Front cover illustration:
The front cover illustration shows immunofluorescence picture of a rat fibroblast highlighting the intracellular localisation of myosin VI, a unique retrograde motor protein. Myosin VI (green) is present in endocytic clathrin coated pits and vesicles at the plasma membrane. The actin cytoskeleton is labelled in red and the nucleus in blue. (Buss, F., et al. Annu Rev Cell Dev Biol 20, 649-676).

Back cover illustration:
The picture shows a cultured HeLa cell transiently co-transfected with a mutant form of the hereditary spastic paraplegia protein spastin (red) and green fluorescent protein-tagged wild-type form of atlastin (GFP-atlastin, green), which is another protein associated with hereditary spastic paraplegia. The mutant spastin protein induces the appearance of and decorates abnormally bundled microtubules. GFP-atlastin is normally located on the endoplasmic reticulum (ER), but in the presence of mutant spastin, it and the ER marker calreticulin are redistributed to co-localise with the abnormal microtubule bundles. Structures that are labeled by spastin, atlastin and calreticulin appear white. (See p25 Luzio)
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The Wellcome Trust/MRC Building which houses Cambridge Institute for Medical Research and the MRC Dunn Human Nutrition Unit. Behind and to the left is the Hutchison/MRC Research Centre. Behind and to the right is the MRC Laboratory of Molecular Biology. In front and to the right is the University of Cambridge Clinical School.
Cambridge Institute for Medical Research (CIMR) is a cross-departmental institute, within the University of Cambridge Clinical School, that is housed in the Wellcome Trust/MRC Building on the Addenbrooke’s campus. It provides a unique interface between basic and clinical science that underpins its major goal of determining and understanding the molecular mechanisms of disease. Currently, CIMR comprises approximately 250 scientists, about a fifth of whom are graduate students. They are organised in 36 research groups each led by a Principal Investigator (PI) who, along with their group members, is also a member of one of seven home University departments (Medicine, Surgery, Pathology, Medical Genetics, Clinical Biochemistry, Haematology or Oncology). Half of our present PIs have personal salary support in the form of fellowships, with 4 being Principal Research Fellows funded by the Wellcome Trust and 11 being Senior Research Fellows funded by the Wellcome Trust or MRC. CIMR grant expenditure, which was just under £15 million in the most recently completed financial year, constitutes about a third of the research grant spend in the Clinical School and has been rising steadily since the Institute opened in 1998 (see p54). Approximately 70% of our grant income comes from the Wellcome Trust and 15% from the MRC. Since the establishment of CIMR in 1998, we have aimed to maintain a healthy proportion (around 40%) of PIs who are medically qualified and clinically active. Fifteen of our 36 current PIs fulfil this criterion. We have also encouraged collaboration amongst our scientists and it is pleasing to note that out of 29 recorded collaborations between current PIs, 25 have led to joint publications and 22 are cross-departmental. It is also a pleasure to record that our scientists continue to win awards, prizes and promotions (a full list is printed on p56). Since our Institute opened, 4 of the senior scientists with research groups in CIMR have been elected FRS and 16 have been elected FMedSci. A particularly encouraging feature in this Report’s list of award winners is the number of scientists who are not yet PIs who are winning prizes and intermediate fellowships. This bodes well for the future academic health of the Institute.

In the last couple of years our Institute has learnt to cope with PI turnover without there being a noticeable drop in any quantifiable measure of scientific activity. Our grant income continues to grow and our publication output remains at about 200 peer reviewed items per annum. Of the 40 PIs listed in the first Research Report in 2000, 19 have already moved on and a further 4 of the original PIs are expected to leave CIMR over the next 18 months. In the cases of Professors Bruce Ponder and Steve O’Rahilly, the re-location of their CIMR groups will coincide with the opening of major new research facilities on the Addenbrooke’s campus. Bruce Ponder moved into the Hutchison/MRC Research Centre next to the Wellcome Trust/MRC Building in 2001 but remained a CIMR PI with a research group in CIMR that included his senior colleague Doug Winton. During 2006 the Cancer Research UK (CRUK) Cambridge Research Institute, of which Bruce is Director, will open. In addition to Bruce’s group, CIMR will also lose
Gill Murphy and her group to the CRUK Cambridge Research Institute. Steve O’Rahilly has maintained an active obesity research group in CIMR since its inception but will move into the new Cambridge Institute of Diabetes, Endocrinology and Metabolism (CIDEM) when it opens in 2007. The expected loss of these research groups has created an opportunity for CIMR to re-assess its scientific direction, without losing sight of the requirement to select as PIs the best possible scientists. About a year ago we advertised for new PIs explaining that we would support those we selected in applications to major funding bodies for personal fellowships. We received about a hundred serious inquiries/applications and have selected a few to support at various levels. We particularly encouraged applications from those pursuing research in structural biology or at the interface of immunology and cell biology. We are now supporting fellowship applications at a senior level from scientists working in these areas.

Although there will be some change of focus for CIMR in the next few years, we will remain an Institute that is not disease specific. We expect to maintain and develop our major strengths in medical genetics, immunology, structural biology, molecular cell biology and developmental/stem cell biology, which are brought to bear on a number of diseases. I hope that in reading the entries from individual PIs in this Research Report you will get a flavour of the excellent work going on in these areas. One of the highest profile CIMR contributions to understanding disease has been that from the Diabetes and Inflammation Laboratory (DIL) headed by John Todd and Linda Wicker which is making major strides in identifying genetic susceptibility loci for the autoimmune disease, type 1 diabetes. In a recent interview, John explained how the DIL is currently engaged in one of the world’s largest case-control, whole-genome association studies of type 1 diabetes, using high density microarrays and multiplexed genotyping assays to test a panel of more than 7000 non-synonymous single nucleotide polymorphisms that change the sequences of proteins. Another major contribution to understanding the molecular mechanisms of disease has come from the structural biologists in CIMR including David Lomas, Robin Carrell, Randy Read and Jim Huntington, working on the conformational diseases characterised by protein mis-folding including the serpinopathies. However, other research groups continue to work on normal cellular function. Our cell biology groups led by PIs Margaret Robinson, David Owen, Matthew Seaman, Hisao Kondo, Folma Buss, Karin Römisch, Symeon Siniossoglou and myself have generated much new information about the molecular mechanisms of intracellular membrane traffic and the way in which proteins are sorted to different locations within cells. Understanding the normal function of cellular processes such as membrane traffic underpins the comprehension of molecular changes that cause disease. It is particularly encouraging to note the many collaborations in CIMR between the cell biologists and, for example, those whose primary interest is immunology (Paul Lehner), serpinopathies (David Lomas), codon reiteration diseases (David Rubinsztein), or single gene disorders (Dick Sandford,
Fiona Karet) that have led and will lead to new insights into the underlying pathology of different diseases.

The excellent work being done by our research groups is underpinned by a core scientific support structure including bioinformatics, microscopy and fluorescence activated cell sorting (FACS) that is funded in large part by a Wellcome Trust strategic initiative award which runs until the end of 2006. We also remain extremely 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. These have now been accessed by 17 of our research groups via a CIMR employee who works alongside the Dunn scientists.

Every 2 years our International Scientific Advisory Board (ISAB) visits CIMR and gives advice to the Director, the Institute Management Committee and the Strategy Committee. Whilst the ISAB has been complimentary about the overall development of CIMR, it has made many suggestions which we have learnt to consider very seriously. The ISAB strongly advised us to start a regular internal seminar series for our post-docs and students to talk about work in progress. Our Management Committee had been somewhat resistant to this idea when it had come up earlier, largely because there are already so many seminars and group meetings as well as an annual Research Retreat. Nevertheless, we started the series and now one student and one post-doc speak to a full, or nearly full, lecture theatre every Monday lunchtime. The popularity of these talks may be because of the bright orange paper used to advertise them or because of the free tea/coffee and chocolate frogs on offer afterwards to those who attend. However, it seems more likely that the ISAB had spotted something that was missing. It is clear that the series is now making a major contribution to the scientific ethos of CIMR.

I have already mentioned that there has been a significant turnover of senior scientists associated with CIMR in the past couple of years. In ending this foreword I want to pay particular tribute to Martin Bobrow who recently retired from the chair of Medical Genetics and to Sir Keith Peters who retired from his post as Regius Professor of Physic last September. Martin chaired the committee that selected many of the PIs who came into CIMR at its start, as well as being involved in the planning and fund raising for the Wellcome Trust/MRC Building. All at CIMR wish him well in his new role as Deputy Chairman of the Board of Governors of the Wellcome Trust. Without Keith Peters CIMR would never have happened. It was his vision and drive to secure funding that resulted in the Wellcome Trust/MRC Building which was the first of several new research buildings on the Addenbrooke’s campus. Keith was a great friend and supporter of CIMR as well as an excellent chairman of our Strategy Committee. His successor as Regius Professor, Patrick Sissons, already has a track record of consistently supporting CIMR including regular attendance at our Research Retreats. At CIMR we look forward to Patrick’s stint as chairman of our Strategy Committee.

Paul Luzio
January 2006
# 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>Jennie Blackwell</td>
<td>University Chair (endowed Glaxo Holdings Ltd)</td>
<td>Medicine</td>
</tr>
<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>Krish Chatterjee</td>
<td>University Chair</td>
<td>Medicine</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>Leukaemia Research Fund Senior Research Associate</td>
<td>Haematology</td>
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<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>
<td>Haematology</td>
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<td>Fiona Gribble</td>
<td>Wellcome Trust Senior Research Fellow in Clinical Sciences</td>
<td>Clinical Biochemistry</td>
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<td>James Huntington</td>
<td>MRC Senior Research Fellow</td>
<td>Haematology</td>
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<td>Brian Huntly</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>Hisao Kondo</td>
<td>Wellcome Trust Senior Research Fellow in Basic Biomedical Science</td>
<td>Clinical Biochemistry</td>
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<tr>
<td>Paul Lehner</td>
<td>Wellcome Trust Senior Research Fellow in Clinical Sciences and Personal Chair</td>
<td>Medicine</td>
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<tr>
<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>
<td>Clinical Biochemistry</td>
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<td>Kerstin Meyer</td>
<td>Royal Society Research Fellow</td>
<td>Pathology</td>
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<td>Gillian Murphy</td>
<td>University Chair</td>
<td>Oncology</td>
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<td>Stephen O’Rahilly</td>
<td>University Chair</td>
<td>Clinical Biochemistry</td>
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<tr>
<td>David Owen</td>
<td>Wellcome Trust Senior Research Fellow in Basic Biomedical Science and University Reader</td>
<td>Clinical Biochemistry</td>
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<tr>
<td>Andrew Peden</td>
<td>MRC Career Development Fellow</td>
<td>Clinical Biochemistry</td>
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<td>Roger Pedersen</td>
<td>University Chair</td>
<td>Surgery</td>
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<td>Bruce Ponder</td>
<td>University Chair</td>
<td>Oncology</td>
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<td>Lucy Raymond</td>
<td>University Senior Lecturer</td>
<td>Medical Genetics</td>
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<td>Randy Read</td>
<td>Wellcome Trust Principal Research Fellow and Personal Chair</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), Jennie Blackwell (CIMR, Faculty Board),
Andrew Bradley (Surgery), John Danesh (IPH, Faculty Board), Tony Green (Haematology), David Lomas
(Deputy Director, CIMR), James Lupski (Medical Genetics), Paul Luzio (Director, CIMR), Stephen O’Rahilly
(Clinical Biochemistry), Bruce Ponder (Oncology), John Todd (Diabetes and Inflammation Laboratory),
Andrew Wyllie (Pathology), Head of Department of Medicine.

Current Membership of the International Scientific Advisory Board:
Nick Hastie (Chairman, University of Edinburgh), Dennis Ausiello (Harvard University), Chris Haslett
(University of Edinburgh), Carl Nathan (Cornell University), Janet Thornton (EMBL Hinxton),
Graham Warren (Yale University).

↑ CIMR currently has a number of works of art on long-term loan from the Arts Council Collection through the Hayward
Gallery, including “The Fugitives” by Ingrid Kerma (reproduced with permission).
Our laboratory has specific interest in leishmaniasis, tuberculosis, leprosy and toxoplasmosis. Our research involves projects in Brazil, pan-Europe, India, Malawi, Sudan, USA and Vietnam. We work with human populations to identify susceptibility genes, and we use yeast, mouse and cell culture models to study function. Highlights of our research in 2004–2005 include:

• We showed that Slc11a2, but not Slc11a1, complements EGTA-sensitivity in smf1/2/3 KO yeast, consistent with divalent cation/proton symport function. In contrast, Slc11a1, but not Slc11a2, complement divalent cation stress in Bsd2/Rer1 KO yeast. Slc11a1 is therefore acting as an antiporter to export divalent cations from yeast against a proton gradient. This is the first assay of Slc11a1 transport function in yeast. Using Slc11a orthologues we know that divergence of Slc11a1 and Slc11a2 functions post-dates Drosophila and pre-dates chicken, consistent with the role of chicken Slc11a1 in infectious disease susceptibility. Chimaeric molecules and mutagenesis will determine the key to antiport versus symport function.

• Genome scans on multicase families with visceral leishmaniasis from Sudan showed that Y chromosome haplotypes define lineages carrying village-specific genes for susceptibility on chromosomes 1p22 (LOD LOD=5.6; p=1.7x10⁻⁷) and 6q27 (LOD score 3.8, p=1.7x10⁻⁵). Significant allelic association with polymorphisms at DDAH1 suggests dimethylarginine dimethylaminohydrolase, an inhibitor of nitric oxide synthase, as the probable etiological gene under the 1p22 peak.

• Candidate gene analysis of babies that develop clinical signs when infected with toxoplasmosis in utero showed that, after adjusting for trimester of infection and country of origin of grandparents, polymorphisms in ABR and COL2A1 genes are associated with ocular disease.

• In screening 100 novel antigens in a murine model of Leishmania major infection we found antigens that exacerbate disease as well as those that protect. We showed that interleukin 10 from regulatory T cells is responsible for vaccine failure for these exacerbatory antigens.

Funding: The Wellcome Trust, National Institutes of Health (USA), Guide Dogs for the Blind Association

Key publications


Group members
Léa Castellucci
Lee-Anne de Roubaix
Michala Eichner-Teachau
Michaela Fakiola
Sarra Jamieson
E Nancy Miller
Hiba Mohamed
Jean-Francois Popoff
Madhuri Raju
Ellie Wheeler

A yeast assay showing the ability of Slc11a1 to rescue bsd2/rer1 knockout yeast from sensitivity to high cadmium levels. This confirms that Slc11a1 is acting as an antiporter that is transporting divalent cations out of the yeast cell against a proton gradient.
How are organelles and vesicles transported around cells and how do chromosomes segregate and cells divide and migrate? Two dynamic cytoskeletal systems play a central role in these intracellular movements, which are powered by motor proteins moving along these cytoskeletal tracks. Long distance transport of vesicles, protein complexes and even small organelles is believed to involve kinesin and dynein motor proteins, whereas short range movements require myosin motor proteins interacting with actin filaments. The myosins are a diverse superfamily of mechano enzymes that use the energy from ATP hydrolysis to generate force for stepping movement along the actin filament tracks. In the last five years great excitement has been generated by the identification of 18 distinct classes of myosins in eukaryotes; more than 40 myosins belonging to 12 distinct classes are expressed in humans.

Our studies focus on identification and molecular characterisation of the intracellular functions of myosin VI. This myosin is unique, because unlike all the other myosins so far characterised, it moves in the reverse direction along actin filaments and therefore is considered to have unique molecular properties and intracellular functions. The absence or mutations in the myosin VI gene are associated with deafness syndromes, cancer cell migration, cardiomyopathy and even neurodegeneration. At the cellular level we have localised myosin VI in endocytic and secretory vesicles, the Golgi complex and in membrane ruffles. Furthermore we have shown that myosin VI is a multifunctional motor protein involved in a variety of different intracellular functions such as clathrin mediated endocytosis from the apical domain of polarised cells as well as maintenance of Golgi complex morphology and secretion. These diverse roles of myosin VI are mediated by interaction with a range of different binding partners, which are currently one of the main areas of our research.

Funding: The Wellcome Trust

Key publications
In the largest worldwide cohort of subjects with Resistance to Thyroid Hormone (RTH) and thyroid hormone receptor β mutations, we are defining the human phenotype and molecular mechanisms of the disorder. The genetic basis of RTH which is not associated with TRβ gene mutations is also being investigated. From the phenotype of TRα mutant mice, we aim to identify the homologous human disorder.

Defects in the peroxisome proliferator activated receptor γ (PPARγ) gene are associated with lipodystrophic insulin resistance. Our research is elucidating the action of dominant negative receptor mutations in this disorder. In addition, we have used such dominant negative receptor mutants in collaborations, to define the role of PPARγ in angiogenesis, hepatic stellate cell differentiation and endothelial function. We are studying altered PPARγ-dependent gene expression in subjects harbouring receptor gene defects and envisage that these subjects will provide a unique opportunity to delineate the role of this receptor in human biological processes.

We have previously conducted short and long-term placebo controlled trials of dehydroepiandrosterone (DHEA) hormone replacement in adrenal insufficiency and shown significant improvement in well-being. We have now shown that DHEA treatment has significant immunomodulatory effects, particularly on regulatory T-cells.

Funding: The Wellcome Trust, European Union

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Key publications


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“Human PPARγ mutations (Pro467Leu, Val290Met) (left panel), associated with lipodystrophic insulin resistance are in proximity to a C-terminal alpha helix (red) which interacts with coactivator (yellow). Fluorescence anisotropy measurements (right panel) indicate that the mutations destabilise this helix and increase its mobility, providing a mechanism for altered mutant receptor interaction with cofactors.”
Our aim is to develop and apply statistical methods in genetic epidemiology and, to a lesser extent, in other aspects of biostatistics. A 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 is an important part of our work.

In common with other groups, a major concern of our recent work has been the prospects for mapping genes for complex diseases using population association with single nucleotide polymorphisms (SNPs). Of particular interest is the “indirect” method based upon linkage disequilibrium between groups of “haplotype tag” SNPs and unobserved causal variants. We have developed algorithms for optimal choice of tag SNPs in genes or genetic regions of interest. We have also developed optimal tests for association between a group of tags and disease and, having found convincing evidence of this, further methods to help in identifying sub-regions more likely to contain a causal variant.

Further development of methods for the analysis of candidate region studies is a continuing interest. Recent work has considered improvement of tag SNP methodology when the causal variant has a recessive effect, and further extensions when the pattern of gene-gene interaction is such that power can be enhanced by consideration of several loci together.

A major commitment over the next two years will be the Wellcome Trust Case-Control Consortium. This is a whole-genome association study in which 2000 cases of each of 8 different diseases will be compared with two shared control groups, together comprising 3000 subjects. Each subject will be typed for ~700,000 SNPs. I co-chair the analysis group for this study and my group will be responsible for developing much of the analysis software and, together with other members of the analysis group, providing the initial analysis of this study.

Funding: The Wellcome Trust, The Juvenile Diabetes Research Foundation, Medical Research Council

Key publications


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. Work in my group combines 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 and early endothelial transcriptional networks. To this end, we have developed a new suite of bioinformatics tools for the top-down computational identification of gene regulatory elements from the human genome sequence with predicted in vivo activity (1,2). In parallel, we are performing transgenic and molecular studies to dissect the transcriptional regulation of LMO2, SCL and endoglin, three key regulators of early blood and endothelial development (3,4). The latter bottom-up studies continue to inform the design of our 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 and endothelial development. Future work will address how these transcriptional programmes are perturbed in specific subtypes of leukaemia and may thus open up new avenues for the development of targeted therapies.

Funding: Leukaemia Research Fund, Cambridge MIT Institute, BBSRC, The Wellcome Trust

Key publications


Our laboratory is focused on understanding the mechanisms by which inflammation prevents autoaggressive T cells from being controlled. In particular, we use murine models of type 1 diabetes (T1D), where the insulin producing β-cells in the islets of Langerhans are destroyed by CD8 T cells. These models of T1D are helping us to address the importance of the proinflammatory cytokine TNFα in overcoming CD8 T cell tolerance. Using a series of transgenic and gene knockout models, we have established a link between TNFα and TNF/TNFR family members in the expansion of a unique population of CD4+CD25+FoxP3 regulatory T (Treg) cells whose job is to control autoaggressive CD8 T cells. In addition, we have established that CD8 T cells can resist regulation under certain conditions, a finding that has major implications for therapy. We are continuing our investigations on the mechanisms by which TNFα and TNF/TNFR family members impact on both Treg development/survival and sensitization of CD8 T cells to regulation.

We have also established that the capacity of TNFα to promote diabetes in genetically susceptible mice, is dependent on the presence of unique disease causing alleles. Our preliminary evidence suggests that these alleles target the CD8 T cell population, making them more responsive to islet antigens. We are presently trying to determine the genes present in these alleles that mediated this event.

Finally, we have recently established that there is a new regulatory pathway that does not involve Treg cells, but instead functions to control aggressive CD8 T cells in a non-CD4 T cell-dependent way. This pathway is thwarted if B cells are present. The mechanism by which B cells over-ride this new regulatory pathway is the subject of further investigations.

Funding: The Wellcome Trust

Key publications


Haematopoietic Stem Cells and Leukaemia  Tony Green

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. In collaboration with Addenbrooke’s Haematology Department we are studying the molecular pathogenesis and treatment of the MPDs. Recent highlights include (i) demonstration that an acquired V617F mutation of JAK2 is present in virtually all patients with polycythaemia vera and approximately half those with thrombocythaemia and idiopathic myelofibrosis (Lancet 365: 1054-61, 2005); (ii) demonstration that V617F+ essential thrombocythaemia represents a forme fruste of polycythaemia vera (Lancet, in press, 2005); (iii) publication of the MRC PT1 study, the largest randomised clinical trial of any MPD yet performed (N Engl J Med 353: 33-45, 2005).

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 an HSC enhancer (EMBO J 21: 3039-3050, 2002); (ii) identification of a second enhancer targeting HSCs and progenitors (Mol Cell Biol 24: 1870-1883, 2004); (iii) identification of an erythroid enhancer which targets primitive but not definitive erythropoiesis (Mol Cell Biol, 25: pp 5215-5225, 2005).

Funding: The Wellcome Trust, Medical Research Council, Leukaemia Research Fund, Cambridge MIT Institute, BBSRC
Recent years have witnessed a surge in the interest in hormones from the gastrointestinal tract, as it has become evident that they are not only involved in the local regulation of gut physiology but also play more far-reaching roles in diverse processes such as the control of appetite and insulin secretion. The two major “incretin” hormones implicated in the meal-related stimulation of insulin release are GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic peptide). Incretins have been the focus of recent wide attention because GLP-1 has been found to normalise insulin secretion in type 2 diabetes, and a range of GLP-1 based therapies are currently at various stages of clinical trials. Other products of the L-cell, peptide YY (PYY) and GLP-2 are also under development for the treatment of obesity and gastrointestinal disorders.

Despite the interest in using GLP-1 based therapies for the treatment of type 2 diabetes, very little is known about the mechanisms underlying release of the incretin hormones. In our group we employ an electrophysiological and fluorescence imaging approach to study the events involved in stimulus detection and hormone secretion in intestinal endocrine cells. Changes in plasma membrane potential, ionic currents, intracellular [Ca\textsuperscript{2+}] and GLP-1 release can be detected following application of a variety of nutrients, hormones and pharmacological agents. Glucose, for example, was found to trigger GLP-1 release by a combination of classical ATP-sensitive potassium (K\textsubscript{ATP}) channel closure, and a novel glucose-sensing pathway involving the electrogenic activity of Na\textsuperscript{+}-coupled glucose transporters. Amino acid sensing pathways are also diverse and include electrogenic uptake mechanisms as well as activation of cell surface receptors.

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.

Funding: The Wellcome Trust, Diabetes UK, St John’s College, Cambridge

Key publications


Serpins are the predominant protease inhibitors in the higher organisms and are responsible for the control of many highly regulated processes, including blood coagulation. The serpin inhibitory mechanism can be compared to a spring-loaded mousetrap, where nibbling of the peptide loop bait springs the trap and crushes the unsuspecting protease. The complexity of the serpin mechanism provides many advantages over the simpler lock-and-key type mechanism utilized by other inhibitors: serpins provide stoichiometric, irreversible inhibition, and the dependence on serpin and protease conformational change is exploited for signaling and clearance. The potential for regulation is also an inherent part of such a complex mechanism, as illustrated by the heparin activation of serpins controlling haemostasis, antithrombin (AT), heparin cofactor II (HCII) and protein C inhibitor (PCI). Our lab studies the molecular mechanisms involved in the regulation of the haemostatic response. We are particularly interested in the mechanisms by which heparin-like glycosaminoglycans activate the inhibition of coagulation proteases by serpins. Over the last five years we have solved the crystal structures of the final serpin-protease complex which illustrates the general serpin mechanism of protease inhibition, and of the initial Michaelis complexes of HCII and AT with thrombin. These complexes reveal the detailed interactions which confer the exquisite specificity required of haemostasis.

We have expanded our research from the inhibitors of the coagulation factors to encompass the general issue of how substrate specificity is determined by the interaction of the haemostatic proteases with cofactors and substrates. This effort is centered on the final protease in the coagulation cascade, thrombin, which cleaves at least twelve different substrates. We are crystallizing several thrombin cofactor/substrate complexes to determine the molecular basis of recognition, and we are also investigating the role of thrombin alloster in determining specificity.

Funding: Medical Research Council, British Heart Foundation, Tesny-Perry Trust, Isaac Newton Trust, National Institutes of Health (USA)

Key publications

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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 is fundamental to improving treatment outcomes in leukaemia. Using a combination of genetic experiments in mouse models and functional genomics we intend to identify novel self-renewal pathways and to examine putative self-renewal pathways in leukaemia stem cells.

Previously, tissue specific stem cells have been thought to be the sole targets for malignant transformation. Our recent work challenged this dogma by demonstrating that committed myeloid progenitor cells, which inherently lacked self-renewal, could demonstrate self-renewal properties in vitro and generate transplantaible acute myeloid leukaemia (AML) in vivo mouse models, following expression of the leukaemia associated transcription factor fusion $MOZ-TIF2$. However, this property was not generic to leukaemia associated oncogenes, as expression of the activated tyrosine kinase $BCR-ABL$ fusion did not confer the same properties. This paradigm is currently being extended to determine if other transcription factor fusions confer similar self-renewal properties. In addition, this system also provides a platform to identify self-renewal genes/genetic programmes, and we are currently analyzing gene expression array signatures from $MOZ-TIF2$ expressing progenitors. Further work will seek to prioritise candidate genes for functional validation.

In addition to this gene discovery programme, we intend to interrogate a putative self-renewal pathway, that of clustered Hox genes, by generating a conditional Cdx4 knockout mouse. Cdx4 is a haematopoietic Hox gene master regulator and its inactivation is lethal in zebrafish. As a global mediator of Hox gene expression its conditional activation will bypass previous problems with Hox gene redundancy in the interrogation of the role that these genes play in haematopoiesis and leukaemogenesis.

**Key publications**


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-IC 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.

To elucidate the relevant physiology, we adopted an initial genetic approach, studying 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 phenotypically 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 loss-of-function mutations in two genes (ATP6V1B1 and ATP6V0A4), encoding kidney-specific B1 and a4 subunits of the α-IC surface proton pump, as the causes of recessive dRTA.

In moving from genetic to functional studies we demonstrated abnormal targeting of AE1 causes autosomal dominant distal renal tubular acidosis. Nat Genet 33, 125-127.


We have discovered different, kidney-enriched isoforms for the a, C, d and G subunits, all encoded by separate genes; the B1 isoform was identified some years ago. Loss of proton pump function via mutations in B1 or a4 cause distal RTA with deafness. a4 interacts with PFK-1. d2 is also expressed in osteoclasts.

Other studies are focusing on additional novel tissue-specific subunits, and identifying the molecular pathways responsible for various forms of stone disease.

Funding: The Wellcome Trust
The Golgi apparatus occupies a central position in the secretory pathway, where it receives the entire output of de novo synthesized proteins from the ER, and functions to distil, posttranslationally process, and sort cargo for delivery to different destinations. The Golgi is fragmented into thousands of vesicles and short tubules during mitosis and is rapidly reassembled from fragments within each daughter cell. Experiments using an in vitro function assay, which mimics Golgi reassembly at the end of mitosis, showed that reassembly from membrane fragments requires at least two ATPases; N-ethylmaleimide-sensitive factor (NSF) and p97 (also known as VCP). The role of NSF has been well characterized, while much less is known about the mechanism of action of p97. We previously identified two cofactors, namely p47 and VCIP135 (VCP/p97/p47 complex-interacting protein, p135). p47 forms a tight complex with p97. The SNARE protein (soluble NSF attachment protein [SNAP] receptor), syntaxin5 is a receptor in Golgi membranes for the p97/p47 complex, with p47 mediating the binding of p97 to syntaxin5. VCIP135 binds to the p97/p47/SNARE complex and dissociates it via p97 catalyzed ATP hydrolysis.

We also reported that the mitotic phosphorylation of p47 is important for Golgi disassembly at the onset of mitosis. The microinjection of p47(S140A), which is unable to be phosphorylated, allows the cells to maintain Golgi stacks during mitosis. The membrane fusion mediated by the p97/p47 complex is thought to be important for the reassembly of organelles at the end of mitosis. Recently, we have discovered a novel membrane fusion pathway, the p97/p37 pathway. The novel p97-mediated membrane fusion is necessary for the maintenance of the Golgi and ER during interphase.

Funding: The Wellcome Trust

Key publications


The MHC class I antigen presentation pathway plays a critical role in defence against viruses and other intracellular pathogens. The recognition of viral peptides in the context of class I molecules enables cytotoxic T lymphocytes (CTLs) to kill infected cells. Our work has focused on the identification of viral immunoevasions. We identified the K3 and K5 genes from the Kaposi’s sarcoma-associated herpesvirus (KSHV) which downregulate cell surface MHC class I molecules and other critical immunoreceptors (ICAM1, CD86, CD1d) to evade immune recognition. These viral proteins contain novel RING-CH domains and ubiquitinate cell surface receptors, leading to internalisation and lysosomal degradation. Thus K3 and K5 are membrane-associated ubiquitin E3-ligases and establish a new class of viral immunoevasion genes. We have identified the molecular mechanisms governing the specificity of class I ubiquitin chain linkage in vivo and shown that class I molecules are modified by a lysine-63 ubiquitin chain linkage, establishing a novel mechanism for the downregulation and disposal of mammalian cell surface receptors. These viral genes have been pirated from the vertebrate genome and our ongoing work aims to identify the substrates and mechanism of action of both viral members of the K3 family as well as the ten mammalian RING-CH E3 ligases. We collaborate with Professor Paul Luzio to identify the cellular components involved in internalization and trafficking of ubiquitinated class I molecules to late endosomes for degradation.

The recruitment and activation of naive T-cells is controlled by professional antigen presenting cells – dendritic cells (DCs). Heat shock proteins are pro-inflammatory and remarkable for their ability to both activate the innate immune system and exert specificity, which is derived from peptide binding. Picomolar concentrations of HSP70-bound peptides are sufficient to prime DC to generate antigen-specific CTL and we have recently shown that mycobacterial HSP70 specifically activates human DC through CCR5, the HIV co-receptor.

Funding: The Wellcome Trust, The Lister Institute

Key publications


The Serpinopathies and Alzheimer’s Disease: Disease Mechanisms and Therapeutic Interventions

One in twenty-five of the Northern European population carry 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. The profound lack of circulating α1-antitrypsin predisposes the Z α1-antitrypsin homozygote to early onset emphysema. We have shown that the polymeric conformation of α1-antitrypsin is present in the lungs of patients with Z α1-antitrypsin deficiency related emphysema and is chemotactic for human neutrophils in vitro. We are currently investigating the mechanism by which polymers mediate this chemotactic response and their role in the pathogenesis of lung disease. Alpha-1-antitrypsin is a member of the serine protease inhibitor 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. Funding: Medical Research Council, The Wellcome Trust, Merck, Sharpe and Dohme, Wenner-Gren Center.

Key publications

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Scanning electron microscopy of Drosophila melanogaster used to develop fly models of the dementia FENIB and of Alzheimer’s disease. The fly faithfully reproduces many features of the human disease and is providing new insights into the pathways of neurodegeneration.
Secretion and endocytosis are fundamental processes occurring in all nucleated mammalian cells. Our group is interested in understanding how newly synthesised proteins are delivered from the Golgi complex to endocytic compartments and 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. Lysosomes have traditionally been viewed as the end point of the endocytic pathway that takes up macromolecules including nutrients and membrane proteins from the cell surface. In contrast it is now clear that lysosomes are dynamic organelles receiving membrane traffic input from the biosynthetic, endocytic and autophagic pathways. They are capable of fusing with late endosomes to form hybrid organelles where digestion of endocytosed macromolecules occurs and from which lysosomes are re-formed. Lysosomes can also fuse with the plasma membrane in response to cell surface damage to effect membrane repair. A key protein for these fusion processes is the membrane protein Vamp7. We have discovered binding partners of Vamp7 which appear to be involved in either ensuring that Vamp7 traffics correctly to lysosomes, or in regulating its function. We are also studying the function of ESCRT (endosomal sorting complex required for transport) proteins in health and disease. Evan Reid leads a subgroup interested in the function and molecular pathology of genes involved in the hereditary spastic paraplegias (HSPs), genetic conditions in which the long axons of motor neurons degenerate. There is an emerging functional relationship between HSP proteins and membrane traffic processes and we are investigating how abnormalities of the HSP proteins, spastin, spartin, atlastin and NIPA1, lead to functional deficits in traffic, or vesicle and organelle transport, resulting in axonal degeneration.

Funding: Medical Research Council, The Wellcome Trust
We are interested in two broad areas. 1) What normally controls energy balance and how does that go wrong in human obesity? 2) What are the normal mechanisms of insulin action and how do these go wrong in human states of insulin resistance? We take a multidisciplinary and highly collaborative approach to these problems. Our work in extreme human phenotypes has been particularly productive and we have identified seven previously unrecognized monogenic or oligogenic diseases resulting in human obesity or diabetes. We collaborate closely with Dr Ines Barroso at the Sanger Institute and Dr Nick Wareham at the MRC Epidemiology Unit and have created a formal consortium – the Genes for Energy balance and Metabolism (GEM) consortium to work on extreme phenotypes and large populations. Our work in functional genomics encompasses studies in \textit{in vitro} and \textit{ex vivo} cellular systems, in genetically modified animals and \textit{in vivo} physiological studies in human subjects. The research group is housed partly in the CIMR and partly in the home Department of Clinical Biochemistry. While the CIMR largely have the scientists involved in the obesity programme, there is continued exchange of expertise and personnel between groups in the two locations.

Funding: Medical Research Council, The Wellcome Trust, EU 6th Framework

a. Brain derived neurotrophic factor (BDNF) induces neurite outgrowth in PC12 cells stably expressing wild type TrkB, the receptor for BDNF.

b. We found a denovo mutation in TrkB (Y722C) in a patient with severe obesity and developmental delay. In cells transfected with the mutant TrkB, BDNF mediated neurite outgrowth is severely impaired.

\[ \text{Picture of neural outgrowth with BDNF in PC12.} \]
Transmembrane proteins and phospholipids are trafficked between intracellular compartments and the plasma membrane in carrier vesicles. Once the appropriate cargo has been sorted and concentrated into a forming vesicle, the vesicle buds from the donor membrane, is transported to and then fuses with the target membrane. The mechanical clathrin scaffold that surrounds clathrin-coated vesicles (CCVs) is linked to the phospholipid membrane and the transmembrane cargo embedded in it by a diverse group of proteins termed clathrin adaptors.

Adaptors are multidomain proteins or complexes of multidomain proteins built on a common design principle. Folded domains bind to protein cargo and phospholipids headgroups. For instance, AP complexes bind to motifs found on many cargo proteins such as YxxΦ motifs whilst other clathrin adaptors, termed CLASPs, bind only to a specific class of cargo such as arrestins to 7-transmembrane-helix, G-Protein Coupled Receptors (GPCRs) and ARH to Low Density Lipoprotein receptors. Multiple short motifs in unfolded regions that link adaptors’ folded domains bind with μM K\textsubscript{D}s to clathrin, the appendage domains of AP complexes and GGAs and other components of the CCV formation machinery. These interactions along with regulatory phosphorylation/dephosphorylation facilitate the assembly and disassembly of the dynamic network of proteins that are a CCVs coat. Other transport intermediates use non-clathrin containing cargo-selective coats such as COPI (Golgi to ER) and retromer (Endosome to Golgi) but that are constructed according to the same underlying principles as CCV coats.

We use X-ray crystallography biochemical and cell biological techniques to study the structure and function of components of cargo-selecting vesicle coats. Our current work focusses on AP2 and AP1, COPI complex (with Rainer Duden, University of London) and retromer (with Matthew Seaman, CIMR). In collaboration with Stefan Honing (University of Cologne) and Margaret Robinson (CIMR), we are also studying the role of cargo, small GTPases and phospholipid composition in clathrin adaptor recruitment to artificial membranes.

Funding: The Wellcome Trust, EMBO Young Investigator Programme
One of the most fundamental unresolved questions in cell biology is how cells manage to preserve the organization and integrity of the endocytic and exocytic systems, while maintaining the transport of lipids and proteins between these specialized organelles. 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 these vesicles with membranes is regulated in part by the specific interactions of a family of molecules known as SNAREs. In mammalian cells there are at least 38 SNAREs, each one being localized to a different compartment and involved in a subset of transport pathways. However, the precise role of many of the SNAREs has still to be elucidated. The aim of my research is to define the SNAREs involved in Trans Golgi Network (TGN) to endosome and TGN to cell surface transport by using a combination of mouse genetics, RNAi and cell based transport assays. This research will provide insight into how specificity is achieved in membrane transport and may also provide a framework for better understanding diseases caused by defects in membrane trafficking to the cell surface and endosomes.

Funding: Medical Research Council

Key publications


Recent developments in the stem cell field have highlighted the potential for medical applications arising from studies of human embryonic stem cells. Our group has chosen to focus on understanding fundamental mechanisms that underlie the biology of these pluripotent cells as the foundation for future progression to their possible therapeutic use. Our principal objective is to define the molecular and genetic basis for the maintenance of the pluripotent status of human embryonic stem cells, and similarly, the basis for their differentiation into the primary body lineages: mesoderm, endoderm and ectoderm. Previous studies had revealed that pluripotency of human embryonic stem cells was not maintained by similar mechanisms as for mouse embryonic stem cells, whose self-renewal depends on Leukemia Inhibitor Factor and Bone Morphogenetic Protein. Accordingly, we have examined the effects of other growth factors known to be important in cell fate decisions of mammalian and other vertebrate embryos. Surprisingly, we found that signaling through the Activin/Nodal pathway is critical for maintenance of pluripotency and that basic Fibroblast Growth Factor augments this pathway. Because Activin and Nodal are considered responsible for directing differentiation along the mesoderm and endoderm lineages during embryonic development, we hypothesise that their effects in human embryonic stem cells involve alternative intermediate transcription factor(s) and target genes. Of particular interest are Smad binding partners capable of altering the epigenetic status of the cells. As background for understanding such epigenetic mechanisms, we have analysed the expression of imprinted genes and their regulation by DNA methylation in human embryonic stem cells. We find that the overall epigenetic status of human embryonic stem cells is relatively stable during their derivation and extended culture, in marked contrast to that of mouse embryonic stem cells. Taken together, these findings illustrate the distinct biological nature of human embryonic stem cells in comparison to their mouse counterparts and underscore the need for further studies of the mechanisms underlying their differentiation into clinically useful lineages.

Funding: Medical Research Council, The Wellcome Trust, British Heart Foundation, Juvenile Diabetes Research Foundation, Department of Trade and Industries, National Institutes of Health (USA)

Key publications

Fig. 1 Human embryonic stem cell colony containing several hundred cells, surrounded by mouse fibroblast (“feeder”) cells.

Fig. 2 Human embryonic stem cell colony consisting of a mixture of green fluorescent protein and red fluorescent protein-expressing cells, illustrating their utility for gain-and loss-of-gene function studies (photo by Isabelle Bouhon).

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The group aims to understand the molecular mechanisms underlying intellectual disability in humans. To this end, our main focus is on families with X linked disease. In collaboration with The Wellcome Trust Sanger Institute, we are using a new approach to disease gene identification using systematic searches for mutations through the whole of the X chromosome. We have established a substantial collection of samples from families with X linked mental retardation (XLMR) by collaborating with genetics centres throughout the UK, Ireland, Australia, USA and Europe. We have identified new families with mutations in known XLMR genes and have identified a novel gene DLG3 that causes X-linked mental retardation. DLG3 forms part of the post synaptic density and is the first XLMR gene that has linked directly to NMDA receptor-mediated signalling and synaptic plasticity.

We are continuing to identify novel genes that cause X-linked mental retardation by screening the whole X chromosome in a cohort of 300 patients with intellectual disability. We are also determining the sequence variance of the X chromosome in these individuals that will subsequently provide invaluable sequence data for the wider genetics community.

The group has also characterised clinically and molecularly a new chromosome disorder on chromosome 3q29 associated with moderate intellectual disability. All affected individuals have an almost identical ~1.5 Mb deletion of genomic sequence and it is associated with haploinsufficiency of DLG1 and PAK2, genes closely homologous to known XLMR genes.

Future directions include the identification of genes underlying specific areas of intellectual disability using autozygosity mapping in consanguineous families and the development of functional assays of intellectual disability in the disease genes we have identified.

**Funding:** The Wellcome Trust, Medical Research Council, Birth Defects Foundation, Department of Health, Isaac Newton Trust

**Key publications**


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 proteins to study, we focus on potential drug or vaccine targets, the structures of which can be exploited in the development of new therapies.

One area we focus on is mechanisms by which viruses evade the host immune response. For instance, some viruses produce proteins that downregulate the expression of MHC class I, thus blocking the major mechanism by which virally-infected cells are detected. Other viruses produce proteins that intercept molecules such as chemokines and cytokines, thereby blocking signals that help to coordinate the immune response. We are also interested in the biochemical mechanisms of bacterial toxins, such as pertussis toxin.

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. A version of Phaser that solves structures by molecular replacement (i.e. using the known structures of related proteins) was released in mid-2004, and has already been credited with solving a number of structures that had eluded other programs. A new version, which will also solve novel structures using experimental phasing methods such as single-wavelength anomalous diffraction (SAD) and multiple isomorphous replacement (MIR), is currently under development.

Funding: The Wellcome Trust, National Institutes of Health (USA)

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Structure of the vRING domain of the K3 protein from Kaposi’s sarcoma-associated herpesvirus. K3 acts to downregulate surface expression of MHC class I by recruiting cellular ubiquitin-conjugating enzymes to target it for destruction. This structure was determined by NMR methods in collaboration with the group of Mark Bycroft (Cambridge Centre for Protein Engineering), as part of a collaboration with Paul Lehner in CIMR. The work is described in R.B. Dodd et al., *J. Biol. Chem.* 279, 53840-53847 (2004).
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. The coats on these vesicles consist primarily of two components: clathrin and adaptor complexes. The AP-1 adaptor complex is associated with vesicles budding from intracellular membranes, and the AP-2 complex with vesicles budding from the plasma membrane. We have discovered two additional adaptor complexes, AP-3 and AP-4, which appear to be able to function independently of clathrin. A subset of patients with the genetic disorder Hermansky Pudlak syndrome (HPS) have mutations in AP-3 subunits, resulting in less efficient trafficking of cargo proteins to lysosomes and related organelles, such as pigment granules.

In addition to the adaptor complexes, it is now clear that there are also alternative adaptors. Our working hypothesis is that for each trafficking pathway, there will be a number of different adaptors, each recruited independently onto the appropriate membrane. Once on the membrane, the various adaptors would all work together to package different types of cargo into the newly forming vesicle, by binding to distinct sorting signals on cargo proteins and at the same time interacting with each other. One such alternative adaptor is epsinR, which we found initially as a binding partner for AP-1, and which we have recently shown to be an adaptor for the SNARE protein vti1b. Current studies in the laboratory include searching for new alternative adaptors and sorting signals, and then matching the two together; and investigating how the HIV-1-encoded protein Nef is able to exploit adaptor-mediated trafficking to evade the immune system of the host.

Funding: The Wellcome Trust, Medical Research Council

Key publications


Codon Reiteration Diseases – Pathogenic Pathways and Therapeutic Strategies

David Rubinsztein

Key publications


We are studying 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. Our research aims to elucidate pathogenic pathways and to develop therapeutic strategies. We have developed a range of tools to allow us to study these diseases ranging from stable inducible cell models, through Drosophila and zebrafish transgenic models to transgenic mice. Current major collaborators include Steve Brown, Cahir O’Kane and Paul Goldsmith/DanioLabs.

Our recent HD work has focussed on the factors regulating the levels of the toxic product that is formed after proteolytic cleavage of full-length huntingtin. We showed that cleavage is regulated by cdk5-mediated huntingtin phosphorylation. Steady-state levels of mutant huntingtin fragments are also regulated by clearance, which may be more therapeutically tractable. We showed that autophagy is a key pathway regulating the clearance of mutant huntingtin fragments and other aggregate-prone proteins. Autophagy can be upregulated by rapamycin via mTOR inhibition and we have demonstrated therapeutic efficacy of this compound in cell, fly and mouse models of HD. We have been characterising new pathways for inducing autophagy that are mTOR-independent and have demonstrated that dyneins are a key component of the autophagic machinery. Ongoing work is aiming to elucidate other novel components of the autophagic machinery and signalling pathways that regulate this process.

Recent OPMD work has focussed on our new transgenic OPMD mouse model. We have been investigating therapeutic approaches and found that doxycycline or trehalose reduced aggregate formation and attenuated toxicity in vivo. Since these are safe drugs, they may represent viable therapeutic strategies.

Funding: Medical Research Council, The Wellcome Trust, EU, DTI (Knowledge Transfer Partnership), Wyeth, SienaBiotech, Muscular Dystrophy Campaign

Electron micrograph in intranuclear aggregate of PABPN1 in mouse model of oculopharyngeal muscular dystrophy generated by Rubinsztein lab.
Autosomal dominant polycystic kidney disease (ADPKD) is a common nephropathy characterised by multiple renal cysts and renal failure. It affects 1:1000 of the population. Mutations in PKD1 and PKD2 account for almost all cases. PKD1 encodes polycystin-1, a multi-domain membrane spanning glycoprotein that functions as part of a large cell surface mechanosensitive ion channel and signalling complex. It is localised to the basolateral plasma membrane and more recently has been shown to be part of the centrosome/basal body/cilial complex.

The primary focus of research in my group is to determine the structure and function of individual polycystin-1 domains and therefore elucidate the mechanisms underlying the development of renal cysts. In particular we are studying individual protein domains and their ligands and motifs that regulate polycystin-1 localisation and signalling. Important polycystin-1 ligands identified so far include members of the tyrosine phosphatase family, microtubule binding proteins and several novel centrosomal proteins of unknown function. Intriguingly most of these are centrosomal/cilial proteins. We are also studying the multiple PKD domains of polycystin-1 and their possible role in mechanotransduction. This work is complemented by the use of model organisms such as mouse, zebrafish and drosophila to look at cilial function and its role in renal cystogenesis. Further work focuses on the regulation of polycystin-2, the product of the PKD2 gene, which forms a calcium permeable ion channel complex with polycystin-1.

Because of our developing interest in the centrosome my group is also examining the role of novel centrosomal proteins in other human diseases.

Funding: The Wellcome Trust

Renal epithelial cells have a single primary cilium projecting from their apical surface. Abnormalities in the primary cilium are implicated in the pathogenesis of several types of renal cystic disease including autosomal dominant polycystic kidney disease (ADPKD). Cells have been stained with antibodies to acetylated alpha-tubulin (red) to identify the cilia and nuclei (blue) have been stained with DAPI. A novel protein that interacts with polycystin-1 is seen using a GFP tag. It can be clearly seen in the centrosome-derived basal bodies at the base of the cilium and also concentrated at the cell membrane, a pattern that overlaps extensively with polycystin-1.
Eukaryotic cells are organised and compartmentalised by many membrane-bound intracellular organelles each with a specific function and set of resident proteins. Transport between organelles is mediated by vesicular or tubular carriers that are formed through the action of cytoplasmic ‘coat’ proteins. A good example of these processes is the transport of acid hydrolases from the trans-Golgi network (TGN) to the lysosome. This is mediated by specific receptors that cycle between the TGN and pre-lysosomal endosomes. The cation-independent mannose-6-phosphate receptor (CI-MPR) is responsible for much of the sorting and delivery of acid-hydrolases to the lysosome and as such cycles rapidly between the TGN and endosomes.

We are interested in the endosome-to-TGN retrieval pathway and have been focusing our efforts on the characterisation of a putative coat complex called ‘retromer’. Retromer comprises 5 proteins which are conserved from yeast to humans (see Fig. 1). Studies in yeast and mammalian cells have shown that retromer is necessary for endosome-to-TGN retrieval.

Our current hypothesis is that VPS35, VPS26 and VPS29 recruit cargo whilst SNX1/SNX2 drive vesicle and/or tubule formation. SNX1 (and also SNX2) contain PX domains that bind to phosphatidylinositol 3-phosphate (PtdIns 3-P) and also BAR domains that can drive tubulation. Through a collaboration with Dr David Owen (CIMR) the crystal structure of VPS29 has been solved and found to be very similar to protein phosphodiesterases (see Fig. 2). Using the structural data, point mutations in both yeast and mammalian VPS29 have been engineered and expressed in order to determine the functional significance of the similarity of phosphodiesterases.

We are also attempting to identify proteins that function with retromer in the endosome-to-TGN retrieval of the CI-MPR and we are investigating what motifs or signals are present in the CI-MPR tail that mediate its retromer-dependent retrieval.

Funding: Medical Research Council

![Fig. 1. Schematic diagram of retromer. The retromer complex assembles on the endosome membrane selecting cargo such as the CI-MPR. The co-ordinated action of the PX domains and BAR domains enable the SNX proteins to drive vesicle and/or tubule formation.](image1)

![Fig. 2. Ribbon diagram of the crystallographic structure of VPS29. This is similar to the structure of known phosphodiesterases such as PP2A.](image2)
The nuclear envelope forms a selective boundary around chromosomes that consists of two concentric lipid bilayers, the outer and the inner nuclear membrane, joined with one another at the nuclear pore complexes. In all eukaryotic cells the nuclear membrane expands during the cell cycle to accommodate changes in chromatin structure and content. In yeast nuclear membrane expansion allows anaphase to take place within the confines of an intact nucleus that partitions between mother and daughter cell. In metazoan cells the nuclear membrane expands at the end of mitosis to accommodate chromatin decondensation and later on DNA replication. We are interested in understanding 1) how do cells coordinate nuclear membrane growth with cell cycle progression 2) how is newly synthesized membrane incorporated into the nuclear envelope 3) what are the factors that control the size of the interphase nucleus.

We have recently shown that the yeast lipin Smp2 is phosphorylated by mitotic cyclin-Cdc28/Cdk1 and dephosphorylated by the nuclear membrane bound phosphatase Nem1-Spo7. Loss of dephosphorylated Smp2 causes transcriptional upregulation of key endoplasmic reticulum enzymes involved in lipid biosynthesis concurrent with a massive expansion of the nucleus. Therefore Smp2 is a key factor coupling membrane biogenesis with nuclear growth. We are now using a combination of genetics and biochemistry to characterize the function of downstream effectors of Smp2. We are also investigating how chromatin anchoring to the inner nuclear membrane could regulate nuclear size.

Smp2 belongs to a large family of evolutionarily conserved proteins present in eukaryotic species. Mammals express three Smp2 homologues, Lipin 1, required for adipocyte differentiation and whose mutation results in fatty liver dystrophy in mice, Lipin 2 and Lipin 3. We are currently investigating the function of the conserved Nem1 phosphatase/Lipin network in nuclear envelope dynamics in higher eukaryotes.

Funding: The Wellcome Trust

Key publication
The immune system has evolved to defend us from infection, but defects in the regulation of immunity can give rise to autoimmune disease. We have two inter-related research programmes aimed at understanding how defective immune regulation impacts on human disease.

The first aims to increase our understanding of the regulation of immune reactivity, and the role that defects in this play in predisposition to autoimmunity, infection and transplant rejection. We have examined in detail an inhibitory immune receptor, FcγRIIb, which acts as a “brake” on the immune system. We have shown that when naturally occurring polymorphisms render this “brake” ineffective, mice are predisposed to autoimmune diseases such as systemic lupus erythematosus (SLE). These SLE-associated polymorphisms are common in wild mice, suggesting they may provide an evolutionary advantage by protecting from infection. This led to the discovery that FcγRIIb controls the balance between defence from infection and susceptibility to septic shock. More recently we have shown that a single transmembrane domain mutation in FcγRIIb in humans abolishes its inhibitory effect by excluding it from lipid rafts, a novel mechanism for altering receptor function. This mutation is not only associated with SLE, but it may protect from certain infectious diseases, helping explain the evolution of human predisposition to autoimmune disease.

We are studying a number of other aspects of inhibitory receptor function, and mechanisms by which these receptors can be manipulated for therapeutic ends.

To pursue our second programme, the Cambridge Hinxton Centre for Translational Research in Autoimmune Disease (CHiC TRIAD) was established. This is a collaboration between clinicians from Addenbrooke’s Hospital, immunologists and clinician scientists from the CIMR (led by Paul Lyons), and bioinformaticians from the European Bioinformatics Institute. The project is integrating clinical and laboratory data to examine how gene expression signatures determined by microarray can be used to study autoimmune diseases such as SLE and vasculitis, as well as transplant rejection. The aim is to predict therapeutic responses, allow tailoring of treatment in individual patients, and deepen our understanding of the aetiology and pathogenesis of these important medical problems.

Funding: The Wellcome Trust, Medical Research Council, Genzyme Renal Innovations Programme, Arthritis Research Campaign, Kidney Research UK, Roche Ltd

Key publications

Fig 1. CD4 T cell gene expression profiles distinguish vasculitis patients pre- and post-treatment. Patients with ANCA-associated vasculitis had their leucocyte subsets purified and assessed by microarray before and three months after treatment with either rituximab (a B cell depleting antibody) or cyclophosphamide. Data is shown for 759 genes that show > 2-fold change in expression following treatment, for the first 5 patients (all of whom went into clinical remission). Hierarchical clustering using data from 3343 genes called present on every array clearly distinguishes samples obtained pre- and post-treatment, and shows evidence of treatment-specific changes in gene expression.

Fig 2. The lupus-associated T232 polymorphism in the transmembrane domain abolishes the inhibitory function of FcγRIIb by excluding the receptor from lipid rafts. Intracellular calcium measurements in the human U937 monocyte cell line, either untransfected (black), or transfected with FcγRIIb T232 (red) or FcγRIIb T232 (blue), after FcγRI aggregation at 0 seconds. The insert shows the average peak calcium response normalized to untransfected cells (see Floto et al. Nature Medicine 2005).
Our aim is to discover the molecular bases 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. We have discovered three of the genes in type 1 diabetes, the immune recognition genes HLA class II on chromosome 6p21, a sequence repeat variant of the insulin gene promoter on chromosome 11p15 and, most recently, the immune homeostasis gene CTLA4 on chromosome 2q33. We have confirmed a fourth gene, PTPN22, and have strong evidence for a fifth, the CD25/IL2RA gene on chromosome 10p. We aim to further understand the functional consequences of these disease-associated variants as well as to identify other genes in our search for therapeutic opportunities that are based on disease mechanism and genotype.

Our research efforts are embedded within the Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory, which facilitates the collaboration between other investigators in the CIMR, Linda Wicker, David Clayton, and beyond, in the Department of Biochemistry (Kevin Brindle), the Department of Paediatrics (David Dunger), the Wellcome Trust Sanger Institute and the MRC Epidemiology Unit. Our goals include the training and career development of individuals, at all levels from technical staff through PhD studentships to senior research associates, to become fully competent medical researchers, skilled in computing, statistics, genetics and biological techniques.

Funding: The Wellcome Trust, Juvenile Diabetes Research Foundation, Medical Research Council, Cambridge-MIT Institute, National Institutes of Health (USA)

Key publications


Genotypes of the type 1 diabetes-associated single nucleotide polymorphism, Arg620Trp, in the PTPN22 gene, which encodes the lymphoid specific phosphatase, in approximately 800 type 1 diabetes cases and 800 controls from Great Britain. The fluorescence signal intensity results for the two alleles are shown in blue and red, and were generated using a new highly multiplexed genotyping technology (MegAllele).
The idea of a well resourced and focused effort to elucidate the genetics and mechanisms of the common autoimmune disease type 1 diabetes (T1D), which became the JDRF/WT DIL, was based initially on discussions in November 1999 between John Todd, the JDRF and the Wellcome Trust. An application was submitted to the JDRF and Wellcome Trust in April 2000 and awarded October 2000. The five-year award funded a major computing effort, including expert network and hardware support, data management, genome informatics and statistical genetics. Coupled to this new infrastructure are other facilities including capillary-based high throughput DNA sequencing for SNP harvesting, high throughput genotyping, collection costs for large numbers of families and cases-controls, immunology and cell biology including FACS and microscopy. We have created a world-class facility and team to locate, identify and analyse the function of genes determining T1D risk.

Last year, the JDRF/WT DIL was extended for another five years to 2010. Our goals remain the same – genes and mechanisms in T1D – with immediate challenges of genome-wide searches for susceptibility genes and the study of immunological phenotypes in human blood and their correlation with genotypes that determine T1D and autoimmune disease development.

Key publications


Defence of the organism is an indispensable function of the genome, and a significant fraction of human genes is dedicated to immune responses. Some immune genes continually evolve in response to novel pathogens. Their roles are reflected in their organisation and polymorphism. We have chosen to study a key cluster of human genes, the human major histocompatibility complex (MHC), because many of the expressed genes in its ~4 Mbp are related to immunity. 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, may 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. Class I molecules interact with αβ and γδ receptors on T cells, for example. Further information on the state of health of a cell is provided by their interaction with other receptors, such as those 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.

Funding: The Wellcome Trust, Medical Research Council, Cancer Research UK

Key publications


Our group is focused on understanding the molecular and cellular mechanisms of autoimmune syndromes such as type 1 diabetes (T1D) by identifying and characterising 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, including its absolute insulin-dependence. We have discovered that in both species, differential expression of CTLA-4 splice forms alters disease susceptibility. Following the discovery of a disease gene we next attempt to correlate the disease-
protective and disease-resistant genotypes with phenotypic changes in immune cell populations that contribute to the destruction of self-tissues. In humans, a correlation of the CTLA-4 genotype with the accumulation of a CD8-positive memory T cell subset in the peripheral blood of healthy donors has been discovered suggesting that reduced negative regulation mediated by a CTLA-4 susceptibility allele may be evident early in the disease process. Such alterations in peripheral blood cell populations could serve as a clinical biomarker in the future.

Another molecule encoded by a mouse T1D gene under study in the laboratory is IL2, a lymphokine absolutely required for the maintenance of immune homeostasis in humans and in mice. Analogous to humans and mice sharing CTLA4 as a T1D gene, humans have a T1D susceptibility gene encoding CD25, the alpha chain of the IL2 receptor, and mice have IL2 alleles that alter the amount of IL2 produced. DNA variants that mediate a very modest reduction in IL2 production in NOD mice correlate with increased beta cell destruction, a reduced ability to respond to the induction of donor-specific transplantation tolerance, and reduced numbers and functionality of CD4-positive regulatory T cells. Defining how autoimmunity genes control such cellular phenotypes will contribute to understanding disease pathogenesis.

Funding: The Welcome Trust, Juvenile Diabetes Research Foundation, Cambridge-MIT Institute, National Institutes of Health (USA)
We are involved in a number of autosomal recessive diseases that cause mental and physical handicap but the predominant focus of our research is MCPH, which appears to be a primary disorder of neuro-genic mitosis. The MCPH brain is small but architecturally normal and the only effect 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 – there are at least eight and we have identified four of these. Now we are also trying to find what these genes do and how their perturbation leads to a small human brain. Two major unexplained problems in neurogenesis are: how does the neuro-epithelium containing the neural precursors know how many neurones to produce; and how is the switch from symmetric (progenitor expansion) to asymmetric cell division (which generates neurones) controlled. It is likely that MCPH is a disease of one of these processes, but which one?

This work benefits families, as we can offer DNA testing. But also it may help unravel the complexities of neurogenesis, with implications for neural stem cell therapy. Finally, it appears that the same MCPH genes that when mutated can make a small brain, are also involved in making out species brain so large. Studies of the MCPH1 and MCPH5 genes show that they have undergone positive selection in the primate lineage. Throughout the primate lineage there has been a step wise increase in brain size, culminating in our brains being three times the relative size of our nearest ape relatives, the chimp and gorilla. Only dolphins have a brain almost as large as ours!

Funding: The Wellcome Trust, Birth Defects Foundation, Pfizer Ltd

**Key publications**


Age-related macular degeneration (AMD) is the leading cause of visual impairment in the elderly and the commonest cause of blindness in the developed world. AMD is a multifactorial disorder in which both genetic and environmental factors are important. Identifying the genes involved should contribute to understanding the pathogenesis of the disease. The main aims of the research are to obtain better data on the genetics of AMD and to investigate candidate susceptibility genes. Clinical evaluation and sampling has been completed in 700 cases and 400 controls and is ongoing. Clinical data on 170 siblings of index cases are currently being analysed to determine which components of the phenotype are most heritable and provide better estimates of $\lambda_S$. Association studies in the case-control sample have confirmed that the e2 allele of the apolipoprotein E gene confers increased risk of AMD. No evidence of association has been found with polymorphisms in the genes for angiotensin I converting enzyme, cystatin C, cathepsin D or fibulin 6. It has recently been shown that the common polymorphism Y402H (1277T>C) in the complement factor H gene is an important determinant of risk for AMD. We have confirmed this in our sample and shown that the risk is similar for the two end-stage forms of AMD, geographic atrophy and choroidal neovascularisation, and applies to smokers and non-smokers. We are now investigating other genes in the alternative complement pathway.

Funding: Medical Research Council

Key publications
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.
Extracellular proteinases are key players in the regulation of the cellular environment, acting as major effectors of both cell-cell and cell-extracellular matrix (ECM) interactions. They are involved in modifying ECM integrity, growth factor availability and the function of cell surface signalling systems, with consequent effects on cellular differentiation, proliferation and apoptosis. Epithelial tumours evolve in a multi-step manner, involving both inflammatory and mesenchymal cells. Although intrinsic factors drive malignant progression, the microenvironment of neoplastic cells is a major feature of tumourigenesis. Our premise, that proteinases are integral to the regulation of extrinsic effectors, is the basis for our work and for our plans to dissect events at the cellular and molecular level, as well as proceeding to complex tumour models addressing tumour-stromal interactions.

Our research is currently focussed on cell surface associated forms of the zinc-dependent proteinases, notably the membrane type matrix metalloproteinases (MT-MMPs) and the disintegrin-type metalloproteinases (ADAMs), and the natural inhibitors that control them, the tissue inhibitors of metalloproteinases, TIMPs. We aim to elucidate how these metalloproteinases and inhibitors function and what their importance is as effectors of both physiological processes and pathologies, such as cancer. The development of novel reagents for disease therapy and diagnosis will emerge from the fundamental data accrued.

The Murphy Group will be moving into the Cancer Research UK Cambridge Research Institute in the summer of 2006.
We have a long term interest focusing on the relationship between tissue stem cells and cancer using transgenic inducibility systems. Recently a fundamental relationship has been posited: that cancers retain populations of stem-like cells analogous to those in the renewing epithelia in which many of them arise. Such cancer stem cells are speculated to be pluripotent, divide infrequently and be a small subpopulation with properties significantly differing from those of the bulk tumour. Yet relatively little is known about the biology of normal stem cells, let alone how their properties are altered or retained within cancers. Our transgenic strategy to understand the processes normally controlling stem cells and how these are subverted during carcinogenesis has been to introduce specific gene mutations into fully formed adult gut epithelia and to follow any resultant genotype over time.

The development and validation of an appropriate system has been the work of many years. Last year we described a transgenic approach for transcriptionally switching on the site specific recombinase, Cre, using a cytochrome P450 (CYP1A1) promoter following brief induction with fat-soluble xenobiotic. The power of the model is in allowing control of the timing and amount of recombination at any appropriately engineered Cre-target loci in the intestinal epithelium.

Subsequent developments and applications have been rapid. One obvious candidate for analysis was the APC (Adenomatous polyposis coli) tumour-suppressor gene loss of which is associated with greater than 85% of sporadic colorectal cancers and is a central mediator of Wnt signalling. In collaboration with a group in Cardiff we determined the primary consequence of deleting APC within the intestine. Within 5 days of Cre-mediated deletion of both copies of APC there was dramatic dysplasia throughout the intestine. Affymetrix array analysis of the epithelium confirmed that all known targets of aberrant Wnt signalling were perturbed and identified new targets which are the subject of further characterisation.

Currently the model is (or has) been applied to look at other major signalling pathways (Notch, integrin), to act as a clonal marker of stem cells by low density recombination, and validated for other tissue systems including liver and epidermis.

The Ponder/Winton Group will be moving into the Cancer Research UK Cambridge Research Institute in the summer of 2006.
Principal Investigators who expect to move on from CIMR shortly

Kerstin Meyer  Regulation of Immunoglobulin Gene Diversification

One of the key features of our immune response is its ability to maintain a memory of a previous infection. When we meet a pathogen for the second time, our immune system reacts faster and the response is more specific. The increase in specificity is in part due to the generation of antibodies able to bind the invading pathogen more tightly. At the molecular level this is achieved by diversifying the antibody or immunoglobulin genes.

To better understand this process we have studied the chicken IgL locus in the chicken B cell line DT40 which can diversify its antibody genes either by gene conversion or somatic hypermutation. Both these processes are closely linked to the transcriptional regulation of the locus. Using knock-out analysis we have demonstrated that the IgL 3’ enhancer is essential for the activation and maintenance of gene expression and is able to activate gene conversion via the transcription factor E2A. Interestingly E2A activates diversification without an apparent increase in the rate of IgL transcription.

Key publications


Karin Römisch  Protein Transport Across the ER Membrane in Health and Disease

Communication between cells is mediated by secreted molecules and transmembrane proteins at the cell surface. Breakdown of communication has severe consequences, such as cancer, diabetes, and autoimmune diseases. Protein trafficking to the cell surface is therefore tightly controlled. Protein quality control in the first compartment of the secretory pathway, the endoplasmic reticulum (ER), prevents misfolded proteins from entering ER-to-Golgi transport vesicles, and results in export of misfolded proteins to the cytosol for degradation. I am aiming to understand the processes leading to protein misfolding in the ER, protein export across the ER membrane, and degradation in the cytosol.

In the future, I will focus specifically on two areas, misfolding of proteins in the ER lumen, and the structure/function relationship of the protein translocation channel in the ER membrane. I will use comparative genomics and proteomics in conjunction with biochemical experiments to characterize the ER folding environment and ER translocation machinery in extremophile vs. temperate organisms, and in parasitic protozoa vs. mammalian ER to gain a better understanding of ER-related protein processing. In addition, I will investigate the effects of specific mutants in the ER protein translocation machinery which are linked to human diseases.

Key publications


Principal Investigators who have moved on from CIMR since Research Report 2004

Moved on to: Contact at:

**Martin Bobrow**
Deputy Chairman, Board of Governors, Wellcome Trust
Retired from the Chair of Medical Genetics
Contact at: http://www.wellcome.ac.uk

**Heather Cordell**
Chair of Statistical Genetics Institute of Human Genetics University of Newcastle upon Tyne International Centre for Life Central Parkway Newcastle upon Tyne NE1 3BZ
Contact at: http://www.ncl.ac.uk/ihg/

**Rainer Duden**
Chair of Cell Biology & Biochemistry School of Biological Sciences Royal Holloway University of London Egham Surrey TW20 0EX
Contact at: http://www.rhul.ac.uk/Biological-Sciences/

**Penny Stein**
NHS Specialist Registrar & Wellcome Trust Senior Research Fellow in Clinical Sciences Department of Medical Biochemistry University of Cambridge Addenbrooke's Hospital Hills Road Cambridge CB2 2QQ
Contact at: http://www.clbc.cam.ac.uk
About 60 of our 250 scientists in CIMR are postgraduate students carrying out research towards a PhD degree. Most students are carrying out standard 3-year PhD programmes, supported by Research Council Studentships, Clinical Training Fellowships, or with awards from overseas funding bodies. There is a balance of clinicians (clinical training fellows or MB, PhD students) and basic scientists working towards a PhD.

**Wellcome Trust 4-year PhD Programme in Infection and Immunity**

This is a joint venture between CIMR, other departments in the Clinical School, the Department of Pathology, and the Veterinary School and has an intake of 5 students each October. The Director of the Programme is Professor Douglas Fearon FRS (Department of Medicine) who is a member of the CIMR Institute Management Committee.

**Aim of the programme:** Infectious diseases remain the major cause of mortality and morbidity throughout the world. Intriguingly, reduction in infectious disease burden associated with successful interventions, and/or a rise in socio-economic status, leads to an increase in allergic and autoimmune disease prevalence. Our ability to understand and control these changing disease patterns will be dependent upon the training of a new generation of scientists equipped with a set of analytical and technical skills which will allow them to study Infection and Immunity in new and exciting ways. The aim of this 4-year PhD programme in Cambridge is to contribute to the training of this new generation of scientists.

We have brought together a unique combination of research scientists (about 50% of them in CIMR) to act as mentors and supervisors to the students selected for our 4-year PhD programme.

Our broad programme in infection and immunity is underpinned by scientists who can provide training in genetics (including genetic statistics, biorobotics, and bioinformatics), immunology, infection, cell biology, developmental biology, and structural biology. Clearly no student can become the ultimate expert in all of the areas mentioned above. Our aim is to provide exposure to a wide spectrum of laboratories and experimental approaches in the first year. This allows the student to gain postgraduate level knowledge and technical knowledge of these areas prior to selection of a main PhD project. A major goal of our programme is to encourage projects that will bring together groups working on infectious and autoimmune diseases with basic science partners in the intellectual development and supervision of the student’s main PhD project. In this way we hope to open doors that will permit our students access to areas of science too often compartmentalised, and to encourage them to think laterally in the development of their own project area.

**MRC Studentships**

CIMR has several MRC research students, each with 3 years funding, working towards a PhD. Each year, CIMR receives sufficient funds from the University’s MRC doctoral training grant to select 3 students for PhD training. All Principal Investigators in CIMR are eligible to be PhD supervisors of MRC students. Selection of applicants, as in the case of the Wellcome Trust 4-year PhD programme, is on the basis of academic excellence and research potential. Applicants may apply to work with any Principal Investigator as their supervisor. An application timetable is published on the CIMR website.
14–15 March 2005
Wellcome Trust Conference Centre, Hinxton, Cambridge

The 2005 Retreat was once again a time for post-doctoral fellows and graduate students to present their work to the whole Institute. The presentations were of a universally high standard which allowed discussion and cross-fertilisation of ideas between research groups. Andres Floto (Ken Smith’s group) was awarded the prize for the best post-doctoral presentation and Richard Page (David Lomas’ group) was awarded the prize for the best presentation by a graduate student. Our congratulations to both speakers. We were extremely fortunate this year to have three outstanding presentations from external speakers. The first two, Tim Hunt and John Walker, both being Nobel Laureates. Tim Hunt gave a wonderful description of the discovery of cyclins and their role in cell biology whilst John Walker gave a superb presentation on the structural biology underlying the function of F1 ATPase. The third presentation was a tour de force by Julie Ahringer who demonstrated the power of genome-wide RNAi screening in C. elegans. Overall the Retreat covered a great deal of high quality science and was enjoyable for all those who attended.

David Lomas
Deputy Director
A core team of approximately 40 staff headed by the Institute’s Administrator, Sarah Smith, supports the Institute’s scientific work and aims to provide an efficient, effective and approachable support service to all members of the Institute.

The Administrator’s team is divided into three discrete functions. The Administrator has specific responsibility for personnel issues and grants functions whilst providing a direct link with the University central staff. A Finance Officer, Susan Reeder, has specific responsibility for the day-to-day management of the grants and accounting functions, whilst Dave Cheesman, who we are pleased to welcome following the retirement of Ian Flack, manages the third area, laboratory and facilities. He is assisted by a team of technicians and is responsible for overseeing the provision of core laboratory services as well as management of the building facilities.

Within the core support team is the IT Officer whose staff look after the Institute’s computer network and provide a support service to users, including setting up and maintaining the Institute’s internet and intranet pages. Additionally, one of the IT staff looks after the running of a Graphics Unit.

There have been a few changes to the structure of the administrative support team since the last report, which were implemented to reflect changes in the wider environment and ensure that the administration is in a position to respond to these changes appropriately. One area that has expanded, partly as a result of new legislation, is the personnel field. Conversely, the Accounts Payables and Purchasing Sections have been amalgamated which has enabled greater flexibility as each member of the unit is able to carry out tasks performed by other team members. As a direct result of this, we have been able to reduce the number of staff employed. Additionally, by amalgamating the glasswash and media kitchen functions under a supervisor, we have also been able to streamline the unit whilst maintaining the level of service provided. These reorganisations have thus released resources for areas of direct scientific support which will be utilised as required.

Additionally, some of the support staff, although managed by CIMR, are jointly funded by the University and the MRC. These include the building services and maintenance unit, receptionists and custodial services. However, other services such as security, cleaning and catering are contracted out.
Funding of CIMR

Total grant income continues to be in the region of >£14 million p.a. Overall Wellcome Trust support remains at approximately 70% 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.

Recurrent Costs for CIMR
August 2003 – July 2004

Recurrent Costs for the Wellcome Trust/MRC Building & CIMR
August 2003 – July 2004

Recurrent Costs for CIMR
August 2004 – July 2005

Total Value of Grants Held in CIMR

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<th>Year</th>
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<th>Wellcome</th>
<th>Other</th>
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Other Information

Honours, Awards and Personal Fellowships

Principal Investigators

Heather Cordell: Wellcome Trust Senior Research Fellowship in Basic Biomedical Science 2004.
Allison Green: Wellcome Trust Senior Research Fellowship in Basic Biomedical Science 2004.
Brian Huntly: Jose Carreras young investigator prize of European Haematology Association 2005; MRC Senior Clinical Research Fellowship 2005.
Hisao Kondo: Wellcome Trust Senior Research Fellowship in Basic Biomedical Science 2005.
Paul Lehner: FMedSci 2004; Lister Institute Research Prize for 2004 (£150,000); Personal Professorship 2005.
Lucy Raymond: University Senior Lectureship 2005.

Research Scientists

Menna Clatworthy: Medical Research Society Young Investigator of the Year 2005 (UK wide); AEG Raine Award, British Renal Association 2005.
Sadaf Farooqi: House of Commons Science, Engineering and Technology Young Researcher of the Year (Bioscience category) 2005.
Andres Floto: Medical Research Society Young Investigator of the Year 2004 (UK wide); Best Postdoctoral Presentation Prize, CIMR Annual Research Retreat 2005.
George Follows: Leukaemia Research Fund Senior Clinical Research Fellow 2004.

Kouki Harasaki: Five University of Cambridge scientists were named the UK’s brightest biotechnology prospects after winning the final of a national competition ‘Biotechnology YES’ (the team received £1,000) 2003.
Christopher Johnson: Wellcome Trust Clinical Research Training Fellowship 2005.
Stefan Marciniak: Wellcome Trust Research Travelling Fellowship 2005.
James Nathan: Wellcome Trust Research Training Fellowship 2005.
Evan Reid: Wellcome Trust Advanced Fellowship for Medical & Dental Graduates 2004.
Aiwu Zhou: Alpha-1 Foundation Postdoctoral Fellowship 2004; British Heart Foundation Basic Science Lectureship 2005.
Editorial Boards of Journals

Jennie Blackwell is a member of the editorial boards of Immunology and Genomic Medicine.

David Clayton is a member of the editorial boards of Annals of Human Genetics and The Stata Journal.

Heather Cordell is on the editorial board of Annals of Human Genetics.

Tony Green is on the editorial boards of British Journal of Haematology, Journal of Experimental Haematology and Blood Reviews.

Fiona Gribble is on the editorial board of Endocrinology.

David Lomas is an associate editor of Thorax and on the editorial boards of the Journal of Chronic Obstructive Pulmonary Disease and Current Respiratory Medicine Reviews.

Paul Luzio is on the editorial board of Traffic.

Stephen O’Rahilly is on the editorial boards of Journal of Clinical Endocrinology & Metabolism and PhD Biology.

Bruce Ponder is Editor in Chief of Breast Cancer Research and a member of the editorial board of Cancer Cell.

Karin Römisch is on the editorial boards of Molecular Biology of the Cell and Biomed Central Cell Biology.

David Rubinsztein is on the editorial committee of Foxwell and Davies Publishers (Clinical Science) and on the editorial boards of Human Molecular Genetics, Autophagy and the Journal of Applied Biomedicine.

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

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

John Todd is on the editorial board of Human Molecular Genetics.

John Trowsdale is on the editorial boards of European Journal of Immunology, Human Immunology and Immunogenetics; an editor of Immunology and an associate editor of Tissue Antigens.

Linda Wicker is advisory editor of Journal of Experimental Medicine.

Staff Affiliations

Jennie Blackwell is a member of the Beit Memorial Research Fellowship Selection Committee and of the MRC Research Advisory Board.

Krish Chatterjee is a member of the MRC Research Advisory Board.

David Clayton is Foreign Adjunct Professor, Karolinska Institute, Stockholm; World Health Organisation appointed co-ordinator of the Karonga prevention trial (a large-scale immuno-prophylactic leprosy trial) and a member of MRC ASTRAL Trial Steering Committee.

Tony Green is chairman of the Scientific Advisers to the Kay Kendall Leukaemia Fund; chairman of the Education Committee of the European Haematology Association; a member of the Scientific Programme Committee of the European Haematology Association and a member of the Joint MRC and UK Stem Cell Foundation Scientific Advisory Board.

Fiona Gribble is a member of the National Kidney Research Fund External Referee Panel.

Fiona Karet is on the Grants Committee of the National Kidney Research Fund and is on the Program Committees for the American Society of Nephrology’s 2006 Annual Meeting and the International Society of Nephrology’s 2007 meeting.

David Lomas is a member of the British Lung Foundation Grants Committee; a member of the Alpha One Foundation Grants Committee (vice-chair); a member of the Alpha-one antitrypsin Laurell Training Award (ALTA) Grants Committee; a member of the MRC College of Experts and a member of the Executive Committee of the Association of Physicians.

Paul Luzio is a member of the Research Councils’ Individual Merit Promotion Panel and a member of the MRC College of Experts.

Stephen O’Rahilly is chairman of the Medical Research Society; a member of the Academy of Medical Sciences Council; a member of The Royal Society Sectional Committee 10 and the Biological Sciences Awards Committee; a member of the Scientific Advisory Council of the Dublin Molecular Medicine Centre and the Dublin Centre for Human Proteomics and a member of Sub-panel 5 of the Research Assessment Exercise 2008. Also chairman & co-founder of Cambridge Clinical Research (UK); a member of the Scientific Advisory Board of Biovitrum, Paradigm, Prosidion and Cambridge Antibody Technology.

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

John Todd is on the editorial board of Human Molecular Genetics.

John Trowsdale is on the editorial boards of European Journal of Immunology, Human Immunology and Immunogenetics; an editor of Immunology and an associate editor of Tissue Antigens.

Linda Wicker is advisory editor of Journal of Experimental Medicine.

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Bruce Ponder is a member of the Scientific Advisory Board, OncoMethylome Sciences; a member of the Committee AACR/Dorothy Landon Prize; Visiting Professor, University of Shantou; a member of the International Scientific Advisory Board, Istituto dei Tumori, Milan; a member of the International Scientific Advisory Board, King Faisal Specialist Hospital & Research Centre, Riyadh; a member of the Board of Scientific Advisors, Genome Institute of Singapore and Singapore Cancer Syndicate and a member of the Cancer Research UK Scientific Programme Committee.

Randy Read is a member of the Executive Committee of CCP4 (Collaborative Computing Project 4) and of the Scientific Advisory Committee of e-HTPX.

Karin Römisch is a member of the Faculty of 1000.

David Rubinsztein is a member of the MRC College of Experts; the Scientific Advisory Board, DanioLabs Ltd; the Scientific Board of EUROSCA; the Scientific Planning Committee, British Society of Human Genetics; the Programme Committee, World Congress on Huntington’s Disease.

Matthew Seaman is a member of the Faculty of 1000.

Ken Smith is a member of the Research Grants Committee of the National Kidney Research Fund; a faculty member of the Immune Response section of the Faculty of 1000; a member of the Leukaemia Research Fund Medical & Scientific Advisory Panel; a member of the MRC College of Experts; a member of the British Transplantation Society Basic Science Review Committee; Visiting Professor, University of Shandong and Programme Director, NIH – University of Cambridge Biomedical Research Graduate Programme.

John Trowsdale is a member of the MRC College of Experts; on 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 of the Immunological Sciences Study Section, Center for Scientific Review, National Institutes of Health (2002–2006) and chair (2006–2007); a member of the Medical Science Review Committee of the Juvenile Diabetes Foundation International and chair and member of Type 1 Diabetes Repository Advisory Committee, National Institutes of Health.

Fellows of the Royal Society
Martin Bobrow
Robin Carrell
Stephen O’Rahilly
Bruce Ponder

Fellows of the Academy of Medical Sciences
Jennie Blackwell
Martin Bobrow
Robin Carrell
Krish Chatterjee
Tony Green
Fiona Karet
Paul Lehner
David Lomas
Paul Luzio
Gillian Murphy
Stephen O’Rahilly
Bruce Ponder
Margaret Robinson
David Rubinsztein
John Todd
John Trowsdale

EMBO Members
Margaret Robinson

CIMR and the MRC Dunn Human Nutrition Unit hold an annual Christmas party on the top floor of the Wellcome Trust/MRC Building.


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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 Welcome 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.
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) of the Institute
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

Director (Chairman) of the Institute and Deputy Director (Deputy Chairman) of the Institute
1 There shall be a University office of Director (Chairman) of the Cambridge Institute for Medical Research, which may be held concurrently with another University office.
2 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.
Front cover illustration:
The front cover illustration shows immunofluorescence picture of a rat fibroblast highlighting the intracellular localisation of myosin VI, a unique retrograde motor protein. Myosin VI (green) is present in endocytic clathrin coated pits and vesicles at the plasma membrane. The actin cytoskeleton is labelled in red and the nucleus in blue. (Buss, F., et al. Annu Rev Cell Dev Biol 20, 649-676).

Back cover illustration:
The picture shows a cultured HeLa cell transiently co-transfected with a mutant form of the hereditary spastic paraplegia protein spastin (red) and green fluorescent protein-tagged wild-type form of atlastin (GFP-atlastin, green), which is another protein associated with hereditary spastic paraplegia. The mutant spastin protein induces the appearance of and decorates abnormally bundled microtubules. GFP-atlastin is normally located on the endoplasmic reticulum (ER), but in the presence of mutant spastin, it and the ER marker calreticulin are redistributed to co-localise with the abnormal microtubule bundles. Structures that are labeled by spastin, atlastin and calreticulin appear white. (See p25 Luzio)