An RNAi screen identified TRC8 as a novel E3 ligase in human cytomegalovirus (HCMV) mediated MHC I dislocation. We find TRC8 complexed with MHC I, HCMV encoded US2 and signal peptide peptidase.

(Image courtesy of D. Bhella & S. J. Butcher, MRC Virology Unit/University of Helsinki, and P. J. Lehner, CIMR)

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Progenitor populations in the developing human brain. Human embryonic neuroepithelium, CS22, showing the relative positions of apical progenitors and their processes (nestin, green), basal progenitors (Tbr2, red) and neurons (tubulin III, blue).

(Illustration courtesy of Geoff Woods.)
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The Cambridge Institute for Medical Research (CIMR) has now completed its first decade housed in the Wellcome Trust/MRC Building, as a cross-departmental institute of the University of Cambridge Clinical School. Throughout that time our Institute has focussed on providing a unique interface between basic and clinical science and has retained as its major goal, the determination and understanding of the molecular mechanisms of disease. Our cohort of Principal Investigators (PIs) has changed over the years but we have always had over 40% who are medically qualified and clinically active. Several of these have pursued the therapeutic and diagnostic potential of discoveries made in the CIMR through interactions with the NHS and industry together with the establishment of clinical trials. Thus, we are a translational institute with some PIs interested mainly in very basic molecular mechanisms, others mainly in pathogenesis of particular diseases, but all committed to developing the interface between basic and clinical science that we regard as essential in the process of translating excellent basic research into clinical benefit. Our efforts as a translational institute have been greatly aided by holding a Wellcome Trust Strategic Award that supports our core scientific facilities, provides PhD studentships and provides funds to attract young clinicians back into research.

The CIMR has a very important function in training the next generation of academic leaders in medicine. In addition to its own 4 year PhD programme for non-clinical scientists funded through the Wellcome Trust and MRC, it plays a significant role in the Wellcome Trust Infection and Immunity 4 year PhD programme. In the past two years the CIMR has taken on responsibility for the Capacity Building Scheme for the Cambridge National Institute for Health Research Biomedical Research Centre. This scheme provides three year fellowships for clinical graduates to undertake a PhD anywhere within the University of Cambridge. The Deputy Director of the CIMR, David Lomas, is additionally responsible for the Wellcome Trust Clinical PhD programme that funds 5 clinical fellows per annum within the University. We have also appointed our first two ‘Next Generation’ Fellows in a CIMR scheme funded through our Wellcome Trust Clinical PhD programme that funds 5 clinical fellows per annum within the University. We have also appointed our first two ‘Next Generation’ Fellows in a CIMR scheme funded through our Wellcome Trust Clinical PhD programme.

In the CIMR there are four main research themes that transcend individual research groups, namely misfolded proteins and disease, intracellular membrane traffic, autoimmune disease and haematopoietic stem cell biology. Within these themes the Institute’s present scientific goals include: (i) determination of the molecular mechanisms of intracellular protein aggregate formation and breakdown in health and disease, including the identification of novel therapeutic targets for protein conformational diseases; (ii) identifying and characterising the molecular machinery of intracellular membrane traffic and determining how traffic pathways are coordinated, regulated and modified in health and disease; (iii) the identification of genes, proteins and pathways increasing susceptibility to, or protection from, autoimmune diseases; (iv) determining the transcriptional regulation of haematopoietic stem cells. Many of our research groups are trying to understand protein localisation, function and metabolism in a range of diseases in which genetic studies have identified the causative genes.

Over the past ten years CIMR has developed its own scientific focus and ethos. It has also played an important role in the development of the Clinical School and biomedical science on
our campus. Former PIs in CIMR include Sir Bruce Ponder FRS, Ashok Venkitaraman, Stephen O’Rahilly FRS and Roger Pedersen who have gone on to head new institutes/major laboratories, respectively the CRUK Cambridge Research Institute, the MRC Cancer Cell Unit (joint director with Ron Laskey FRS), the Institute of Metabolic Science (co-director with Nick Wareham) and the Anne McLaren Laboratory for Regenerative Medicine. We maintain interactive links with PIs in all of these newer institutes and in the case of the Institute of Metabolic Science/Metabolic Research Laboratories, three of their PIs (Stephen O’Rahilly FRS, Sadaf Farooqi and their new Wellcome Trust Principal Research Fellow David Ron) are CIMR Affiliated PIs and contribute to our seminar and student programmes. Within the Clinical School departments, many CIMR PIs also play a full role. At present Tony Green is Head of the Department of Haematology and John Todd FRS is Acting Head of the Department of Medical Genetics. Later this year Ken Smith will become Head of the Department of Medicine. Our PIs have also played a significant role in leading consortia that have brought major grants to the Clinical School. John Todd FRS headed the successful bid to the MRC for a high-throughput sequencing hub (one of four awarded nationally; the Eastern Sequence and Informatics Hub, www.easih.org) and Peter St George-Hyslop FRS led a consortium including researchers from Cambridge, Bristol, Toronto and Germany, that was one of three successful bids to the Wellcome Trust/MRC Neurodegenerative Diseases Initiative.

After ten successful years, our major challenge is both to improve our science and to continue to be a flagship in the UK for interdisciplinary research at the interface between basic and clinical science.

Paul Luzio
January 2010

Current Membership of the CIMR Strategy Committee:

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

Current Membership of the International Scientific Advisory Board:

Nick Hastie, (Chairman, University of Edinburgh), Dennis Ausiello (Harvard University), Peter Cresswell (Yale University), John Dick (University of Toronto), Louise Johnson (University of Oxford), Carl Nathan (Cornell University), Graham Warren (Max Perutz Laboratories, Austria)
## CIMR Principal Investigators

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<td>Andres Floto</td>
<td>Wellcome Trust Senior Research Fellow in Clinical Sciences</td>
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Our aim is to understand how molecular motor proteins function in intracellular transport processes and how defects in these molecular machines are linked to human diseases. Our primary interests are the myosin motors and their roles in membrane trafficking, cell signalling and actin filament dynamics.

We initially focused on myosin VI, since unlike all the other myosins so far characterised, it moves in the reverse direction along actin filaments and therefore has unique molecular properties and intracellular functions. Mutations or the absence of myosin VI have been linked to such diverse pathological processes as deafness, cardiomyopathy and defects in endocytosis of the cystic fibrosis transmembrane conductance regulator (CFTR).

Our primary goal is to understand the cellular functions of myosin VI and its involvement in disease. We have demonstrated a role for myosin VI in sorting cargo leaving the Golgi complex and established that it is required for the early stages of clathrin-mediated endocytosis and for the delivery of cargo in the later endocytic pathway. We are currently investigating how myosin VI is targeted to specific cellular compartments and how attachment to different cargoes is regulated. We have identified and are characterising using a multidisciplinary approach a number of interacting signalling phospholipids and adaptor proteins. We have also focused on the oncogenic potential of myosin VI, since overexpression of myosin VI in prostate and ovarian cancers causes an increase in secretion of angiogenic factors and enhances cell migration.

The human genome contains nearly 40 different myosins and therefore we are expanding our work to study the complementary roles of the different myosins in membrane trafficking pathways. Our long term goal is to understand how the different motor proteins interact and how their actions are coordinated and regulated within the cell.

The recruitment of myosin VI to the leading edge of migrating cells requires motor activity, since the cargo-binding tail does not target to membrane ruffles.
Our aim is to develop and apply statistical methods in genetic epidemiology and, to a lesser extent, in other aspects of biostatistics. The main focus of this work is provided by the Diabetes and Inflammation Laboratory (DIL). Implementation and dissemination of analytical methods is an important part of our work. To this end, further development of the snpMatrix package has been a priority and this now forms part of the Bioconductor project.

In conjunction with the group of Matt Hurles at the Wellcome Trust Sanger Institute, we have continued our methodological work on testing for association between copy number variation and disease in case-control studies. This, too, has resulted in software which has been accepted for distribution in Bioconductor.

A major commitment over the last two years has been the Type 1 Diabetes Genetics Consortium genome-wide association study. This followed up on the Wellcome Trust Case-Control Consortium (WTCCC), a major commitment of my group in the preceding period, adding another 4,000 cases and 2,500 controls. Together with the Type 1 diabetes (T1D) component of the WTCCC and a US study that we were able to access, the total genome-wide data were boosted to around 8,000 cases and 9,000 controls. Analysis of these data more than doubled the known T1D susceptibility loci, which now number more than 40. The most recent discovery emerging from these data is a paternally imprinted effect – to our knowledge the first convincing example of an imprinted effect in common complex disease genetics. Together with the known HLA effect, these loci now account for a sibling relative recurrence risk of just under 5 – a substantial fraction of the total heritability.

I am also collaborating in the genome-wide study of vasculitis.

Receiver operating characteristic for prediction of type 1 diabetes incidence given genotype at loci susceptibility loci currently identified. For example, about 80% of cases come from the 20% of the population at highest genetic risk.
Antigen Processing in Dendritic Cells and Macrophages

Our research is focused on understanding how antigen processing is controlled by dendritic cells and macrophages and how it may be dysregulated in autoimmune disease and during infections. We are interested in two related areas:

(a) The control of antigen processing by FcγR subtype receptors

We are aiming to understand how receptors for IgG, Fc γ receptors (FcγRs) control antigen processing by dendritic cells and macrophages. FcγR subtypes are variably expressed, have different binding affinities for different IgG subclasses and lead to fundamentally distinct patterns of intracellular trafficking and processing. We are defining how, for given repertoires of expressed FcγR, a specific antigen will be processed and what programme of effector functions will be triggered. Using a variety of live cell imaging, cellular and biochemical techniques, we are defining nodal signalling events controlling lysosomal degradation, cross-presentation and inflammasome activation.

(b) Bacteria-phagocyte interactions

Mycobacteria: We are interested in how dendritic cell and macrophage behaviour is influenced during infection with mycobacterial (TB and Non-TB) species, by heat shock proteins (in collaboration with Paul Lehner), therapeutic manipulation of macro-autophagy (in collaboration with David Rubinsztein) and manipulation of phagosomal function.

Streptococcus pneumonia: Together with Dr Jerry Brown (UCL), we are examining how pneumococcal polysaccharide capsule influences FcγR-dependent and independent uptake and phagosomal function.

A novel anti-inflammatory molecule, A11 and the proton pump inhibitor, bafilomycin (BafA1), decrease acidification of phagosomes containing mycobacteria detected using FAM-Alexa633-labelled M. abscessus as a ratiometric pH indicator.
Haematopoiesis has long served as a model system for studying the molecular processes that control cell fate decisions within complex differentiation cascades. Underpinning the molecular control of haematopoiesis are core circuits of regulatory networks, that when unified define the gene regulatory state of a particular cell. These regulatory networks are composed of both the transcription factors and the cis-regulatory elements they are bound to. Regulatory network reconstruction therefore requires the identification of cis-regulatory elements as well as the upstream factors which bind them.

The long term research goal of the Göttgens group is to decipher the molecular hierarchy of regulatory networks responsible for blood stem cell and endothelial development. To this end, the group uses complementary state-of-the-art approaches including embryonic stem cell and transgenic assays, bioinformatics, high throughput sequencing and mathematical modelling. The cumulative output of more than 40 research papers over the last 4 years has been the development of the most comprehensive network model for any adult stem cell type with over 40 transcription factors and more than 100 in vivo validated direct functional interactions. This integrated approach has resulted in the discovery of previously unrecognised combinatorial interactions between key regulators of blood stem cells with important implications for the transcriptional control of stem cell development and differentiation.

The importance of transcriptional control in both normal and leukaemic cells is underlined by the large number of transcription factor genes that cause leukaemia when disrupted or mutated. Future work will address how transcriptional programmes are perturbed in specific subtypes of leukaemia and may thus open up new avenues for the development of targeted therapies.

Further details can be found at http://hscl.cimr.cam.ac.uk/
Haematopoietic Stem Cells and Haematological Malignancies

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

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

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

Nuclear JAK2 phosphorylates histone H3Y41 and prevents the binding of heterochromatin protein 1α (HP1α) to a novel binding site on chromatin. The exclusion of HP1α at the promoters of genes is associated with increased gene expression and may account for other oncogenic phenomena.
Glucagon like peptide 1 (GLP-1), released from enteroendocrine L-cells in the gut epithelium, plays an important role in post-prandial glucose homeostasis and appetite control. Following the recent therapeutic successes of antidiabetic drugs aimed at either mimicking GLP-1 or preventing its degradation, attention is now turning towards the L-cell, to address whether it would be both possible and beneficial to stimulate the endogenous release of GLP-1 \textit{in vivo}. Understanding the mechanisms underlying GLP-1 release from L-cells is key to this type of approach, and recent studies have identified a variety of signalling pathways that underlie the physiological responses of L-cells to food ingestion. Our initial work in the GLUT ag cell line demonstrated that electrical activity and GLP-1 secretion were triggered by uptake of glutamine or glucose by sodium coupled transporters. As coupled uptake systems play an important role in nutrient absorption at the enterocyte brush border, the results suggest that electrogenic transporter activity at the apical membrane of L-cells may play a more generalised role in luminal nutrient sensing.

Our more recent work has focussed on studying primary L-cells, identified by cell specific fluorescent labelling in transgenic mice. L-cells from the transgenic models can be purified by flow cytometry, or identified in primary cultures for electrophysiology and fluorescence imaging. Primary murine L-cells exhibit electrical activity and intracellular calcium transients in response to a range of nutrients, including glucose and amino acids. By expression analysis, they possess a range of transporters and G-protein coupled receptors that may play a role in the sensing of ingested sugars, amino acids and fatty acids, as well as complex lipids and bile acids. The purification and characterisation of primary L-cells provides a route to identify novel pathways and receptors in L-cells that might be targetable for the treatment of diabetes and obesity.


Primary mouse colonic cultures stained for proglucagon (top left) and Peptide YY (top right). Primary GLP-1 producing L-cells are electrically active and glucose responsive (bottom).
Cytotoxic T lymphocytes (CTL) and Natural Killer (NK) cells use polarized secretion to destroy virally infected and tumorigenic target cells. Specialised secretory lysosomes, containing the pore forming protein perforin and a series of serine proteases, termed granzymes deliver the lethal hit in a specialized domain of the immunological synapse. Our research is focused on understanding the molecular basis of polarized secretion from CTL. We have used a series of rare genetic diseases including Hermansky-Pudlak and Haemophagocytic syndromes to identify the roles of proteins involved in secretion from CTL and NK cells. We have discovered that CTL and NK cells use a novel secretory mechanism, with the centrosome polarizing to the precise site of secretion within the immunological synapse. Our current research is aimed at understanding the basis of centrosomal localization within the immunological synapse and the mechanisms which determine cell polarity, secretory lysosome movement, docking and degranulation.

A cytotoxic T lymphocyte (white) polarises the centrosome (red) towards the immunological synapse (actin, green). Nuclei shown by Hoechst stain (blue).
Haemostasis (blood coagulation) is a complex process under tight regulatory control. Dysregulation leads to bleeding if the response is insufficiently robust, and to thrombosis if coagulation is not limited. Understanding these regulatory mechanisms is crucial for the diagnosis, prevention and treatment of diseases such as haemophilia, deep vein thrombosis, pulmonary embolism, heart attack, and stroke. My lab studies the structures of individual coagulation factors and of the multi-protein complexes they form, using the techniques of X-ray crystallography and NMR, in order to understand how coagulation is controlled. One project focuses on the final protease generated by the blood coagulation cascade, thrombin. Thrombin is the effector of blood clotting and cleaves a wide range of substrates with the aide of several cofactors. Another project concerns the large multi-protein complexes responsible for the burst of thrombin formation, the tenase and prothrombinase complexes. Finally, all of the proteases generated during the haemostatic response must eventually be inhibited to avoid dissemination of the clot. This is the job of protease inhibitors of the serpin family. We have a long-standing project studying how the serpins antithrombin (AT), heparin cofactor II, protein C inhibitor and protease nexin 1 are regulated by cofactors such as heparin to shut down the clotting response. The importance of serpins in regulating blood coagulation is supported by the occurrence of thrombosis in patients deficient in AT. This deficiency is often caused by missense mutations in the AT gene that lead to the accumulation of AT in the secretory cells through a process known as polymerization. We recently solved a crystal structure of a dimer of AT formed \textit{in vitro} that suggested a radical new ‘domain-swap’ mechanism of serpin polymerization. We are engaged in an active effort to determine if this and/or another mechanism may be responsible for serpin polymerization in cells.

**Molecular Recognition in Haemostasis**

Ty Adams
Robert Frasson
Daniel Johnson
Bernhard Lechtenberg
Giles Lewis
Wei Li
Genichi Nakamura
Timothy Sendall
Masayuki Yamasaki

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British Heart Foundation
Medical Research Council
National Institutes of Health (USA)
Wellcome Trust


Crystal structure of stable (self-terminating) antithrombin dimer revealed a large domain swap, including strands 4 and 5 of \(\beta\)-sheet A.
The aims of our group are broadly to study mechanisms of leukaemogenesis. In particular we aim to characterise leukaemia stem cells (LSC) at the molecular and cellular level in myeloid haematological malignancies. Leukaemias and many other cancers have recently been demonstrated to be wholly dependent upon a population of so-called cancer stem cells for their continued growth and propagation. These cells represent the most critical targets for treatment of leukaemia and a greater understanding of their biology and its interface with normal haematopoietic stem cell (HSC) function is fundamental to improving treatment outcomes. Our focus on this interface complements a local consortium of research groups (Profs Green, Warren and Drs Göttgens and Ottersbach) with interests in normal and leukaemic stem cells all based at the CIMR/Addenbrooke’s campus.

We utilise a combination of functional and genomic assays in complementary mouse models and human primary cells to study leukaemogenesis and LSC biology. Current interests of the lab include: identifying novel and characterising known self-renewal pathways downstream of leukaemia-associated fusion oncogenes such as MOZ-TIF2 and NUP98-HOXA9; examining the mechanisms of transcriptional dysregulation associated with these fusions and characterizing transcriptional dysregulation in primary acute myeloid leukaemia (AML) patient samples; identifying genes which are required for LSC function but are dispensable for normal HSC function; and characterising the LSC hierarchy and biology of the preleukaemic myeloproliferative neoplasms using analysis of highly purified populations of stem and progenitor cells from patients and a number of recently discovered mutations (i.e. JAK2 V617F or TET2) as clonal markers. Our studies will shed light on the cellular and molecular biology of these disorders, will inform the normal processes of haematopoietic self-renewal and myeloid differentiation and should identify therapeutic targets. Our group will then be ideally placed to further investigate the clinical utility of exploiting these targets.
We aim to characterise molecular mechanisms governing human renal tubular homeostasis, with a major focus on acid-base balance associated stone disease.

Fine-tuning of acid-base balance is the chief job of α-intercalated cells (α-IC) in the distal renal tubule. Intact α-IC functions (secretion of protons into the urine coupled to bicarbonate reclamation) are necessary for appropriate excretion of the acid load of a normal diet, and for generation of adequate amounts of bicarbonate for buffering. However, the transporters responsible, and their regulatory pathways, are incompletely understood.

We initially studied rare single-gene disorders (the distal renal tubular acidoses, dRTAs) where α-IC function is inadequate, imparting large quantitative effects on the kidney’s ability to maintain normal body fluid pH. Clinically, dRTA is 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 three genes in inherited dRTA: SLC4A1 (encoding the basolateral anion exchanger AE1), ATP6V1B1 and ATP6V0A4 (encoding kidney-specific B1 and a4 subunits of the α-IC surface proton pump). We showed that the latter two also participate in normal inner ear function.

Moving from genetic to functional studies, we have shown that essential membrane targeting motifs for AE1 reside in its C-terminal tail; that it is regulated by GAPDH and interacts with the sodium pump, and that binding of the glycolytic enzyme PFK-1 is essential for normal proton pump function.

Studies currently focus on finding novel regulatory partners for AE1, on regulation of the proton pump via phosphorylation, on characterizing the human urinary exosomal proteome and on clinical and laboratory studies of other tubulopathies.
Receptor Regulation by Viral and Cellular Ubiquitin E3 Ligases

We are interested in microbial evasion of the immune system and study the role of endogenous and virally-encoded ubiquitin E3 ligases in immune receptor regulation. All cells need to communicate with each other and the outside world through receptors which are tightly regulated to prevent desensitisation or uncontrolled signalling. Much of our work focuses on MHC class I molecules, which display peptides from endogenous and viral proteins for immunosurveillance by cytotoxic T lymphocytes (CTL) and play a critical role in defence against intracellular pathogens. In their attempts to escape immune recognition, viruses have evolved multiple mechanisms to evade class I molecules, and the importance of the class I pathway is emphasized by the remarkable strategies employed by different viruses to decrease cell surface expression of MHC class I and evade CTL recognition.

To achieve our goals we have developed novel tools to identify (i) E3 ligases in degradative pathways (ii) substrates for E3 ligases by quantitative mass spectrometry and (iii) novel receptors down-regulated following viral infection. In particular we have used focused RNAi screens and quantitative mass spectrometry to address immunological and cell biological problems. For example, in a recent siRNA based ‘ubiquitome’ screen we identified a novel ubiquitin ER-associated degradation (ERAD) ligase, TRC8 which is recruited by human cytomegalovirus (US2) to target MHC I molecules for proteasome-mediated degradation. This is of particular interest as TRC8 is implicated in both genetic and sporadic forms of renal cancer. Using SILAC labeling and differential membrane proteome mass spectrometry analysis we identified new physiological substrates of TRC8 which will be critical to understand its role in the pathogenesis of renal cancers.

An RNAi screen identified TRC8 as a novel E3 ligase in human cytomegalovirus (HCMV) mediated MHC I dislocation. We find TRC8 complexed with MHC I, HCMV encoded US2 and signal peptide peptidase. (Image courtesy of D. Bhella & S. J. Butcher, MRC Virology Unit/University of Helsinki.)
One in twenty-five of the Northern European population carries the Z allele of α₁-antitrypsin (342Glu→Lys). 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 the formation of ordered polymers in which the reactive centre loop of one molecule inserts into β-sheet A of another. Alpha-1-antitrypsin is a member of the serine protease inhibitor or serpin superfamily of proteins. Mutants of other serpins, antithrombin, C1-inhibitor and α₁-antichymotrypsin also form polymers in association with plasma deficiency that causes thrombosis, angioedema and emphysema respectively. Perhaps most striking is our description of the same process in a neurone specific serpin, neuroserpin in association with an inclusion body dementia that we have called familial encephalopathy with neuroserpin inclusion bodies (FENIB). In view of their common mechanism we have grouped these conditions into a new class of disease that we have called the serpinopathies. The structure and significance of the pathological loop-sheet polymers has been defined using biochemical, biophysical, crystallographic, and cell biology studies and with monoclonal antibodies and animal models of disease. We are now using this information to undertake in silico screens to identify compounds that can bind to, and prevent the polymerisation of, mutant α₁-antitrypsin in vitro and in vivo. In parallel with this work Dr Stefan Marciniak is assessing the consequences of endoplasmic reticulum protein misfolding on tissue growth and survival. His team are using Drosophila and mammalian models to dissect pathways that link endoplasmic reticulum dysfunction with cell cycle progression. More recently, Dr Damian Crowther has 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.
Lysosomes are small membrane-bound organelles ~0.5µm in diameter, which are full of proteases and other hydrolytic enzymes as well as internal membranes. They function late in the endocytic pathway that takes up macromolecules from the cell surface, by fusing with endosomes, but also play a key role in phagocytosis, autophagocytosis and probably cell surface membrane repair, the latter by fusing with the plasma membrane. The late endosomes that fuse with lysosomes are observed as MVBs (multivesicular bodies) in the electron microscope and sorting of membrane proteins into the lumenal vesicles of these MVBs is mediated by ESCRT (endosomal sorting complex required for transport) proteins. Our main focus is on how cells achieve sorting and delivery of endocytosed macromolecules to lysosomes. A key protein in fusion events involving lysosomes is the membrane protein VAMP7. This is targeted to lysosomes through interactions with the clathrin adaptor AP-3 and also by binding to the clathrin adaptor Hrb, that ensures its retrieval from the plasma membrane. We are currently investigating another VAMP7 binding partner likely to be required for regulating lysosome-endosome fusion. We are also studying the role of different protein machineries including the ESCRT proteins in preparing endosomes for fusion with lysosomes. Our structural studies are in collaboration with David Owen and we also collaborate with Paul Lehner on the intracellular sorting of Class I MHC molecules following downregulation from the cell surface by viruses. Our group maintains an interest in diseases of membrane traffic and Rhys Roberts has recently shown that Charcot-Marie-Tooth Disease Type 4C is caused by mutations in a Rab11 effector that prevents its correct targeting to recycling endosomes.
Haematopoietic stem cells (HSCs) have been intensely studied for many decades as a model system for stem cell biology. Our work focuses on the emergence and regulation of the first HSCs in the mouse embryo in order to identify the basic mechanisms that control their generation from precursors and their initial expansion and dissemination to the different haematopoietic organs. Knowledge of these early regulatory pathways has proven to be invaluable for understanding how adult HSCs can be manipulated for clinical purposes and how interference with these processes may result in blood-related disorders. Our research therefore complements that of several groups on the Addenbrooke’s site which also work on various aspects of normal and leukaemic stem cell biology.

Adult-type HSCs are first detected at day 10.5 during mouse development in a region of the embryo that comprises the developing dorsal aorta, gonads and mesonephros (AGM region). A day later these cells can also be detected in the yolk sac and the foetal liver. Our previous work has identified the placenta as another organ that harbours HSCs during development.

We have recently further defined the region of the AGM where HSCs are first detected and have incorporated this information into the design of a number of microarray experiments with the aim of identifying novel regulators of HSC generation in the AGM. Functional validation experiments have revealed a role for the cell cycle regulator p57Kip2 and the growth factor Igf2 in the generation, maintenance and/or migration of the first pool of HSCs in the AGM. Furthermore, many genes involved in the development of the tissues surrounding the dorsal aorta were also upregulated during HSC emergence. We are therefore currently investigating how the regulation of HSC generation may occur in coordination with the development of other organs.
Transmembrane proteins are moved between organelles in transport vesicles. Once cargo has been sorted into a forming vesicle, the vesicle buds from the donor membrane and is then transported to and fuses with the target membrane. Most post-Golgi transport is mediated by clathrin-coated vesicles (CCVs) although some steps use other types of vesicles/tubules such as those coated with retromer. CCV coats are composed of an outer clathrin scaffold linked to the membrane by clathrin adaptors including the heterotetrameric AP complexes. Clathrin adaptors have membrane-proximal folded domains, which bind to membrane phospholipid headgroups and/or the membrane-associated forms of small GTPases of the Arf or Rab families. Some of these domains are also responsible for selecting transmembrane proteins as vesicle cargo. Clathrin adaptors also possess at least one extended ‘string-like’ region that contain short motifs that bind to clathrin and other CCV components resulting in the formation of the dynamic protein network that is a CCV coat.

At least three distinct mechanisms of cargo recognition operate non-competitively and in parallel in most CCVs. Short motifs that are found on many cargoes of widely different function are recognised by subunits of AP complexes (YxxΦ by µ subunits and DExxLL by α subunits) and GGAs (DxxLL by V-HIS domains) whilst poly-ubiquitinated cargo is recognised by epsins and GGAs. The 30 post-Golgi SNAREs, which provide much of the energy and specificity for transport vesicle: organelle membrane fusion, are mostly recognised through a unique interaction of a folded portion of a SNARE with a low-abundance CCV coat component.

In collaboration with various groups both within and outside the CIMR we are taking an integrated structural/functional approach to studying the interactions between proteins and protein complexes involved in transport vesicle and organelle biogenesis, with a focus on mechanisms of cargo recognition.


C The molecular details of the interaction with residue side chains whose mutation that abrogates [ED]xxxLL-binding are coloured dark red.

D Liposome-based SPR binding assay showing mutations (boxed in C) abolish [ED]xxxLL binding.
Proteins and lipids of the endocytic and secretory pathways are transported between organelles via small membrane bound transport vesicles, which bud from one compartment and fuse with another, thereby delivering their contents. The targeting and fusion of transport vesicles is driven by the specific interactions of a family of molecules known as SNAREs. The human genome encodes at least 40 SNAREs, with each one being localized to a defined set of membranes and involved in a specific set of fusion reactions. Disruption or mis-localisation of SNAREs will lead to the incorrect targeting of proteins and lipids and so causes membrane dysregulation and disease.

Although specific SNAREs are present on defined subsets of membranes, the mechanism by which SNAREs are specifically sorted to their target membranes is not fully elucidated. Early in my career I showed that VAMP4 (V4) a post-Golgi SNARE is enriched in clathrin coated vesicles, and it interacts with the AP-1 adaptor complex, a component of the machinery involved in vesicle biogenesis and cargo recognition.

V4 is thought to play a key role in the transport of proteins and lipids to and from the trans-Golgi network. In collaboration with the group of Professor T Y Chang we have shown that depletion of V4 and its cognate SNAREs using siRNA leads to a reduction in cholesterol esterification and my lab has shown that disruption of V4 in mice causes defects in cholesterol homeostasis. Taken together this data strongly suggests that V4 and its cognate SNAREs play an important role in cholesterol transport and homeostasis.

We are interested in (1) understanding how V4 and its cognate SNAREs (STX6, 16 and vt1a) are recognised and packaged into transport vesicles (2) determining the role of V4 and its cognate SNAREs in cholesterol transport and homeostasis (3) identifying and characterising novel SNARE dependent pathways.

Depletion of V4 in Hela cells using siRNA reduces cholesterol esterification (A) and disruption of V4 in mice elevates serum cholesterol levels (B).
The group aims to understand the molecular mechanisms underlying intellectual disability in humans and our main focus is on families affected with X-linked disease. We have established a large international collaboration iGOLD (International Genetics of Learning Disability Study) with genetics centres throughout the UK, Ireland, Australia, USA and Europe where we have collected clinical details and samples from many families with multiple males affected with intellectual disability. We have recently published a systematic, large-scale re-sequencing screen of the X-chromosome coding exons in 208 families and have identified 9 novel genes that cause disease.

We are continuing to identify novel genes that cause disease by determining the rare and common copy number variants (CNVs) on the X chromosome in this cohort. In addition, we are investigating the high number of rare sequence variants that are present in the cohort in order to distinguish pathogenic mutations from rare passenger polymorphisms.

These data sets are informing our knowledge of the X chromosome architecture, its variance and the proportion of disease caused by different molecular mechanisms.

Future directions include developing assays of the disease genes we have identified to date to aid further understanding of the disease and establishing better experimental models of disease for systematic investigation of this complex neurological disease.

**Figure shows a diagrammatic representation of the human X chromosome with the names and location of genes that we have identified to cause X-linked intellectual disability or X-linked nystagmus in the case of FRMD7.**

**The Genetic Basis of Learning Disability**

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**Lucy Raymond**

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**Lorraine Shepherd**

**Annabel Whibley**

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Research in my group is in the field of protein crystallography. Crystallography is the primary method for determining the three-dimensional structure of a protein, which provides an essential framework for a detailed understanding of its biochemistry. We work both on extending the scope and power of the methods used in protein crystallography, and on applying those methods to determine the structures of proteins. In choosing what to study, we focus on proteins involved in pathogenesis and disease, the structures of which can be exploited in the development of new therapies.

We have a long-standing interest in the mechanism of action of bacterial toxins. By engineering pertussis toxin (produced by the bacterium that causes whooping cough) to act as its own substrate we gained the first view of enzyme-substrate interactions for a large family, including cholera and diphtheria toxins.

Dr Aiwu Zhou leads work on members of the serpin family, which undergo an extraordinary conformational change on cleavage by proteases. A collection of structures of hormone-binding globulin have revealed how these serpins exploit their conformational change to deliver the hormones corticosteroid and thyroxine.

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

Thyroxine bound to thyroxine-binding globulin (Zhou et al., 2006). The binding site was verified by locating anomalous scattering from the iodine atoms (magenta mesh) with Phaser.


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Molecular Cellular Pathology of Axonal Degeneration

Our research is focused on the hereditary spastic paraplegias (HSPs), genetic conditions in which there is a length-dependent distal axonopathy that mainly affects the corticospinal tract axons. We study these conditions to understand molecular mechanisms crucial for axonal function.

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

1. Understanding the functions of spastin. Mutations in the gene encoding spastin are the most frequent cause of HSP. Spastin is a microtubule severing protein and our work has suggested that it is recruited to membrane traffic sites, where it probably couples microtubule regulation to membrane modelling processes. A larger isoform of spastin functions at the early secretory pathway, where it co-operates with two other HSP proteins, atlantin and REEP1, in endoplasmic reticulum morphogenesis. A smaller isoform is strongly recruited to endosomes. We are investigating the role of spastin at both of these membrane traffic sites.

2. Understanding the role of other endosomal HSP proteins. We are examining the role of spartin, NIPA1 and strumpellin at endosomes. We are especially interested in examining whether all of these proteins are endosomal regulators of Bone Morphogenetic Protein (BMP) signaling. If so, we aim to examine the mechanism by which the proteins regulate this signaling pathway, and explore how disrupted BMP signaling could cause axonopathy.

Mutant spastin (green) expressed in HeLa cells redistributes microtubules (red) into elongated bundles. Structures labelled with both spastin and microtubule markers appear yellow.
After a meal a range of hormones is released from specialised intestinal cells, the enteroendocrine cells, which coordinate the body's response to the availability of nutrients. My research interest currently focuses on glucose-dependent insulinotropic polypeptide (GIP), a hormone that stimulates insulin release and fat deposition. The insulinotropic action of GIP, underlying the so-called incretin effect, is shared with another hormone, glucagon-like peptide-1, which is the focus of Fiona Gribble's group, with whom I collaborate closely. The direct action of GIP on adipose tissue, however, seems unique, underlined by the fact that GIP-receptor knock-out mice are protected from becoming obese on a high fat diet. Little is known about the molecular events underlying GIP release, partially due to the scattered localisation of GIP-secreting cells, the so-called K-cells, throughout the proximal small intestinal epithelium. I have recently made a mouse strain in which all cells that produce GIP also make a yellow fluorescent protein. Living GIP-secreting cells can therefore be identified and purified on the basis of their yellow fluorescence. This allows the use of electrophysiological and fluorimetric imaging techniques for the characterisation of stimulus-secretion coupling events in K-cells with the goal of identifying agents and pathways that could be targeted therapeutically to control GIP release in mice and man. Such agents would be hoped to open new avenues for the treatment of type 2 diabetes and obesity.

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

K-cells express functional sodium-glucose-cotransporter-1 (SGLT1):

- a) apical localisation of SGLT1 (red) on a duodenal K-cell (green)
- b) GIP secretion from murine duodenal epithelial cells in 1° culture
Proteins are transported between the various organelles of the cell by vesicles, which bud from one membrane and fuse with another. The formation of these vesicles and the selection of the right sort of cargo are dependent on coat proteins. Several types of coated vesicles have been described, the best characterised of which are the clathrin-coated vesicles (CCVs). The coats on CCVs consist primarily of two components: clathrin and adaptor protein (AP) complexes. Recently, we and others have shown that in addition to the AP complexes, there are also “alternative” adaptors. Our working hypothesis is that for each trafficking pathway, there are a number of different adaptors, each of which is recruited independently onto the appropriate membrane. Once on the membrane, the various adaptors would work together to package different types of cargo into the newly forming vesicle.

To look for novel adaptors and other components of the CCV machinery, we are using two approaches. One is a proteomics analysis of CCVs, both to establish the protein composition of the vesicles and their coats and to gain insights into the functional relationships between the various components by carrying out “CCV profiling”. The second approach is to screen a human genome-wide library for siRNAs that disrupt clathrin-mediated trafficking. Among our top hits are known CCV machinery, proteins involved in endosomal dynamics, and completely uncharacterized proteins. Other ongoing studies include investigating how the HIV-1-encoded protein Nef hijacks adaptor-mediated trafficking to evade the immune system of the host; exploiting Drosophila as a model system to elucidate the function of the GGAs and other adaptors; and developing a new rapid and inducible inactivation system (which we call a “knock-side- ways”) to explore the role of various coat components in both cells and organisms.
We are studying diseases caused by codon reiteration mutations, like Huntington's disease (HD) and oculopharyngeal muscular dystrophy (OPMD). These diseases are associated with intracellular aggregate formation. We are addressing the following questions:

1. **What are the pathological changes that occur in HD and other codon reiteration diseases?**
   
   We use a range of biochemical and genetic approaches in model organisms to identify genes and pathways that modify the severity of HD and related diseases. Identification of such pathways can give clues to potential therapeutic strategies.

2. **Can one attenuate polyglutamine toxicity by inducing autophagy?**
   
   The polyglutamine expansion mutation confers a novel toxic novel function on huntingtin. Thus, it is important to understand how its levels are regulated. We showed that mutant huntingtin is an autophagy substrate and that autophagy upregulation is protective against mutant huntingtin toxicity in fly and mouse models. We found that this strategy is relevant to other diseases caused by intracytoplasmic aggregate-prone proteins, including certain spinocerebellar ataxias, forms of Parkinson's disease (mutant alpha-synuclein), and certain dementias (tauopathies). Currently, the only autophagy-inducing drug that is known to reduce mutant huntingtin levels effectively in mammalian brains is rapamycin, which has significant side-effects and is not that well-tolerated. Thus, we have been using a range of drug-screening strategies and genetic and biochemical approaches to characterise autophagy better. Our data have revealed novel druggable pathways that regulate autophagy and we have provided proof-of-principle for some of these pathways in animal models of HD.

3. **Are there common mechanisms causing pathology in the different diseases associated with intracellular protein aggregation?**
   
   It is important to test if the different diseases associated with intracellular aggregate formation share common pathways, as this may inform the fundamental understanding of the relationship between the aggregation process and cell dysfunction/death.
The focus of my laboratory is the study of signal transduction in T-cells of the immune system, and the manner by which these pathways control immune various functions. Our work has relevance to cell biology, immunology and the control of opportunistic infections, anti-tumour immunity as well as immune-based pathologies such as autoimmunity. My laboratory was the first to discover that cell surface receptors interact with protein-tyrosine kinases with the identification of the CD4 and CD8–p56lck complexes. These complexes initiate the activation of T-cells. Our current interests include the identification and function of ‘adaptor proteins’, proteins that carry binding modules/sites that integrate proximal signals at the plasma membrane with downstream events. Two of our adaptors termed adhesion- and degranulation-promoting adapter protein (ADAP; also Fyn-binding protein, FYB) and src kinase-associated phosphoprotein-55 (SKAP1) control the important ‘inside-out’ pathway by which the antigen-receptor complex (TCR/CD3 complex) activates integrin-mediated adhesion. SKAP55 interacts with RapL in the control of T-cell migration and the formation of conjugates between T-cells and antigen-presenting cells (APCs). ADAP can also signal for LFA-1 induced T-cell polarisation, while an ADAP mutant inhibits infection by the human immunodeficiency virus (HIV-1). Our overall interest is to define a structure-function approach in defining signalling pathways, and the way they regulate cytokine production, adhesion and responses to antigen.

The second area of interest concerns the mechanism by which co-receptors CD28, CTLA-4 and PD-1 control immunity. These co-receptors modify signals from the antigen-receptor with differences in the threshold of signalling and nature of cytokine production. We recently showed that CTLA-4 modulates immune function by controlling cell motility and reversing the stop-signal needed for T-cell-APC interactions. Our interests are to understand the molecular basis of these responses and their involvement in autoimmunity and in responses to tumours and foreign antigen.

Funding:
Wellcome Trust


Molecular Dissection of the Mechanisms of Neurological Disease

My laboratory focuses upon understanding the causes and molecular mechanisms of neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease and Frontotemporal dementia. We and others have shown that these diseases are frequently caused by the intracellular or extracellular accumulation of neurotoxic protein aggregates. We employ genetics, molecular biological, cell biological and animal modelling strategies to identify: 1) disease-causing genes; and 2) the molecular pathways by which these genetic variants lead to neuronal death. Thus, we have shown that mutations/polymorphisms in a variety of genes including amyloid precursor protein (APP), presenilin 1 (PS1), presenilin 2 (PS2), SORL1 and apolipoprotein E all cause Alzheimer’s disease, and presumably do so by modulating the handling of a neurotoxic proteolytic fragment of APP, termed Aβ peptide. We have shown that the presenilin proteins are part of a multimeric, membrane-bound protein complex which has the unusual function of cleaving Type I transmembrane proteins within the hydrophobic transmembrane domain (termed γ-secretase cleavage). Ongoing experiments are designed to understand the structure of the presenilin complex using a variety of structural biological approaches including single particle analysis of electron microscopic images of the intact complex, and X-ray crystallography of individual components of the complex. A parallel set of experiments have been initiated to understand how extracellular protein aggregates such as extracellular Aβ injure neurons, and uses a variety of methods including single molecule imaging to investigate which species of Aβ oligomer bind to neuronal surfaces, and what they bind to. Finally, a third set of experiments are designed to investigate the molecular mechanisms of neuronal injury caused by intracellular aggregates of proteins such as TDP-43 (which occurs in some cases of Frontotemporal dementia). To accomplish this, we have recently generated C. elegans expressing either wild-type or mutant TDP-43, and shown that the latter cause neuronal injury.


Correct protein localization is an integral part of cellular homeostasis and there are now numerous examples of genetic disease resulting from mislocalization of membrane proteins. For a membrane protein to be accurately targeted to its site of function it must be recognized by cellular sorting machinery to direct it into a vesicle or tubule that will carry the protein to its destination.

In my lab we study the endosome-to-Golgi retrieval pathway that is required to maintain a specific set of membrane proteins within the Golgi. One of these membrane proteins is the cation-independent mannose-6-phosphate receptor (CI-MPR) that sorts lysosomal hydrolases for delivery to lysosomes. The CI-MPR is recognized by the retromer complex at the endosomal membrane which directs the CI-MPR into a tubule for retrieval to the Golgi. Other proteins that require retromer for their proper localization include Wntless, a membrane protein required for Wnt secretion and SorLa/Sorl1, a protein that mediates the trafficking of amyloid precursor protein (APP) and is therefore implicated in the pathogenesis of Alzheimer’s disease.

We have recently shown that the recruitment of retromer to the endosomal membrane requires the activity of the small GTPase rab7. Retromer associates with rab7 by co-immunoprecipitation and loss of rab7 expression using small inhibitory (si) RNA causes retromer to become cytosolic and no longer associated with endosomal membranes. During these studies we identified a novel retromer-interacting protein, TBC1D5, that is a member of the rab GTPase activating protein (GAP) family of proteins. We found that overexpression of TBC1D5 results in retromer becoming cytosolic and that rab7 is also displaced from the membrane.

The native immunoprecipitation methodology we have adopted and developed has been successful in identifying several more retromer-interacting proteins and we are currently functionally characterizing these retromer-interacting proteins in order to determine their role in endosome-to-Golgi retrieval.

A siRNA knockdown (KD) of rab7 redistributes VPS26 to the cytoplasm. B. Native immunoprecipitation from cells expressing VPS29-GFP identifies TBC1D5 as a novel retromer-interacting protein.
Lipids play essential roles as building blocks for membranes and their regulated production during development often underlies striking morphological changes in a variety of specialized cell types. In addition, lipids act as signals by which organelles and cells communicate with each other and as energy storage molecules. Imbalance of lipid metabolism or distribution can lead to a large number of disorders such as metabolic syndrome or cancer.

The aim of our laboratory is to understand how lipids regulate the structure and function of biological membranes and organelles. Our current studies focus on lipins, a conserved family of enzymes that catalyze a fundamental reaction in lipid biosynthesis, namely the dephosphorylation of phosphatidic acid into diacylglycerol (DAG). We have recently shown that the yeast lipin Pah1p and the regulators of its enzymatic activity are required for the maintenance of a spherical nuclear shape. We proposed that changes in the lipid composition of the nuclear/ER membrane, controlled by Pah1p, could be necessary for the nuclear remodelling that takes place during cell division. More recently, we have identified additional enzymes that function in this pathway and we are now addressing their function in nuclear structure.

In addition to their roles in phospholipid biosynthesis, lipins are also required for the synthesis of the fat triacylglycerol (TAG). We have recently shown that the lipins 1 and 2 perform distinct and non-redundant functions during the differentiation of fat cells (adipocytes). We are now studying how lipins, normally soluble enzymes, are recruited onto membranes to generate DAG required for fat production. We are also investigating current evidence that, besides their enzymatic functions, lipins can translocate into the nucleus to regulate gene expression.

Linking Phospholipid Metabolism to Membrane and Organelle Function

Lipins catalyze the dephosphorylation of phosphatidic acid to diacylglycerol (left panel). Loss of lipin 1 inhibits lipid accumulation in adipocytes (upper panels, red:lipid, blue:DNA, bar: 5µm). Loss of the lipin Pah1 causes nuclear/ER membrane expansion in yeast (lower panel, arrows point to the expanding nucleus in green, bar: 1µm).
We aim to discover how genetically determined variation in immune regulation balances the risks of autoimmune disease and infection. Initially focussing on the B cell, which remains a major interest, we investigate the function of inhibitory receptors such as CD22 and FcγRIIb, which act as “brakes” on the immune system. We have shown that even subtle changes in expression of FcγRIIb on B cells can prevent or induce SLE in mice. Natural polymorphisms in FcγRIIb are associated with autoimmune diseases such as systemic lupus erythematosus (SLE) in both mouse and man. Some reduce function and are common in Asia and Africa, where malaria is endemic. We have used mouse models of malaria, in vitro assays with cultured Plasmodium falciparum and human cells, and human genetics (in collaboration with the KEMRI/Wellcome Trust Unit in Kilifi, Kenya), and have shown that FcγRIIb deficiency can protect against severe malaria, perhaps contributing to the evolution of predisposition to SLE in some ethnic groups. Further work on the interaction between malaria and autoimmunity is an ongoing priority. Other lab members are defining how abnormal control of plasma cell function and migration contributes to autoimmunity, and are studying specific micro-RNAs we have shown to control B cell development, activation, and oncogenesis.

We have established a programme in human autoimmunity, working with patients with vasculitis, SLE, inflammatory bowel disease and renal transplants (and led with Paul Lyons) in both Cambridge and Singapore. By performing detailed transcriptomic studies of purified white blood cells we have discovered novel biomarkers now being assessed for their ability to guide therapy to improve efficacy and reduce treatment toxicity, and have indentified novel disease-associated pathways requiring further investigation. We initiated the European Vasculitis Genetics Consortium and are coordinating extensive genetic studies in ANCA-associated vasculitis.

These programmes provide a resource which allows us to interrogate mouse and human biology in an integrated fashion, increasing our capacity to probe immunity and disease.

Plasma cell survival niches in the bone marrow: Plasma cells (green, indicated by white arrows) are found in close contact with IL6- (red) and FDCMO-expressing cells (blue) (Figure M Espeli).

**References**


Our aim is to further characterise the molecular basis for the autoimmune inflammatory disease type 1 (insulin-dependent) diabetes. We use an integrated combination of genetics, in large collections of type 1 diabetic families and case/control, statistics, genome informatics and data mining, and gene expression and functional studies. Our major effort now is to correlate susceptibility genotypes with biomarkers and phenotypes e.g. we have correlated plasma and cellular levels of the soluble form of the interleukin-2 receptor with the genotypes of the IL-2RA gene that are associated with type 1 diabetes susceptibility. This is a first step towards identifying disease precursors that could be used in the evaluation of future therapeutic studies. To achieve this we have helped build a local biobank of healthy volunteers in whom we can study the effects of disease-associated genotypes (The Cambridge BioResource: www.cambridgebioresource.org.uk/). Our research efforts are part of the Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory (DIL), which includes the laboratories of Linda Wicker and David Clayton, as well as collaborations with the Department of Haematology (Willem Ouwehand), the Department of Paediatrics (David Dunger), and the Wellcome Trust Sanger Institute.

Funding:
Wellcome Trust
Juvenile Diabetes Research Foundation
Medical Research Council
National Institutes of Health (USA)
NIHR Cambridge Biomedical Research Centre
European Commission


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

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

JDRF/WT DIL Staff
John Todd
Director
Linda Wicker
Wellcome Trust Principal Research Fellow and Co-Director
David Clayton
Wellcome Trust Principal Research Fellow
Research Group (Todd)
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Lucy Davison
Kate Downes
Marcin Pekalski
Nada Saleh
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Jan Clark
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Laura Esposito
Jason Hafler
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Oliver Burren (Head)
Premanand Achuthan
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Neil Walker (Head)
Nigel Ovington
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Sarah Nutland (Head)
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Simon Hacking
Rachel Simpkins
Pippa Tagart
Maureen Weisner

Funding:
Wellcome Trust
Juvenile Diabetes Research Foundation
National Institutes of Health (USA)
NIHR Cambridge Biomedical Research Centre
Medical Research Council (MRC Next Generation Sequencing Hub Facility)

European Commission


We study proteins encoded in a key set of human genes, the human Major Histocompatibility Complex (MHC). This dense cluster of polymorphic loci influences susceptibility to a huge number of human diseases. These include most, if not all, autoimmune conditions, many infections and other diverse conditions, from Narcolepsy to Schizophrenia.

The key products of the MHC are Class I and Class II molecules. These play a pivotal role in alerting the immune system to infection by presentation of antigenic peptides to receptors on T cells. A major part of our approach concerns the regulation and functions of these molecules. Our early work involved discovery of antigen processing molecules encoded in the MHC, such as the TAP peptide transporter and immunoproteasome subunits (J. Immunol. 2008. Pillars of Immunology: antigen presentation: discovery of the peptide TAP). Following on from this, we found a novel molecule, TAPBPR, which is related to the MHC-encoded TAPASIN molecule. TAPBPR appears to modulate MHC class I expression and may have a profound affect on immune recognition. Louise Boyle is leading a project to elucidate the function of TAPBPR in order to understand the role of this new player in MHC class I processing and presentation.

Further information on the state of health of a cell is provided by interaction of MHC class I molecules with other receptors on Natural Killer (NK) cells. Like some MHC genes, NK receptors form an extensive, polymorphic gene family. We are particularly interested in understanding the interplay between NK receptors and MHC class I molecules, in relation to disease.

Genetic and Functional Relationships between Immune Receptors

We study proteins encoded in a key set of human genes, the human Major Histocompatibility Complex (MHC). This dense cluster of polymorphic loci influences susceptibility to a huge number of human diseases. These include most, if not all, autoimmune conditions, many infections and other diverse conditions, from Narcolepsy to Schizophrenia.

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Further information on the state of health of a cell is provided by interaction of MHC class I molecules with other receptors on Natural Killer (NK) cells. Like some MHC genes, NK receptors form an extensive, polymorphic gene family. We are particularly interested in understanding the interplay between NK receptors and MHC class I molecules, in relation to disease.
Our group is focused on understanding the molecular and cellular mechanisms mediating 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 humans. In both humans and mice, functional variants at more than fifty genes are known to alter T1D susceptibility and it is likely that this number will continue to grow. Some T1D-associated genes and molecular pathways are shared by humans and mice as exemplified by variants affecting PTPN22, a phosphatase that negatively regulates signalling in immune cells, CTLA-4, a negative regulator of the immune system, and the IL-2 pathway, which is critical for immune homeostasis. The interaction of IL-2 with its trimeric receptor, which includes the IL-2 receptor alpha chain (IL-2Rα, also called CD25), is necessary for the function of FOXP3⁺CD25⁺CD4⁺ regulatory T cells, a T cell subset that dampens the immune response and that is less functional in T1D patients and NOD mice.

To link the gene variants that cause autoimmune disease with their biological effects within the immune system, we study the peripheral blood of T1D patients and healthy volunteers accessed through the Cambridge BioResource. The genotypes of our donors at genes causing T1D are determined and correlated with phenotypes ranging from the expression of the protein encoded by the disease-causing gene to parameters of immune cell activation and differentiation. One phenotype for which we have discovered a genotype correlation is the expression level of CTLA-4 in FOXP3⁺CD25⁺CD4⁺ regulatory T cells (see Figure). CTLA-4, which is critical for the function of this regulatory T cell subset, is more highly expressed in donors having a protective genotype at CTLA4 as compared to donors having a susceptible CTLA4 genotype.

Using multi-colour flow cytometry, CTLA-4 expression within FOXP3⁺CD25⁺CD4⁺ regulatory T cells, which are 2-4% of the CD4⁺ T cells in the peripheral blood, is measured in fresh whole blood (shaded histogram) and following 3 hours of activation in the presence of brefeldin (red histogram). The black histogram represents the isotype control. CTLA-4 is constitutively expressed in FOXP3⁺CD25⁺CD4⁺ regulatory T cells and is upregulated following activation.
Our primary focus is to understand a human disease primary microcephaly (MCPH) where children are born at birth with small but architecturally normal brains – about the size of our primate relative's brains. The condition causes mental retardation but not physical retardation and with no effect outside of the central nervous system. So MCPH appears to be a model disorder in which to study mammalian cerebral cortex growth control – with both disease and evolutionary perspectives. We and others have shown the MCPH genes to be undergoing Darwinian positive selection through the primate lineages. MCPH can be caused by at least 10 genes; 7 have been identified, the last two of which we have not yet published. We continue to find further MCPH genes, determine mutation spectrum and seek genotype/phenotype correlations.

Unexpectedly all MCPH proteins are located at the centrosome and/or spindle pole – but with apparently different roles. We and our collaborators have sought interactions between the MCPH proteins – and found no evidence of a single MCPH protein complex. Cell biology experiments are hampered by our discovery that MCPH mutations, despite being homozygous non-sense are hypomorphs. So we have focussed on rare mutations that cause small protein deletions or in one case a mis-sense mutation to seek perturbations of centrosome function or mitotic progress.

To find where neurogenesis is affected in MCPH we have studied human embryonic brain by immunofluorescence, comparing it to mouse. Disappointingly the three MCPH proteins tested to date, CDK5RAP2, CENPJ and MCPH8, show ubiquitous centrosomal expression in all cell types. Our current unifying hypothesis is that the MCPH proteins all affect daughter centriole maturation – and that this changes the delicate balance between symmetric and asymmetric apical neural precursor divisions.
Core Scientific Facilities at CIMR

Matthew Gratian (Confocal/Imaging)
Nikol Simecek (Bioinformatics/Systems)
Mark Bowen (Confocal/Imaging)
Anna Petrunkina Harrison (Flow Cytometry) (also Affiliated Reader (Privatdozent) in Biomedical Engineering & Reproductive Biology, University of Veterinary Medicine, Hanover and Associate Editor in Reproduction, Fertility, Development)
Kamburapola Jayawardena (Jay) (Proteomics)

The above are all core staff funded as part of CIMR's Wellcome Trust Strategic Award.
The MRC Mitochondrial Biology Unit has evolved from the former MRC Dunn Human Nutrition Unit, and builds on research conducted there over the past 10 years. Its formation by the MRC recognises growing evidence for the involvement of mitochondria and their dysfunction in an ever-increasing range of human diseases, and even, perhaps, in the process of ageing.

The Unit has three major scientific aims:

• To understand the fundamental processes taking place in mitochondria.
• To understand the involvement of these processes in human diseases.
• To exploit knowledge of these fundamental processes for the development of new therapies to treat human diseases.

Today, the Unit has nine independent research 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 studies of mtDNA replication and mitochondrial genetics in relation to mitochondrial disease (Ian Holt and Michal Minczuk), 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. Their activities are focussed on understanding the fundamental biochemical and biological processes which occur in mitochondria. Via collaborations with clinical colleagues in several countries, the Unit is building on its fundamental knowledge to try to understand how mitochondrial dysfunction leads to human disease. In addition, Unit members are engaged in collaborations with pharmaceutical companies, to exploit our fundamental knowledge to generate new therapies. In the coming months, the Unit will be strengthening and developing these latter aspects by making new appointments and by introducing new research activities into our Unit.

Currently, the MRC Mitochondrial Biology Unit has a staff of 106 including 43 PhD students.
Genetics and genomics in leishmaniasis, and the development of novel vaccines for leishmaniasis, underpin the continuing work of the Blackwell laboratory at CIMR. Research involves projects in Brazil, Crete, India, and Sudan. These include:

- As part of the Wellcome Trust Case Control Consortium Phase Two (WTCCC2) we are undertaking genome-wide association studies (GWAS) of visceral leishmaniasis and associated quantitative traits in case-control samples from India, and families from north-eastern Brazil and Sudan (with Shyam Sundar, India; Selma Jeronimo, Brazil; Muntaser Ibrahim, Sudan; Mary Wilson, USA).

- Susceptibility genes for visceral leishmaniasis on chromosomes 1p22 (LOD=5.6; \( P=1.7 \times 10^{-7} \)) and 6q27 (LOD=3.8, \( P=1.7 \times 10^{-6} \)) that were identified on the basis of genome-wide linkage scans are being fine mapped (with Hiba Mohamed and Muntaser Ibrahim, Sudan).

- 20 novel protective antigens are being evaluated to determine cross-species efficacy for different Leishmania spp., using physiological doses of challenge infection in murine models of disease (with Mary Wilson and Diane McMahon-Pratt, USA).

- Phase I/II/III trials of a DNA/MVA prime-boost vaccine based on a specific protective Leishmania antigen in field trials of dogs infected naturally with Leishmania infantum (with Orin Courtenay, Warwick University, UK).

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Molecular Pathogenesis of Neurodegenerative Disease

My group is dedicated to discovering the molecular pathogenesis of neurodegenerative diseases using the fruit fly, Drosophila melanogaster, as our primary tool. Our creation of a fly model of Alzheimer’s disease by expressing the amyloid beta peptide in the insect’s brain has started two interlinked lines of research. The first uses the powerful genetic tools that are available in the fly to find genes that modify the brain’s sensitivity to the toxic effects of the Aβ peptide. Genetic screens have revealed important pathways of disease that we are investigating using biochemical, cell culture and animal modelling approaches.

The second strand, in collaboration with Prof Chris Dobson and Dr Michele Vendruscolo in the Department of Chemistry, correlates the biophysical properties of peptides with their aggregation propensity. The fly allows us to observe the generic toxicity of protein aggregates in vivo.

Group Leader
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**Genetics and Pathophysiology of Human Early Onset Obesity**

We are a team of basic and clinical researchers investigating the genes that contribute to severe early onset obesity and the physiological impact of these disorders. We have recruited 3,500 patients with severe childhood onset obesity to the Genetics of Obesity Study (GOOS). We have shown that mutations in several genes in the leptin-melanocortin pathway cause early onset obesity and that one of these disorders, congenital leptin deficiency, is treatable. As well as our continuing candidate gene approach, we are using hypothesis-free approaches including SNP-arrays and next generation sequencing technologies to identify homozygous regions shared by affected individuals in highly consanguineous pedigrees recruited from around the world. We also study rare copy number variants that we have identified in association with severe obesity and other metabolic and neurobehavioural phenotypes.

We undertake physiological studies in cohorts of patients with these monogenic obesity syndromes to examine the role of the relevant molecules on eating behaviour, energy expenditure and peripheral metabolism. In collaboration with Professor Paul Fletcher, University Department of Psychiatry, we have an interest in using functional MRI to study the pattern of brain activation involved in aspects of eating behaviour, linking specific molecular pathways to brain responses and behaviour. Our ultimate aim is to be able to translate these findings into benefits for patients with severe obesity by developing better diagnostic tools and targeted mechanism-based therapies.

Our research is funded by the Wellcome Trust, MRC, NIHR Cambridge Biomedical Research Centre, EU FP7 NEUROFAST and EUROCHIP and the Bernard Wolfe Endowment.

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**Genetic Analysis of Susceptibility to Tuberculosis and the Host-Pathogen Interaction**

Tuberculosis kills 1.5 million people every year and it is estimated that one third of the global population is infected with the pathogen, *Mycobacterium tuberculosis*. My group is searching for the human genes that carry sequence variants predisposing to pulmonary tuberculosis, the most common and epidemiologically important form of the disease. Discovery of such genes will help us to better understand biological pathways related to tuberculosis and may point to new targets for its prevention. My group is part of the TB-EUROGEN consortium. We have established the world’s largest collection of samples from 5,000 HIV-negative patients with pulmonary tuberculosis and 5,000 healthy subjects. In collaboration with the Wellcome Trust Sanger Institute we now undertake a genome-wide association study to find regions of the human genome associated with tuberculosis, to identify causative variants that control genetic susceptibility to the diseases in various human populations and to discover their functional effects. The TB-EUROGEN consortium has also collected 2,000 clinical *M. tuberculosis* strains from the same tuberculosis patients and now works to characterise genetic variation in these strains to identify virulence factors of the pathogen and to investigate their interaction with the host.

My research is funded by the European Union, the Wellcome Trust and the Royal Society.

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http://www.med.cam.ac.uk/HTML/PI/Nejentsev/index.html
Molecular and Pathophysiological Mechanism in Human Obesity and Insulin Resistance

We have a major focus on understanding the fundamental basis for the heritability of human obesity, insulin resistance and lipodystrophy in the expectation that better knowledge of the pathways that control human energy balance, adipocyte biology and insulin sensitivity will ultimately lead to clinical benefits. We use a wide range of approaches including human genetics, functional genomics, cell biology, physiological studies in humans and murine models and therapeutic trials. Our research is supported by the MRC, including the MRC Centre for Obesity and Related Metabolic Disease, the Wellcome Trust, the NIHR Cambridge Biomedical Research Centre and the EU Framework Programme.

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David Ron


Signaling Pathways in the Cellular Adaptation to Proteotoxicity

Genetic and biochemical observations suggest that polypeptides that fail to attain their proper three dimensional fold reduce fitness. This process, also referred to as “proteotoxicity”, appears to be particularly important to the fate of non-renewable cells of long-lived organisms in which accumulating misfolded proteins can exert their deleterious effects over extended periods of time. The hypothesized contribution of such “proteotoxins” to cellular aging fits our intuitive notions of aging as a time and use-dependent process and proteotoxicity’s contribution to important diseases of aging, such as the Amyloidoses, Alzheimer’s disease and various forms of Parkinsonism is widely accepted. Recent observations also point to a potential role for low-levels protein misfolding in the secretory pathway to the pathogenesis of diabetes mellitus and other metabolic disorders.

The long-term goal of our research is to identify new components of the cellular response to proteotoxic stress in the secretory pathway and to integrate these into an understanding of pathophysiology of common human diseases, with a special emphasis on metabolic disorders.

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The immune system evolved to protect the host from pathogenic assault. Cellular networks collaborate to ensure pathogens are eradicated before they can cause irreversible tissue damage to the host. Sometimes, the immune system turns against our cells destroying our own tissues. This is called autoimmunity. In Type 1 Diabetes, the immune system attacks the insulin producing β cells in the islets of Langerhans, resulting in insulin-deficiency and as a consequence severe vascular, cardiac and nephrological complications. Our lab focuses on understanding why the immune system breaks down and attacks our own β cells as well as how the immune system is regulated in individuals not prone to autoimmune disease. We made a series of novel discoveries: we identified the CD40-CD154 signal pathway as being integral for the generation, maintenance but not functionality Foxp3 regulatory T cells; we showed that in the late stages of diabetes progression CD8+ T cells and B cells collaborate to push the final destruction of β cells and we identified a novel strategy for preventing diabetes progression and initiating β cell regeneration in late disease stages by inducing β cells to transiently secrete TGFβ, a immunosuppressive molecule. Our future directions will consolidate all these findings and initiate translation of the results into the clinical setting with the aim of developing novel therapeutic strategies to tackle autoimmune diseases.

Moving to position of Senior Lecturer in Immunology, Centre for Immunology and Infection, Hull York Medical School, University of York, Wentworth Way, York.

Principal Investigators who will be moving on from CIMR shortly

Allison Green

The immune system evolved to protect the host from pathogenic assault. Cellular networks collaborate to ensure pathogens are eradicated before they can cause irreversible tissue damage to the host. Sometimes, the immune system turns against our cells destroying our own tissues. This is called autoimmunity. In Type 1 Diabetes, the immune system attacks the insulin producing β cells in the islets of Langerhans, resulting in insulin-deficiency and as a consequence severe vascular, cardiac and nephrological complications. Our lab focuses on understanding why the immune system breaks down and attacks our own β cells as well as how the immune system is regulated in individuals not prone to autoimmune disease. We made a series of novel discoveries: we identified the CD40-CD154 signal pathway as being integral for the generation, maintenance but not functionality Foxp3 regulatory T cells; we showed that in the late stages of diabetes progression CD8+ T cells and B cells collaborate to push the final destruction of β cells and we identified a novel strategy for preventing diabetes progression and initiating β cell regeneration in late disease stages by inducing β cells to transiently secrete TGFβ, a immunosuppressive molecule. Our future directions will consolidate all these findings and initiate translation of the results into the clinical setting with the aim of developing novel therapeutic strategies to tackle autoimmune diseases.

Moving to position of Senior Lecturer in Immunology, Centre for Immunology and Infection, Hull York Medical School, University of York, Wentworth Way, York.

Richard Sandford

My research focuses on the molecular pathogenesis of diseases that have their origin in renal and biliary ductal epithelium. My main focus is on renal mendelian diseases such as autosomal dominant polycystic kidney disease (ADPKD) and UMOD nephropathy and the identification of disease associated pathways that may be amenable to pharmacological manipulation. By generating and characterising cell culture and animal models of ADPKD I am investigating the role of various novel therapeutic agents on ameliorating disease progression. In addition I am studying the functional consequences of disease-associated mutations in in vitro models to develop further cell culture models of disease.

Using a combination of linkage analysis for single gene disorders and genome-wide association studies for complex diseases I am also exploring the molecular basis of several liver associated diseases. These include multiple biliary hamartomas and autoimmune biliary diseases such as primary biliary cirrhosis.

Moving as University Reader to University of Cambridge Department of Medical Genetics, Level 6, Addenbrooke’s Treatment Centre, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 0QQ.
Robots, Electron Microscope and Orbitrap Mass Spectrometer at CIMR

Patrycja Kozik (Robinson group) – siRNA robot, funded by the Wellcome Trust

Dan Johnson (Huntington group) – Crystallography robot, funded by the Wellcome Trust

Robin Antrobus (Lehner group) – Orbitrap mass spectrometer funded by the Wellcome Trust

Nick Bright (Luzio group) – Electron microscope, funded by the MRC
Postgraduate Opportunities in the Institute

Introduction
The CIMR offers an exciting and vibrant environment for graduate students. Approximately 30% of the 270 scientists within the CIMR are postgraduate students carrying out research towards a PhD. There are a variety of schemes that we offer to allow both clinical and non-clinically qualified individuals to pursue a PhD within the Institute. Some of these are for three years whilst others are four year programmes funded by the Wellcome Trust and Medical Research Council (MRC). We also offer Wellcome Trust-funded ‘Next Generation’ Fellowships to enable clinically qualified individuals who have previously undertaken an MD or PhD to obtain preliminary data so that they can apply for an intermediate fellowship to work with a PI within the Institute.

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

Non-Clinical Three Year PhD Programmes
The CIMR offers standard three year PhD programmes. These are usually awarded by the Medical Research Council and research charities to individual principal investigators. These are advertised separately from the four year programmes run within the CIMR. The 3 year PhD students have access to the same seminars, equipment and mentoring as four year PhD students.

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

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

The Director of the four year non-clinical PhD programmes, the Biomedical Research Centre clinical training fellowships and the Wellcome Trust clinical PhD programme is Professor David Lomas, the Director for Graduate Studies within the Institute is Dr Lucy Raymond and the Programme Administrator is Sonia Lyne.
The 2009 Research Retreat was blessed with warm spring weather and excellent presentations from the post-doctoral fellows and graduate students. The presentations were polished, all presenters stuck to time and the talks stimulated plenty of questions. The panel of judges awarded the prize for the best student presentation to Mark Dawson with Helen Stagg as the runner-up. Stefan Marciniak received the prize for the best presentation by a post-doctoral fellow with Misty Jenkins as the runner-up. One of the highlights of the Research Retreat is our opportunity to invite distinguished scientists from around Cambridge to address the Institute. This year we were very lucky to have Hugh Pelham, Director of the MRC/LMB who spoke on the control of protein fate by Nedd4-like ubiquitin ligase adaptors and Daniel St Johnston, Acting Head of the Gurdon Institute, who talked about his work on the link between energy metabolism, tumour suppressors and epithelial polarity. Both gave outstanding presentations. Edmund Kunji from MRC Dunn Human Nutrition Unit (now the MRC Mitochondrial Biology Unit) gave a superb presentation on the transport mechanism of mitochondrial carriers by analysis of pseudo-symmetry. We are grateful to all our external speakers and all members of the CIMR for making the retreat such a success.

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

The Administrative Team aims to provide an effective support service to the academic staff by:

• assisting with the development of staff, the building and its laboratory facilities and equipment;

• ensuring regulatory and legal compliance, especially in the fields of human resources and health and safety;

• producing information and facilitating the flow of information within the Institute and wider University community, including production of a monthly CIMR newsletter which is sent out electronically to everyone in the building;

• developing and maintaining effective decision-making processes including reporting to, and servicing committees, and co-ordinating the work of various units;

• utilising new technologies and methods of working and being responsive to changing needs and requirements.

The Administrator has specific responsibility for contributing to the Institute's strategic direction, policy formulation, administrating grant applications, and, assisted by three human resources clerks and a secretary, human resource issues.

The Laboratory & Facilities Manager, Dave Cheesman, is responsible for overseeing the provision of core laboratory services and is also the CIMR Safety Officer. He is assisted by a deputy and a team of technical staff who co-ordinate services on each level. Media kitchen and Glasswash functions are supervised by the Deputy Lab Manager and Senior Level Co-ordinator respectively.

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

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

Ray Woodstock, the Building Services Supervisor, is responsible, with two members of staff, for maintaining the day to day running of the building, including repairs, modifications and alterations.
CIMR Support Organisational Chart

Director
CIMR

Deputy Director
CIMR

Secretary

Administrator

Other Admin
Support Staff

Research Group
Technicians

Laboratory/Facilities
Manager

Building Services
Supervisor

Secretary

Senior
HR Clerk
Admin Officer
(Finance)

Computer Officer

Bioinformatics /
Systems Support

2x Confocal /
Imaging Support

Proteomics
Technician

Head of
Flow Cytometry

2x Purchasing
Clerks

2x Accounts
Clerks

Senior Accounts
Clerk

Systems Support
& Audio Visual

University Funded
Joint University / MRC Funded
Service on Building Wide Basis

Wellcome Trust Infrastructure Funded
Grant Funded / Cost Recovery
University Funded / Cost Recovery
MRC Funded / Cost Recovery

2x HR
Clerks

4x
Receptionists

2x HR
Clerks

Senior Custodian

2x Custodians

2x Glasswash
assistants

2x Media
Technicians

Senior Level
Co-ordinator

1x Assistant
Level Co-
ordinator

1x Level
Co-ordinator

Deputy Lab
Manager

Building
Technician

2x Media
Technicians
Funding of CIMR

Total grant income has continued to increase each year from £12m (2001/2002) to £20m (2008/2009).

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

CIMR Grant Expenditure

Total Value of Grants Held in CIMR
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 2007–July 2008

- £187,323
- £198,855
- £204,516
- £758,994

Recurrent Costs for the Wellcome Trust/MRC Building & CIMR
August 2007–July 2008

- £187,323
- £315,742
- £286,667
- £361,910
- £1,219,479

- £782,814
- £782,814
- £782,814
- £782,814
- £782,814

Wellcome Trust Pay
Wellcome Trust non Pay
University Pay
University non Pay
University/MRC Shared Pay
University/MRC Shared non Pay
Honours, Awards & Personal Fellowships

Principal Investigators:

**Folma Buss:** Wellcome Trust University Award, 2009.

**David Clayton:** Honorary Chair, Department of Epidemiology and Population Health, Medical Statistics Unit, London School of Hygiene and Tropical Medicine.

**Andres Floto:** Wellcome Trust Senior Research Fellowship in Clinical Sciences, 2008.

**Fiona Gribble:** Wellcome Trust Senior Research Fellowship in Clinical Sciences, renewed 2009.

**Allison Green:** Juvenile Diabetes Research Foundation Mary Jane Kugel award.

**Tony Green:** appointed NIHR Senior Investigator, 2008 and elected to Association of American Physicians, 2009.

**Brian Huntly:** University of Cambridge Senior Lectureship, Department of Haematology, 2009.

**Fiona Karet:** Wellcome Trust programme grant, 2009.

**Paul Lehner:** Wellcome Trust Senior Research Fellowship in Clinical Sciences, renewed 2008.

**David Lomas:** Gordon Cummings lecture, Medical Research Society, 2008; Alpha-1 Association (USA) Advancement of Research Award, 2008; Professorial Fellow, St John’s College Cambridge, 2008 and Applebaum Visiting Professorship, University of Florida School of Medicine, 2009.

**Sergey Nejentsev:** Royal Society Fellowship, 2008.

**David Owen:** Professorship of Structural and Molecular Biology in the University of Cambridge, 2009.

**Lucy Raymond:** University of Cambridge Readership in Neurogenetics, 2008.

**Frank Reimann:** Wellcome Trust Senior Research Fellowship in Basic Biomedical Science, 2008.

**Margaret Robinson:** Wellcome Trust Principal Research Fellowship, renewed 2009 and Professorship of Molecular Cell Biology in the University of Cambridge extended.

**David Rubinsztein:** Spinoza Professorship, University of Amsterdam, 2009.

**Peter St George-Hyslop:** the Killam Award, June 2008 and PI for Wellcome Trust and MRC Neurodegenerative Diseases Initiative Awards, 2009.

**Matthew Seaman:** MRC Senior Research Fellowship, renewed 2008.

**Symeon Siniossoglou:** MRC Senior Research Fellowship, 2008.

**John Todd:** National Disease Research Interchange (NDRI) Distinguished Scientist Award, 2008; NIHR Senior Investigator, 2009; PI for MRC’s Eastern Sequence and Informatics Hub (EASIH), 2009, Visiting Professorship, University of Sassari, Sardinia, 2009 and FRS, 2009.

Research Scientists:

**Louise Boyle:** (Trowsdale), Wellcome Trust Career Development Fellowship, 2009.

**Virginia Clowes:** (Reid), MRC Clinical Training Fellowship, 2008.

**George Follows:** (Tony Green), Associate Lecturer in Clinical Medicine, 2008.

**Stephen Graham:** (Owen), Royal Commission 1851 Research Fellowship, 2009.

**Emma Gudgin:** (Huntly), Junior Research Fellowship from Kay Kendall Leukaemia Fund, 2008.

**Thomas Hiemstra:** (Karet), Research Training Fellowship from Action Medical Research, 2008.

**Patrycja Kozik:** (WT 4 yr PhD Student on the Infection & Immunity Programme in Margaret Robinson’s group) received one of three “best poster” prizes awarded at the Final Year Wellcome Trust PhD Students’ Meeting in London, January 2008. The poster title was “Screening for novel trafficking motifs and adaptor proteins”.

**Duncan Massey:** (Rubinsztein), MRC Clinical Training Fellowship, 2008.

**George Mells:** (Sandford), MRC Clinical Training Fellowship, 2008.

**Maja Wallberg:** (Allison Green), RD Lawrence Fellowship from Diabetes UK, 2009.

**Elaine Jolly:** (Smith), MRC Clinical Research Training Fellowship, 2010.
**Editorial Boards of Journals**

**David Clayton** is on the editorial board of *Annals of Human Genetics*.

**Fiona Gribble** is on the editorial boards of *Endocrinology*, *Biological Journal*, *Molecular & Cellular Endocrinology* and *British Journal of Pharmacology*.

**Gillian Griffiths** is on the editorial boards of *Traffic*, *Journal of Biology*, *Journal of Cell Biology* and *Current Opinions in Cell Biology*.

**James Huntington** is on the editorial board of *Biochemical Journal*.

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

**Paul Lehner** is on the editorial board of *Immunology & Cell Biology*.


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

**Margaret Robinson** is on the editorial boards of *Current Opinion in Cell Biology* and *Traffic*.

**David Rubinsztein** is Associate Editor of *Autophagy*; Academic Editor of *PLoS ONE* and on the editorial boards of *Human Molecular Genetics*, *Journal of Applied Biomedicine*, *Cell Death & Differentiation* and *Pathogenetics*.

**Christopher Rudd** is on the editorial boards of *Current Biology*, *Immunology*, *International Journal of Biochemistry*, *European Journal of Immunology*, *Self/Non-Self, Immune Recognition and Signaling*; is guest editor of *Proceedings National Academy of Science*; is academic editor of *PLOS ONE* and editor of *Seminars in Immunopathology* (2010 issue).

**Peter St George-Hyslop** is on the editorial boards of *Journal of Clinical Investigation* and *Neurodegenerative Diseases*.

**Richard Sandford** is on the editorial board of *Nephron*.

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

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

**John Trowsdale** is on the editorial boards of *European Journal of Immunology* and *Tissue Antigens*.

**Linda Wicker** is an Advisory Editor of *Journal of Experimental Medicine*.

**Geoff Woods** is on the editorial board of *Journal of Medical Genetics*.

**Staff Affiliations**

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

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

**Allison Green** is a member of the Infection and Immunity Grant Review Panel, Health Research Board, Dublin, Eire; the Medical and Scientific Review Committee, Juvenile Diabetes Research Foundation, USA; the Cambridge University Home Office Licence Amendment Committee and the Board of Reviewers for the journal ‘Review of Diabetic Studies’, Germany.

**Tony Green** is a member of the American Society of Haematology; the American Association of Physicians; the Association of Physicians; the British Society for Haematology; the British Association for Cancer Research; the European Haematology Association; the European Haematology Association Scientific Program Committee; the International Society for Experimental Haematology; the European School of Haematology Executive Committee; the European Haematology Association, Scientific Programme Committee; the NCR Myeloproliferative Disorder Study Group; the UK Research Assessment Exercise 2008, Panel A5; the American Society of Hematology, Scientific Committee for Hematopoietic Cytokines and Factors; the Scientific Advisory Board, Hemato-Linné Stem Cell Programme; the MRC Translational Stem Cell Research Committee and the European Haematology Association Board; is Head, University of Cambridge Department of Haematology; is Chairman of the Addenbrooke’s Hospital Haematology Senior Staff Group; the Scientific Advisers to the Kay Kendall Leukaemia Fund; the European Haematology Association Education Committee and the European
Brian Huntly is a member of the CRUK Discovery Committee; the LRF Medical and Scientific Advisory Panel; the European Hematology Association, Membership Committee; the European Hematology Association, Member of the Scientific Advisory Committee for the 14th Annual European Hematology Association meeting, Berlin 2009; the European Hematology Association, Member of the Scientific Advisory Committee for the 15th Annual European Hematology Association meeting, Barcelona 2010 and an invited Faculty member, Faculty of 1000.

Fiona Karet is Chair of the Kidney Research UK Grants Committee; a member of the Kidney Research UK Strategy Committee; the Wellcome Trust Clinical Interview Committee; the Association of Physicians Executive; the UK Renal Association Research Committee and the UK Rare Renal Diseases Strategy Group and a Clinical Research Champion of the Academy of Medical Sciences/Medical Research Society.

Paul Lehner is a panel member on the Wellcome Trust Infection & Immunity Board.

David Lomas is Chair of the Asthma UK Grants Committee and the Alpha One Foundation; a member of the MRC Population and Systems Medicine Board; the GSK Respiratory CEDD (Centre of Excellence in Drug Discovery); the Alpha-one antitrypsin Laurell Training Award (ALTA); Director of the Wellcome Trust 4 year PhD programme, CIMR and the Wellcome Trust Clinical PhD Programme and Theme Lead for BRC Fellowships and Capacity Building.

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

Lucy Raymond is a member of the Action Medical Research Scientific Advisory Board Grants Panel.

Randy Read is a member of the Executive Committee of CCP4 (Collaborative Computing Project 4) and Chair of the X-ray Validation Task Force for the worldwide Protein Data Bank.

Evan Reid is a member of the International Scientific Advisory Board of the American Spastic Paraplegia Foundation.

David Rubinsztein is a member of the Wellcome Trust Molecular & Cellular Neuroscience Committee; the MRC College of Experts; the MRC Sub-Committee – Strategic Review of Neurodegeneration and the Parkinson’s Disease Brain Bank Assessment Panel.

Christopher Rudd is a member of the Wellcome Trust Basic Immunology and Infectious Diseases Panel; the Scientific Committee 2nd European Congress of Immunology (Berlin, Sept, 2009); the Organising Committee 15th International Congress of Immunology (Rome, August, 2013); a Trustee and International Secretary of the British Society for Immunology; a Council Member of the International Union of Immunological Societies and a Consultant, Astrazeneca UK.

Peter St George-Hyslop is a member of the Dana Neuroscience Initiative Scientific Advisory Board; the Charles A Dana Foundation Scientific Advisory Board; the World Federation of Neurology Scientific Advisory Board; the Dementia Study Group; the Ontario Brain Research Institute Initiative; the Ontario Scientific Advisory Group; the Deutsches Zentrum für Neurodegenerative Erkrankungen (German Centre for Neurodegenerative Diseases) Scientific Advisory Board and the Alzheimer Research Trust Scientific Advisory Board.

Richard Sandford is a member of the WTCCC3 Management Committee; the PKD Foundation Grant Committee; the Renal Association Clinical Trials Committee; the Clinical Study Group for cystic diseases (Renal Association, KRUK and the UK Kidney Research Consortium (UKKRC)); the Renal Association & British Association for Paediatric Nephrology Strategic Planning Group for rare metabolic & inherited renal diseases and a Medical Advisor of the PKD Charity.

Matthew Seaman is a member and contributor of the Faculty of 1000.

Ken Smith is a member of the Wellcome Trust Clinical Research Facility Scientific Advisory Board; Chairman of the Steering Committee for the Cambridge Immunology Initiative and the Cambridge Steering Committee of the NIH-Cambridge Biomedical Research Graduate Programme.

John Todd is a Governor of Strangeways Research Laboratory, Cambridge; a member of the Type 1 Diabetes Steering Committee; the Cambridge Computational Biology Institute Management Committee, University of Cambridge; the Wellcome Trust Case Control Consortium Management Committee; the Institute of Metabolic Science – Metabolic Research Laboratory Steering Committee; the Cancer Research UK Population and Behavioural Sciences Committee; the Scientific Advisory Board of NIHR Biomedical Research Centre Core Biochemical Assay Lab (CBAL); the Wellcome Trust Sanger Institute Human Genetics Faculty and Career Development Fellows Recruitment Committee; the Juvenile Diabetes Research Foundation UK Scientific Advisory Committee; the Cancer Research UK Biological Sciences Committee; the Wellcome Trust Genome Wide Association Studies Themed Committee and Acting Head, University of Cambridge Department of Medical Genetics.

John Trowsdale is a member of the Faculty of 1000.

Linda Wicker is a member of the Medical Science Review Committee of the Juvenile Diabetes Foundation International and Chairman and member of the Type 1 Diabetes Repository Advisory Committee, National Institutes of Health.

Geoff Woods is Clinical Lead of Medical Genetics – NHS.
Fellows of the Royal Society

Stephen O’Rahilly, Peter St George-Hyslop, John Todd.

Fellows of the Academy of Medical Sciences

Jenefer Blackwell, Tony Green, Gillian Griffiths, Fiona Karet, Paul Lehner, David Lomas, Paul Luzio, Stephen O’Rahilly, Margaret Robinson, David Rubinsztein, Christopher Rudd, Peter St George-Hyslop, Ken Smith, John Todd, John Trowsdale.

EMBO Members

Gillian Griffiths, Stephen O’Rahilly, Margaret Robinson.


Blake-Palmer, K. G. and Karet, F. E. (2009). Cellular physiology of the renal...


Davies, M. J., Miranda, E., Roussel, B. D., Kaufman, R. J., Marciniak, S. J. and...


Greiner, D. L. (2009). Idi loci synergize to prolong islet allograft survival induced by costimulation blockade in NOD mice. 
*Diabetes* 58, 165–73.


analysis of eight novel domain-deletion beta(3) integrin peptides designed for detection of HPA-1 antibodies. J Throm Haemost 6, 366–75.


transcriptional program controlled by the


Christmas Parties

**MEDIEVAL FAYRE**

COME ALL YE LORDS, LADIES, KNIGHTS AND PEASANTS TO THE ANNUAL CHRISTMAS PARTY

THERE WILL BE DRINKING IN YE OLDE TAVERN AND DANCING IN THE SACKLER THEATRE.

A SELECTION OF PERIOD FOOD CAN ALSO BE CONSUMED IN THE CASTLE’S BANQUETING HALL

**DATE:** 15 DEC 2008

**TIME:** 7.30 PM UNTIL MIDNIGHT

**LOCATION:** LEVEL 7 CANTEEN AND SACKLER THEATRE

**TICKET PRICE:** £5 PER PERSON

(3 GUESTS PER STAFF MEMBER)

TICKETS ARE ON SALE NOW FROM THE LEVEL 7 CANTEEN BETWEEN 12.30PM - 1.30PM

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The Wellcome Trust/MRC Building’s annual Christmas Party Posters
The Wellcome Trust/MRC Building which houses the Cambridge Institute for Medical Research and the MRC Mitochondrial Biology Unit
Regulations for CIMR

Management

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

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

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

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

5 The duties of the Management Committee shall be as follows:
(a) to advise the Director (Chairman) of the Institute on strategic issues and the 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.

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.

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

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

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

1 The Strategy Committee shall designate one of its 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
An RNAi screen identified TRC8 as a novel E3 ligase in human cytomegalovirus (HCMV) mediated MHC I dislocation. We find TRC8 complexed with MHC I, HCMV encoded US2 and signal peptide peptidase.

(Image courtesy of D. Bhella & S. J. Butcher, MRC Virology Unit/University of Helsinki, and P. J. Lehner, CIMR)

Progenitor populations in the developing human brain. Human embryonic neuroepithelium, CS22, showing the relative positions of apical progenitors and their processes (nestin, green), basal progenitors (Tbr2, red) and neurons (tubulin III, blue).

(Illustration courtesy of Geoff Woods.)