer.org.uk

**Bruce Ponder**  
Director, Cancer Research UK Cambridge Research Institute & Li Ka-shing Professor of Oncology, University of Cambridge, Cancer Research UK Cambridge Research Institute, Li Ka Shing Centre, Robinson Way, Cambridge, CB2 0RE  
www.cambridgecancer.org.uk

**Doug Winton**  
Group Leader, Stem Cell Biology of the Intestine

**Karin Römisch**  
Professor & Principal Investigator, Laboratory of Molecular Cell Biology, Center for Integrative Biology (CIBIO), University of Trento, Via delle Regole, 101, 38060 Mattarello (TN), Italy  
www.unitn.it
Introduction
The CIMR offers an exciting and vibrant environment for graduate students. Approximately 20% of the 250 scientists within the CIMR are postgraduate students carrying out research towards a PhD. There are a variety of schemes that we offer to allow both clinical and non-clinically qualified individuals to pursue a PhD within the Institute. Some of these are for three years whilst others are for four year programmes funded by the Wellcome Trust and Medical Research Council (MRC). We also offer Wellcome Trust-funded ‘Next Generation’ Fellowships to enable clinically qualified individuals who have previously undertaken an MD or PhD to obtain preliminary data so that they can apply for an intermediate fellowship to work with a PI within the Institute.

Wellcome Trust Four Year PhD Programmes at the CIMR
The CIMR houses 2 four year PhD programmes funded by the Wellcome Trust and the MRC. The Wellcome Trust four year PhD programme in Infection and Immunity (Director: Professor Doug Fearon) offers 5 studentships per annum. Approximately 50% of the faculty for this programme are members of the CIMR with other principal investigators being within the Department of Pathology, the Veterinary School and the School of Clinical Medicine. The CIMR also runs its own four year programme that is funded by the Wellcome Trust and the MRC. All principal investigators within the CIMR serve as faculty for this programme. The four year programmes allow individuals to undertake 3 ten week mini projects in the first year before deciding on the project that they wish to pursue for their three year PhD. These programmes are advertised in November with interviews in January/February. The successful applicants start the programme in October.

Clinical Research Training Fellowships
Clinical training fellowships are available as competitive awards through the Medical Research Council, the Wellcome Trust and the Association of Medical Charities. The CIMR also runs the Capacity Building Scheme for the Cambridge National Institute for Health Research Biomedical Research Centre. These three year fellowships provide salary for clinical fellows to undertake a PhD anywhere within the University of Cambridge. The University of Cambridge has recently been awarded a Wellcome Trust Clinical PhD Programme that funds 5 clinical fellows per annum for 5 years. This scheme will also be run from the CIMR although the faculty for this programme is drawn from the whole of the School of Clinical Medicine and the wider University of Cambridge.

‘Next Generation’ Fellowships
The CIMR was awarded 2 ‘Next Generation’ fellowships per annum as part of the Wellcome Trust-funded Strategic Award. This is aimed at clinically qualified individuals who already have an MD or PhD and who wish to refocus their research career to work with a PI within the CIMR. The fellowships are for 6-18 months to allow the fellow to develop sufficient preliminary data for an application to a major funding body for an intermediate fellowship.

The Director of the four year non-clinical PhD programmes, the Biomedical Research Centre clinical training fellowships and the Wellcome Trust clinical PhD programme is Professor David Lomas, the Director for Graduate Studies within the Institute is Dr Lucy Raymond and the Programme Administrator is Sonia Lyne.

Non-Clinical Three Year PhD Programmes
The CIMR offers standard three year PhD programmes. These are usually awarded by the Medical Research Council and research charities to individual principal investigators. These are advertised separately from the four year programmes run within the CIMR. The 3 year PhD students have access to the same seminars, equipment and mentoring as four year students.
The 8th Research Retreat once again proved to be a great success. Holding the meeting in March allowed members of the CIMR to stroll in the spring sunshine and eat their meals outside. The presentations were given by postdoctoral fellows and graduate students and once again were of an extremely high standard. The judging panel thought the best presentation by a PhD student was given by Nienke Lubben (with Mair Thomas as the runner-up) and the best talk by a postdoctoral fellow was given by Damian Crowther (with the runner-up being Frank Reimann). The CIMR continued its tradition of inviting external speakers to give guest lectures. Fiona Watt spoke on stem cells and lineage selection in mammalian epidermis and Gillian Griffiths (recently awarded a Principal Research Fellowship and soon to join CIMR) spoke on using genetic diseases to identify secretory mechanisms at the immunological synapse. We were also delighted to continue with our tradition of inviting a speaker from the Dunn and Sheila Bingham presented her work on biomarkers in cancer epidemiology.

David Lomas
Deputy Director
The Administrative Team provides an essential support service to all members of the Institute and Sarah Smith, the Institute's Administrator, heads the team which comprises: Personnel; Facilities; Buildings maintenance; IT; Accounts and Purchasing sections.

The Administrative Team has continued to develop both with individual's personal training and the introduction of new working practices. Additionally there has been a restructuring of certain admin units which has increased the flexibility required to respond efficiently and effectively to the changing demands of the University and, in particular, increased legal requirements, especially in the fields of human resources and health and safety.

The Administrator has specific responsibility for contributing to the Institute's strategic direction, policy formulation, administrating grant applications, and, assisted by two personnel clerks and a secretary, personnel issues. She also provides a link with other key University departments and as a method of improving the communication from other sources with the Institute, has introduced a monthly newsletter, which is sent out electronically to everyone in the building.

The Laboratory & Facilities Manager, Dave Cheesman, is responsible for overseeing the provision of core laboratory services. He is assisted by a deputy and a team of technical staff who coordinate services on each level. Media kitchen and Glasswash functions are supervised by the Senior Level Coordinator and Deputy Lab Manager respectively.

Susan Reeder, the Finance Officer, has specific responsibility for the day-to-day management of the grants awarded. She also oversees the running of the Accounts and Purchasing sections, and deputises for the Administrator in her absence, for some administrative matters.

Jonathan Wilson, who leads the IT Team, has responsibility for the Institute's IT facilities, including the provision of a support service to scientific and administrative staff, his team manages the data network within the Institute and maintains the Intranet and Website.

Ray Woodstock, the Building Services Supervisor, is responsible, with two members of staff, for maintaining the day to day running of the building, including repairs, modifications, alterations.
Total grant income has continued to increase each year from £12m (2001/2002) to £16.2m (2006/2007).

Overall Wellcome Trust support is approximately 60% with the remainder of the total value of all current grants held split evenly between the MRC and other sponsors.

In respect of building management and maintenance for the Wellcome Trust/MRC Building and the Cambridge Institute for Medical Research annual recurrent costs remain split between the University and MRC at a ratio (61.65% : 38.35%), directly proportional to the space occupied in the building.
Honours, Awards & Personal Fellowships

Principal Investigators:

**Jennie Blackwell**: University of Cambridge Honorary Senior Visiting Fellow.

**Bertie Göttgens**: University of Cambridge Readership 2007.

**Tony Green**: Specialist Centre for Research in the Myeloproliferative Disorders funded by the US Leukemia and Lymphoma Society (over $6M, the only one in Europe).

**Fiona Gribble**: Lister Institute Research Prize for 2006 (£175,000).

**Gillian Griffiths**: Wellcome Trust Principal Research Fellowship 2007; Professorship of Immunology & Cell Biology in the University of Cambridge Department of Medicine.


**David Lomas** and his team, led by Dr Damian Crowther: one of the five shortlisted research groups in the category of “Outstanding Contribution to Innovation and Technology” in the Times Higher 2006 Awards.


**David Owen**: Hooke Medal for 2006 by the British Society for Cell Biology.

**Randy Read**: Wellcome Trust Principal Research Fellowship renewed 2008.

**Evan Reid**: Wellcome Trust Senior Research Fellowship in Clinical Sciences 2007; elected member of the Scientific Advisory Board of the American Hereditary Spastic Paraplegia Foundation.

**Karin Römisch**: University of Cambridge Readership 2006.

**David Rubinsztein**: Wellcome Trust Senior Research Fellowship in Clinical Sciences renewed 2007; Graham Bull Prize in Clinical Science from the Royal College of Physicians 2007.

**Peter St George-Hyslop**: Wellcome Trust Principal Research Fellowship 2007; Professorship of Experimental Neuroscience in the University of Cambridge Department of Clinical Neurosciences; Member of the Institute of Medicine of the (US) National Academies of Science 2007.


**Ken Smith**: elected Genzyme Professor of Experimental Medicine 2006; Lister Institute Research Prize for 2007 (£200,000).

**Linda Wicker**: Chairperson of the Hypersensitivity, Autoimmune and Immune-mediated Disease Study Section, Center for Scientific Review (Department of Health and Human Services) April 2006 to 30 June 2007. Re-establishment of Professorship of Immunogenetics to tenure.
Research Scientists:

**Menna Clatworthy:** (Ken Smith's group) Wellcome Trust Intermediate Clinical Fellowship 2007; Clinical Lecturer (Medicine) 2007.

**Lucy Davison:** (John Todd's group) Wellcome Trust Intermediate Clinical Fellowship 2007.

**Andres Floto:** (Ken Smith's group) 2007 ERS Maurizio Vignola Award on Innovation in Pneumonology.

**Erik Fung:** (Linda Wicker's group) Juvenile Diabetes Foundation Postdoctoral Fellowship 2006.

**Babak Javid:** (Paul Lehner's group) MRC Clinician Scientist Fellowship 2007.

**Stefan Marciniak:** (David Lomas’ group) MRC Clinician Scientist Fellowship 2007.

**Patrycja Kozik:** (Margaret Robinson’s group) won the 2-year prize in the ‘Science for the Public’ poster competition 2007.

**Sasha Mendjan:** (Roger Pedersen’s group) EMBO Fellowship 2007.

**Richard Page:** (PhD student in David Lomas’s group) won the ‘2006 Westminster Medal and Prize’ for the best poster presentation at the SET Exhib.

**Karine Proulx:** (Steve O’Rahilly’s group) Marie Curie (EC FP6) Intra-European Fellowship 2007.

**Aiwu Zhou:** (Randy Read’s group) British Heart Foundation Basic Science Lectureship 2006.

**Editorial Boards of Journals**

**David Clayton** is on the editorial boards of *Annals of Human Genetics* and *The Strata Journal*.

**Fiona Gribble** is on the editorial board of *Endocrinology* and on the editorial advisory board of *Biochemical Journal*.

**Gillian Griffiths** is on the editorial board of *Journal of Cell Biology* and is co-editor of *Traffic*.

**James Huntington** is on the editorial advisory panel of *Biochemical Journal*.

**Brian Huntly** is on the editorial board of *Experimental Haematology*.

**David Lomas** is an associate editor of *Thorax* and on the editorial boards of *Journal of Chronic Obstructive Pulmonary Disease, Current Respiratory Medicine Reviews, American Journal of Respiratory Cell and Molecular Biology, Open Respiratory Medicine Journal and Clinical Medicine*.

**Paul Luzio** is on the editorial board of *Traffic*.

**Roger Pedersen** is on the editorial boards of *International Journal of Developmental Biology, Stem Cells and Cell Stem Cells* and is an associate editor of *Molecular Reproduction & Development*.

**David Rubinsztein** is on the editorial boards of *Human Molecular Genetics, Autophagy and the Journal of Applied Biomedicine* and academic editor of *PLOSONE*.

**Christopher Rudd** is on the editorial boards of *Current Biology and Immunology*.

**Peter St George-Hyslop** is on the editorial boards of *Journal of Clinical Investigation, Neurogenetics, Journal of Psychiatric Neurogenetics/Journal of Medical Genetics, Journal of Alzheimer Disease, American Journal of Alzheimer’s Disease, Research and Perspectives in Alzheimer’s Disease and Neurodegenerative Diseases*.

**Richard Sandford** is on the editorial board of *Nephron: Experimental Nephrology*.

**Ken Smith** is on the editorial boards of *Medicine and Immunology*.

**John Todd** is on the editorial boards of *Human Molecular Genetics and Expert Reviews in Molecular Medicine*.

**John Trowsdale** is on the editorial boards of *European Journal of Immunology, Human Immunology, Tissue Antigens and Immunogenetics* and a co-editor of *Immunology*.

**Linda Wicker** is an advisory editor of *Journal of Experimental Medicine*.

**Staff Affiliations**

**Folma Buss** is a member of the Cell Biology Theme Panel of the Biochemical Society.

**David Clayton** a member of MRC ASTRAL Trial Steering Committee; a member of the SNP Steering Group, Cancer Research UK and a member of the Council of the International Biometrics Society.

**Tony Green** is a member of the European School of Haematology Executive Committee; the European Haematology Association Scientific Programme Committee; the National Cancer Research Institute (NCRI) including the Myeloproliferative Disorder Study Group and the Haematological Malignancies Group; the Joint MRC and UK Stem Cell Foundation Scientific Advisory Board; the UK Research Assessment Exercise 2008 Panel A5; Scientific Advisor to the Sir Michael and Lady Kadoorie Trust; Chairman of the Scientific Advisers to the Kay Kendall Leukaemia Fund; Chairman of the European Haematology Association Education Committee; Chairman of the European Haematology Association Scientific Working Group.

**Fiona Gribble** is a member of the National Kidney Research Fund External Referee Panel.
Gillian Griffiths is a member of the Wellcome Trust Basic Immunology and Infectious Disease Panel.

James Huntington is a member of the International Advisory Board Serpin Symposium 2008; the ISTH Scientific Program Committee 2007; the Biochemical Society; the British Society for Haemostasis and Thrombosis; the International Society on Thrombosis and Hemostasis; the British Crystallographic Association and the American Crystallographic Association.

Brian Huntly is a member of the European Haematology Association Membership Committee and the CRUK Discovery Committee.

Fiona Karet is Chair of the Kidney Research UK Grants Committee; a member of the Wellcome Trust Clinical Interview Panel; Academy of Medical Sciences Clinical Research Champion; a member of the American Society of Nephrology Annual Meeting Program Committee, a member of the World Congress of Nephrology Program Committee and a member of the East Anglian Regional Training Committee for Renal Medicine.

David Lomas is Co-Chair (Chair from July 2008) of the Alpha One Foundation Grants Committee; Chairman of the Asthma UK Grants Committee; a member of the Alpha-one antitrypsin Laurell Training Award (ALTA) Grants Committee; a member of the Executive Committee of the Association of Physicians; a member of the Respiratory and Allergy Expert Advisory Group to the Commission on Human Medicines; a member of the MRC Physiological Systems and Clinical Sciences Board (PSCSB); a member of the Screening, Detection and Diagnosis Subgroup of the COPD National Service Framework External Reference Group; a member of the Scientific Advisory Board Talecris Biotherapeutics and a member of the Steering Committee Respiratory Global Medical Excellence Cluster (GMEC) and Co-Convenor COPD.

Paul Luzio is Chair of the MRC Molecular & Cellular Medicine Board; a member of the Research Councils’ Individual Merit Promotion Panel and a member of the MRC College of Experts.

Roger Pedersen is a member of UK Stem Cell Bank Management Committee; a member of East of England Stem Cell Network Steering Committee and UK National Stem Cell Network Steering Committee; a member of International Committee International Society for Stem Cell Research; a consultant Stemnion LLC Pittsburgh PA; International Chair Singapore Stem Cell Consortium.

Randy Read is a member of the Executive Committee of CCP4 (Collaborative Computing Project 4) and a member of the BBSRC Biochemistry and Cell Biology Portfolio Evaluation Committee.

Margaret Robinson is a member of the American Society for Cell Biology and a member of the British Society for Cell Biology.

David Rubinsztein is a member of the Wellcome Trust Molecular & Cellular Neuroscience Committee; a member of the MRC College of Experts; a member of the Scientific Board of EUROSCA; a member of the Scientific Planning Committee British Society of Human Genetics; a member of Faculty of 1000 Biology; a member of the Royal College of Pathologists (Part I).

Christopher Rudd is a member of the Wellcome Trust Basic Immunology & Infectious Diseases Panel; visiting Professor Imperial College London; Trustee and International Secretary of the British Society for Immunology (BSI); a council member of the International Union of Immunological Societies (IUIS); a member of the Scientific Programme Committee European Congress of Immunology.

Peter St George-Hyslop is a member of the Fisher Center for Alzheimer’s Disease Research Foundation Alzinfo.org Advisory Panel; the Dana Neuroscience Initiative Scientific Advisory Board, New York; the Charles A Dana Foundation Scientific Advisory Board; New York; the World Federation of Neurology Scientific Advisory Board Dementia Study Group; Canada Research Chair, College of Reviewers; a member of the Canadian Institutes of Health Research Institute of Genetics Planning and Priorities Committee; a member of the Royal Society of London International Conference Grants Incoming and Outgoing Short Visits Review Panel; a member of the Deutsche Forschungsgemeinschaft Excellence Initiative Biochemistry and Biophysics Review Panel; a member of the Deutsche Forschungsgemeinschaft Excellence Initiative Neuroscience Review Panel.

Richard Sandford is a medical advisor to PKD Charity and a member of the External Scientific Advisory Board for the Kansas Interdisciplinary Center for PKD.

Matthew Seaman is a member of the Faculty of 1000.

Ken Smith is Khoo Oon Teik Professor of Nephrology, University of Singapore; a member of Faculty of 1000 Immunology & Medicine sections; a member of the Scientific Advisory Board of WTGRF; a member of the MRC College of Experts; an elected member of the Henry Kunkel Society; a member of the British Transplantation Society Basic Science Review Committee; Programme Director, NIH – University of Cambridge Biomedical Research Graduate Programme; Theme Head Infection and Immunity, NIHR BMRC.

John Todd is a Governor of the Strangeways Laboratory, Cambridge; a member of Cambridge Computational Biology Institute Management Committee, University of Cambridge; a member of the Wellcome Trust Case Control Consortium Management Committee; a member of the Type 1 Diabetes Genetics Consortium Steering Committee; a member of the Institute of Metabolic Science-Metabolic Research Laboratory Strategy Committee and a member of the Cancer Research UK Population and Behavioural Sciences Committee.
**John Trowsdale** is a member of the MRC College of Experts; a member of the Scientific Advisory Board of ONYVAX; a member of the Faculty of 1000 and a member of the Medical & Scientific Advisory Committee of the Anthony Nolan Trust.

**Linda Wicker** is a member (2002-2006) and chair (2006-2007) of the Immunological Sciences Study Section, Center for Scientific Review, National Institutes of Health; a member of the Medical Science Review Committee of the Juvenile Diabetes Foundation International and chair and member of the Type 1 Diabetes Repository Advisory Committee, National Institutes of Health.

**Fellows of the Royal Society**

Robin Carrell, Stephen O’Rahilly, Peter St George-Hyslop

**Fellows of the Academy of Medical Sciences**

Jennie Blackwell, Tony Green, Gillian Griffiths, Fiona Karet, Paul Lehner, David Lomas, Paul Luzio, Stephen O’Rahilly, Margaret Robinson, David Rubinsztein, Christopher Rudd, Ken Smith, John Todd, John Trowsdale

**EMBO Members**

Gillian Griffiths, Margaret Robinson


Gout, A. M., Ravine, D., Harris, P. C., Rossetti, S., Peters, D., Breuning, M.,


recruitment.
The role of cargo proteins in GGA


Miller, E. N., Fadil, M., Mohamed, H. S., Elzein, A., Jamieson, S. E., Cordell, H. J., Peacock, C. S., Fakiola,


Nogueiras, R., Wiedmer, P., Perez-Tilve, D., Veyrat-Durex, B.,


Phillips, D. R., Ahmad, K. I., Waller, S. J., Meisner, P. and Karet, F. E.


meckelin (MKS3) is mutated in Meckel-Gruber syndrome and the wpk rat. Nat Genet 38, 191–6.


Thomas, M., Boname, J. M., Field, S., Nejentsev, S., Salio, M., Cerundolo, V., Wills, M., Lehner, P. J. (2007). Downregulation of *NKG2D* and *NKP80* ligands by Kapo’s sarcoma-associated herpesvirus K5 protects against NK cell ...
The text contains multiple references and citations. It discusses the role of FoxOs in physiologic oxidative stress and their critical mediation of gene expression in aging. It also mentions the characterization of a novel mutation in the gonadotropin-releasing hormone receptor gene associated with hypogonadism in a Turkish population. Additionally, it references the characterization of a novel mutation in the truncating splice site mutation and the identification of (R)- and (S)-N-hydroxy-2-(N-isopropoxybiphenyl-4-ylsulfonamido)-3-methylbutanamides as potential therapeutics. The text also highlights the functional characterization of a novel insulin receptor mutation contributing to Rabson-Mendenhall syndrome and the role of pro-opiomelanocortin in the modulation of (R)- and (S)-N-hydroxy-2-(N-isopropoxybiphenyl-4-ylsulfonamido)-3-methylbutanamides as potential therapeutics.


Management

1 The Cambridge Institute for Medical Research shall be an institution within the Faculty of Clinical Medicine and shall be under the general control of a Strategy Committee, which shall consist of:
   (a) the Director (Chairman) of the Institute;
   (b) the Deputy Director (Deputy Chairman) of the Institute;
   (c) the Regius Professor of Physic;
   (d) the Heads of the Departments from which staff working within the Institute are drawn;
   (e) the Director of the Diabetes and Inflammation Laboratory;
   (f) two persons appointed by the Faculty Board of Clinical Medicine.

2 The Regius Professor of Physic shall serve as Chairman of the Strategy Committee and the Deputy Director (Deputy Chairman) of the Institute shall serve as Secretary of the Strategy Committee.

3 Subject to the powers of the Council, the General Board, and the Faculty Board of Clinical Medicine, the duties of the Strategy Committee shall be as follows:
   (a) to promote research in, and at the interface of, the clinical and basic biomedical sciences that underpin the Institute's major goal of determining and understanding the molecular mechanisms of disease;
   (b) to co-operate with outside bodies including the Wellcome Trust in the encouragement of such research;
   (c) to establish an Institute Management Committee and receive reports from it relating to the administration of funds allocated to the Institute for the purposes specified in (a) and (b) above and reports on the affairs of the Institute;
   (d) to convene such ad hoc or standing advisory groups as may be appropriate to support the Committee's work;
   (e) to nominate to the Faculty Board of Clinical Medicine for appointment or reappointment by that body the Director and Deputy Director.

4 There shall be an Institute Management Committee consisting of:
   (a) the Director (Chairman) of the Institute, who shall be Chairman of the Committee;
   (b) the Deputy Director (Deputy Chairman) of the Institute;
   (c) the Administrator of the Institute;
   (d) six Principal Investigators appointed by the Strategy Committee. The six principal investigators will serve on the Management Committee for periods not exceeding three years at any one time. The Management Committee may, with the agreement of the Strategy Committee, co-opt additional members.

5 The duties of the Management Committee shall be as follows:
   (a) to advise the Director (Chairman) of the Institute on strategic issues and implementation of strategy as agreed by the Strategy Committee and on other matters concerning the administration of the Institute including health and safety issues;
   (b) in consultation with the relevant Heads of Department, to select new Principal Investigators, using the criteria of scientific excellence and contribution to the aims of the Institute, and to approve applications from Principal Investigators wishing to seek extension of their externally funded fellowships;
   (c) to consider and make recommendations to the Director (Chairman) and Strategy Committee on allocation of space and resources;
   (d) to administer funds allocated to the Institute for the purposes specified in 3(a) above;
   (e) to formulate the Institute's financial strategy, to prepare for the approval of the Faculty Board the Annual Estimates and year end reports, and applications to that Board for School funds;
   (f) to provide such data and reports as may be required by the Strategy Committee, the Faculty Board of Clinical Medicine and any outside bodies, including the Wellcome Trust;
   (g) to maintain records, to be updated at each meeting, of any developments in commercial exploitation, opportunities for the capture of IPR, or planned interactions with commercial companies, on the part of any Institute staff members and/or relating to research conducted by the Institute's staff.

There shall be a University office of Deputy Director (Deputy Chairman) of the Cambridge Institute for Medical Research, which may be held concurrently with another University office.

3 The Director (Chairman) and Deputy Director (Deputy Chairman) of the Cambridge Institute for Medical Research shall be appointed by the Faculty Board of Clinical Medicine on the recommendation of the Strategy Committee. Appointments and reappointments to the offices of Director (Chairman) and Deputy Director (Deputy Chairman) shall be for such periods not exceeding five years at a time as shall be determined by the Faculty Board on the recommendation of the Strategy Committee.

4 Under the general control of the Strategy Committee, and subject to the powers of the Management Committee, the Director (Chairman) of the Institute shall be the administrative Head of the Institute.

5 The Director (Chairman) or his or her nominated deputy shall also represent the Institute on the Wellcome Trust/MRC Building User's Committee.

Procedure for the appointment and re-appointment of the Director (Chairman) and Deputy Director (Deputy Chairman)

1 The Strategy Committee shall designate one of their members to take soundings on their behalf from amongst the Heads of Departments from which staff of the Institute are drawn, the Principal Investigators based in the Institute, and to submit a nomination or nominations to the Strategy Committee. The Strategy Committee shall determine the nomination to be made to the Faculty Board of Clinical Medicine. For the Deputy Directorship the designated person shall be the Director unless the Strategy Committee shall determine otherwise.

2 This procedure shall apply also for re-appointments.

Regulations approved by the Faculty Board of Clinical Medicine, University of Cambridge
Back cover illustration:
The picture shows cultured HeLa cells expressing both a mutant form of the hereditary spastic paraplegia protein spastin (red) and a fluorescent reporter protein (green) used to study the secretory pathway from the endoplasmic reticulum (ER) to the cell surface. Expression of the mutant spastin induces the appearance of, and decorates, abnormally bundled microtubules, disrupts the Golgi complex (blue) and slows the exit of newly synthesised green fluorescent reporter protein from the ER. This results in the yellow colour appearing where the ER aligns on the microtubule bundles, with consequent overlap between the green reporter protein in the ER and spastin. (See also page 27, Evan Reid).