Front cover illustration:
Crystal structure of the lysosomal enzyme galactocerebrosidase which, when defective, causes widespread demyelination resulting in the fatal neurodegenerative disorder Krabbe disease. The structure illustrates how the substrate-mimic galactose binds in the active site. Figure modified from Deane et al. (2011) Proc Natl Acad Sci USA.

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The Cambridge Institute for Medical Research (CIMR), which is housed in the Wellcome Trust/MRC Building, is a cross-departmental institute of the University of Cambridge Clinical School. It provides a unique interface between basic and clinical science, houses over 250 scientists and has as its major goal, the determination and understanding of the molecular mechanisms of disease. Over 40% of our Principal Investigators (PIs) are medically qualified and clinically active, a percentage that has remained steady since the CIMR opened in 1998. Our annual research grant expenditure is now the third highest in the University behind the Departments of Engineering and Physics (Cavendish Laboratory). In the University’s financial year 2010–11 the expenditure exceeded £21M, with about 60% funded by the Wellcome Trust and 15% by the MRC (see p 50).

Research in the CIMR is led by individual Principal Investigators (PIs) who determine their own research priorities and follow their own instincts. It is focussed on four research themes that transcend individual research groups, namely misfolded proteins and disease, intracellular membrane traffic in health and disease, autoimmune disease and haematopoietic stem cells and their disorders. In each of these themes, there have been many recent discoveries and advances that are referenced in this Research Report on the pages of individual PIs. Examples of activities that are further down the translational path to patient benefit include (i) the introduction by Tony Green of the diagnostic use of genetic mutations for frontline investigation of myeloproliferative disorders that are now a central part of national and international guidelines; (ii) Ken Smith’s identification and use of novel transcription signatures to predict prognosis in autoimmune disease; (iii) the clinical safety trial of an autophagy-inducing drug for Huntington’s disease following David Rubinsztein’s pioneering studies of the activation of autophagy to clear mutant huntingtin in cell and animal models of Huntington’s disease; (iv) David Lomas’ high throughput screens to identify small molecules to block serpin aggregation and so treat patients with serpinopathies and (v) the interactions of Fiona Gribble and Frank Reimann with pharmaceutical companies to develop new therapies for type II diabetes. Taken together our four research themes constitute a comprehensive approach to molecular and cellular mechanisms of disease in which there is clear ‘added value’ from the extensive interactions between basic and clinical scientists and across different themes.

A question that is increasingly asked about research activities funded by major grant giving bodies in Universities is how they fit with the University’s overall research strategy. In a recent submission to the Wellcome Trust, the Heads of the Schools of Biological Sciences and Clinical Medicine have pointed out that the ability to attract outstanding biomedical scientists working on important problems increasingly depends upon the establishment of ‘critical mass’ and the provision of optimal research infrastructure. Together, these have required a change in strategic approach exemplified by the establishment and development within the University of cross-departmental, interdisciplinary institutes including the CIMR. There are ten strategic research themes within the basic biological and biomedical sciences that cross the two Schools and the CIMR plays a major role in two of these, Structural and Cell Biology and its Application to Medicine, and Genomics and its Application to Medicine. PIs in the CIMR also make a significant contribution to four other strategic themes, Infection and Immunity, Neurosciences and Mental Health, Stem Cell Biology and Medicine, and Systems Medicine. The research activities in the CIMR are complementary to those in other research institutes and departments of the University and NHS as well as major research institutes in the Cambridge area, with many of whom we have excellent interactions. Through the activities and collaborations of individual PIs and often through the placing of research students from PhD programmes administered through the CIMR, we have active interactions with the Wellcome Trust Sanger Institute, the MRC-Laboratory of Molecular Biology, the Babraham Institute, the CRUK-Cambridge Research Institute, the MRC Cancer Cell Biology Unit, the Wellcome Trust/CRUK Gurdon Institute and the Wellcome Trust Centre for Stem Cell Research. Within the Clinical School, three of our PIs are currently
Heads of Department, namely Ken Smith (Medicine), Tony Green (Haematology) and John Todd (Medical Genetics). We have recently strengthened our relationship with the Institute of Metabolic Science through the appointment of one of their PIs, David Ron to our Institute Management Committee. CIMR PIs also contributed significantly to the recent successful renewal of the NIHR Cambridge Biomedical Research Centre (BRC). John Todd, David Rubinsztein, Ken Smith, Tony Green and David Lomas are all theme leads in the BRC and Peter St George-Hyslop is the lead PI for the new NIHR Cambridge Dementia Biomedical Research Unit.

No research strategy or focus can be meaningful without the appointment and nurturing of outstanding individual scientists. A remarkably high proportion of our PIs have part or all of their salaries funded through very competitive fellowships awarded by biomedical funding agencies. The CIMR presently has the highest number of Wellcome Trust Principal Research Fellows (8, although David Clayton will retire in March 2012), in any institute or department in the country. Amongst these are David Owen and David Rubinsztein who won their awards in the past two years. We are also proud of our record in training and developing young scientists including clinician scientists. In the past two years, two young CIMR clinician scientists, Mark Dawson and Rhys Roberts were awarded Wellcome-Belt Prize Fellowships. It was especially pleasing that Rhys Roberts and also Mike Weekes gained their intermediate fellowships from the Wellcome Trust following periods funded as CIMR Next Generation Fellows to help them back into research from full time clinical posts. We hope that in time all of our intermediate clinical research fellows will do well enough to be competitive for senior fellowships, following in the footsteps of other clinician scientists such as Evan Reid and Stefan Marciniak who became CIMR PIs in recent years. We also take seriously the development and promotion of women scientists. It is a pleasure to note that Katrin Ottersbach has taken up a Bennett Senior Fellowship from Leukaemia and Lymphoma Research and that Janet Deane has been appointed as one of our new PIs following the recent award of a Royal Society University Research Fellowship. In the CIMR we are aware that our track record of consistently having around 30% of our PIs who are women compares favourably with other institutes. However, this proportion must be at least maintained and preferably increased. Therefore, we will fully support Fiona Karet, one of our PIs, in her work leading the Clinical School’s efforts to develop an application for an Athena Swan Silver Award. We must aim to improve our recruitment, retention and promotion of women in the CIMR as well as elsewhere in the Clinical School.

I have referred briefly above to the imminent retirement of David Clayton who has contributed so much to the work of the Diabetes and Inflammation Laboratory in the CIMR. I thank David for his work in the institute and wish him well in the future. There are two other people who will reach retirement in 2012 that I also wish to thank for their support of the CIMR. The first is Sir John Walker FRs, the Director of the MRC Mitochondrial Biology Unit with whom we share our building. I hope that we are able to build up equally good relations with his successor. The second is the Regius Professor ofPhysic, Sir Patrick Sissons who has been a stalwart supporter of the CIMR both as Regius and in his previous role as Head of the Department of Medicine. It has been a great pleasure to work with Patrick who has led the Clinical School with great wisdom and care to a point where it is poised for very exciting developments in the future.

In the CIMR the major challenges are both to continue to improve our science and to be a flagship in the UK for interdisciplinary research at the interface between basic and clinical science. We remain very grateful for the Wellcome Trust Strategic Award, currently extended until late 2012. That award greatly enhances our efforts as a translational institute and specifically supports our core scientific facilities, funds PhD studentships and also provides funds to attract young clinicians back into research. Our high proportion of clinically active PIs allows the rapid translation of scientific breakthroughs into clinical practice. In the coming years such translation is likely to include the identification of new pathways of disease, the identification of new small molecule and cell based therapies to treat protein misfolding diseases and new molecular diagnostics for haematological malignancies. However, there is no simple mechanical route from scientific research to clinical practice and it behoves us all to keep in mind the words of Marie Curie, who in an address to Vassar College in Poughkeepsie, New York on May 14th, 1921 said, “But we must not forget that when radium was discovered no one knew that it would prove useful in hospitals. The work was one of pure science. And this is a proof that scientific work must not be considered from the point of view of the direct usefulness of it. It must be done for itself, for the beauty of science, and then there is always the chance that a scientific discovery may become like the radium a benefit for humanity.”

Paul Luzio
January 2012

Current Membership of the CIMR Strategy Committee:

Patrick Sissons (Chairman, Regius Professor of Physic), Alastair Compston (Clinical Neurosciences), 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), Geoffrey Smith (Pathology), Ken Smith (Medicine), John Todd (Diabetes and Inflammation Laboratory/Medical Genetics).

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), Sandra Schmid (Scripps Research Institute), Patrick Vallance (GlaxoSmithKline plc)
## CIMR Principal Investigators

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<tr>
<th>Principal Investigator</th>
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<tr>
<td>Folma Buss</td>
<td>Wellcome Trust University Award</td>
<td>Clinical Biochemistry</td>
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<td>Janet Deane</td>
<td>Royal Society University Research Fellow</td>
<td>Haematology</td>
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<td>Andres Floto</td>
<td>Wellcome Trust Senior Research Fellow in Clinical Sciences</td>
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<tr>
<td>Bertie Göttgens</td>
<td>Personal Chair</td>
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<td>Tony Green</td>
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<td>Fiona Gribble</td>
<td>Wellcome Trust Senior Research Fellow in Clinical Sciences</td>
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<td>Gillian Griffiths</td>
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<td>James Huntington</td>
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<td>Brian Huntly</td>
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<td>Fiona Karet</td>
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<td>Paul Lehner</td>
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<td>David Lomas</td>
<td>University Chair and Deputy Director CIMR</td>
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<td>Paul Luzio</td>
<td>Personal Chair and Director CIMR</td>
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<td>Stefan Marciniak</td>
<td>MRC Senior Clinical Research Fellow</td>
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<tr>
<td>Katrin Ottersbach</td>
<td>Leukaemia &amp; Lymphoma Research Bennett Senior Fellow</td>
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<td>David Owen</td>
<td>Wellcome Trust Principal Research Fellow and Personal Chair</td>
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<td>Lucy Raymond</td>
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<td>Randy Read</td>
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<td>Evan Reid</td>
<td>Wellcome Trust Senior Research Fellow in Clinical Sciences</td>
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<td>Frank Reimann</td>
<td>Wellcome Trust Senior Research Fellow in Basic Biomedical Science</td>
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<td>Margaret Robinson</td>
<td>Wellcome Trust Principal Research Fellow and Personal Chair</td>
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<td>David Rubinsztein</td>
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<td>Christopher Rudd</td>
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<td>Peter St George-Hyslop</td>
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<td>Clinical Neurosciences</td>
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<td>Matthew Seaman</td>
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<td>Symeon Siniossoglou</td>
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<td>Ken Smith</td>
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<td>John Todd</td>
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<td>Linda Wicker</td>
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<td>Geoff Woods</td>
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Myosin Motor Proteins in Health and Disease

We want 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 actin-based myosin motors and their roles in cargo transport, cell signalling and membrane dynamics.

The main focus of our current research is myosin VI, which is unique because it moves in the opposite direction along actin filaments to all the other myosins. Myosin VI is an extremely versatile motor that functions in membrane trafficking pathways associated with secretion and endocytosis and is thereby linked to cell migration and cytokinesis. We have shown that these diverse roles of myosin VI are mediated by its interaction with a wide range of distinct binding partners (adaptors) that connect it to different cargoes.

Overexpression or mutations or the absence of myosin VI have been linked to such diverse pathological processes as deafness, cardiomyopathy, neurodegeneration and cancer. We are currently unravelling the novel function(s) of the myosins and their cargo adaptors in neurodegenerative diseases such as Alzheimer’s and motor neuron disease. In addition we are investigating the molecular role of myosin VI in cardiomyocytes and heart disease.

The human genome contains 40 distinct myosins and therefore we are expanding our studies to investigate the complementary roles of these different myosins in membrane trafficking pathways. For example we are currently focusing on the role of class I myosins in endocytic membrane recycling.

Our long-term goal is to establish how the different actin- and microtubule-based motor proteins interact together and how their actions are coordinated and regulated to maintain the health and functions of cells.

Cargo attachment of myosin VI is mediated by binding partners identified in Mammals (yellow) and in Drosophila (blue) (from Buss & Kendrick-Jones (2011) PNAS 108, 5927–5928). Myosin VI and its adaptor GIPC colocalise on early endosomes.
Host-pathogen Interactions During *Shigella* Infection

Diseases caused by bacteria, viruses and other parasites are major causes of death, disability, and social and economic disruption for millions of people. Our ability to effectively treat infectious diseases is being progressively depleted due to increasing resistance of microbes to antimicrobial drugs. A top priority today is the development of new low-cost drugs that can replace those that are becoming ineffective. An essential part of developing new therapeutics is a clear molecular understanding of how pathogens evade our immune defences and hijack our cellular components.

Our research focuses on the bacterial pathogen *Shigella flexneri*. This pathogen invades cells of our digestive tract and hijacks components of the actin polymerization pathway in order to aid its movement within our cells and allowing it to spread directly from cell to cell. In this way *Shigella* can limit its detection by our immune system. As an extra defence *S. flexneri* produces proteins that specifically disarm the intracellular immune response to pathogens. We study the structure, interactions and regulation of *Shigella* virulence proteins and the host proteins they target.

In collaboration with the laboratories of Prof Read and Prof Luzio in the CIMR and Prof Cox in the Department of Medicine we are also studying how clinically-identified mutations of the enzyme galactocerebrosidase (GALC) result in Krabbe disease, a devastating neurodegenerative disorder. Our recent structure of GALC has provided new insight into the molecular role of pathogenic mutations and allowed us to identify patients that might be responsive to a new form of therapy known as pharmacological chaperone therapy.

![Structure of the lysosomal enzyme galactocerebrosidase illustrating clinically-identified mutations which cause the fatal neurodegenerative disorder Krabbe disease.](image_url)

Figure taken from Deane et al (2011) PNAS.
Antigen Processing by Macrophages and Dendritic Cells

We are interested in understanding how antigen processing is controlled by macrophages and dendritic cells and how it may be dysregulated in autoimmune disease and subverted by pathogenic bacteria.

Our research is focused on two interrelated areas:

1. Control of phagosomal function
   Particulate antigen and bacteria are internalised into a membrane compartment known as the phagosome that successively fuses with early and late endosomes and finally lysosomes. The behaviour of the phagosome regulates cargo degradation and bacterial killing, cytosolic export of antigen for cross-presentation and inflammasome activation. Using a variety of live cell imaging, cellular and biochemical techniques, we are examining how i) signalling from Fcγ receptors (FcγRs), Toll-like receptors (TLRs) and scavenger receptors interact to control phagosomal function in human macrophages and dendritic cells; ii) how ion channels and transporters modulate phagosomal pH and peri-phagosomal calcium levels to control cargo degradation and lyosomal fusion; and iii) how macro-autophagy pathways interact with phagosomes to determine functional outcomes.

2. Mycobacterial infection
   We are studying how M. tuberculosis and non-tuberculous mycobacteria (NTM) interact with macrophages and dendritic cells particularly i) defining novel host factors controlling bacterial detection, intracellular killing and antigen presentation (through functional screening of genes identified from genetic studies); ii) examining whether therapeutic enhancement of autophagy can be used to improve intracellular killing and how inadvertent pharmacological block of autophagy might predispose to NTM infection; iii) identifying new genetic determinants controlling the pathogenesis of the NTM species M. abscessus through the combination of whole genome sequencing (in collaboration with Julian Parkhill, WTSI), in vitro functional phenotyping and clinical disease characteristics.

Calcium oscillations surrounding phagosomes containing IgG-coated beads (1,2) are detected in primary macrophages using the membrane-targeted calcium reporter Lck-GCaMP3 and are only partially mirrored by plasma membrane calcium signalling (3).
Transcriptional Control of Normal and Leukaemic Blood Stem / Progenitor Cells

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.


The JAK/STAT pathway plays a key role in stem cell biology and is implicated in many human malignancies. A single acquired gain-of-function V617F mutation in JAK2 is present in most patients with a myeloproliferative neoplasm (MPN), a spectrum of clonal haematological malignancies which arise in the haematopoietic stem cell compartment. These disorders are experimentally tractable, permit clonal analysis and provide a window on the earliest stages of tumorigenesis. The Green lab is focussing on the pathogenesis of the MPNs and particularly on the molecular and cellular consequences of JAK2 mutations. Recent highlights of general relevance for stem cell and cancer biology include unexpected insights into chromatin biology, clonal evolution and haematopoietic stem cell function.

Human MPNs represent a spectrum of clonal haematological malignancies, with four main members: polycythaemia vera (PV), essential thrombocythaemia (ET), primary myelofibrosis (PMF) and chronic myeloid leukaemia (CML). A single acquired gain-of-function JAK2V617F mutation is present in most patients with non-CML MPNs. Our subsequent results suggest that V617F-positive ET and PV form a phenotypic continuum and that V617F homozygosity contributes to the PV phenotype. We made the surprising observation that leukaemic transformation is associated with loss of the JAK2V617F mutation and identified a cluster of new JAK2 mutations which define a previously-unrecognised MPN variant. In addition we have demonstrated that inhibition of Bcl-xL deamination represents a novel mechanism underlying DNA damage accumulation. Most recently we have described a novel nuclear function for JAK2 in the phosphorylation of histone H3, have demonstrated that JAK2V617F unexpectedly impairs haematopoietic stem cell function and have identified an unexpected role for STAT1 signalling in MPN pathogenesis. These data are laying the foundation for new approaches to the diagnosis, classification and therapy of the myeloproliferative disorders – JAK2 mutation status is already embedded in clinical guidelines and JAK2 inhibitors are in clinical trials.

Analysis of individual haematopoietic colonies revealed an unexpected role for STAT1 signalling in the pathogenesis of distinct myeloproliferative disorders. Colonies carrying an identical JAK2V617F mutation from patients can exhibit differential activation of the STAT1 signalling pathway which provides an explanation for the distinct clinical phenotypes associated with these disorders (Chen et al. Cancer Cell 2010). ET, essential thrombocythaemia; PV, polycythaemia vera.
Stimulus-secretion Coupling Mechanisms in Intestinal Enteroendocrine Cells

Hormones from the gastrointestinal tract play key roles in the control of appetite and insulin release. Drugs based around one of these hormones, glucagon like peptide-1 (GLP-1), have recently proved to be highly successful for treating type 2 diabetes. This has led to the current focus on developing strategies to enhance the release of endogenous GLP-1 and other gut peptides, in the hope that this may identify novel treatments for diabetes and obesity and mimic the beneficial physiological effects of gastric bypass surgery. Understanding the mechanisms underlying secretion from gut endocrine cells is central to this approach, and forms the focus of our research.

In collaboration with the group of Dr Frank Reimann, we employ a variety of optical and electrophysiological recording techniques to monitor stimulus detection and vesicle release from primary and immortalised GLP-1 secreting L cells. As the identification of living gut endocrine cells was a previous major impediment to this field of research, we have generated transgenic mouse models in which GLP-1-expressing cells, or other target cells of interest, are labelled by cell-specific fluorescent markers. These are amenable to purification by flow cytometry and identification in primary culture for single cell recordings. The combination of single cell recordings with transcriptional analysis of FACS-purified cell populations has generated new models for nutrient sensing by L cells. Detection of nutrients in the gut lumen appears to involve electrogenic ion-coupled transporters located on the apical L cell membrane, generating small electrical signals that are subsequently amplified by voltage gated Ca\(^{2+}\) entry and other signalling pathways such as cAMP elevation and stored Ca\(^{2+}\) release. Comparisons between different enteroendocrine cell types suggest that the pathways identified in L cells are likely to reflect more general stimulus detection mechanisms employed by a wider population of gut endocrine cells.

A. Intracellular [glucose] in GLP-1 secreting cells monitored by a FRET-based glucose sensor, showing that blocking GLUT transporters abolishes glucose uptake.

B. Model of L-cell glucose-sensing.
Control of Secretion at the Immunological Synapse

Cells of the immune system need to communicate in order to co-ordinate an effective immune response. The immunological synapse formed between effector cells and their antigen-presenting cells provides a mechanism for directed communication, either via cell surface receptors or secreted proteins. Secretion is focused within the synapse: in the case of cytotoxic T lymphocytes (CTL) this is essential so that only the infected target is destroyed.

This lab studies the mechanisms that control secretion within the immunological synapse using a range of functional, biochemical and imaging techniques. We have close clinical collaborations that allow us to study CTL from patients with genetic diseases (eg Haemophagocytic Lymphohistiocytosis) that disrupt secretion at the immunological synapse, and thereby identify the machinery required for granule delivery and fusion at the synapse as well as providing a better understanding of the genetic disease.

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. This mechanism, that requires the centrosome to dock at the plasma membrane, bears striking similarities to cilia formation, with endocytosis and exocytosis focused at the point of centrosome docking in both. We are currently exploring the molecular similarities between cilia and synapse formation using genetic, morphological and functional studies.

CTL provide an excellent model for understanding the mechanisms that control centrosome polarization, and we have exploited genetic models in which components of the T cell receptor signaling pathway can be turned off. A key aspect to all of these studies is the use of live imaging to follow synapse formation and secretion in real time, and dissect out the delivery of the secretory machinery to the immunological synapse.

A cytotoxic T cell, with the membrane labelled with CD8 (purple), and microtubules (green) polarised towards a target cell. The secretory lysosomes of the CTL (red) move towards the microtubule organising centre and deliver their contents at the immunological synapse, leading to the destruction of the target. Nuclei of both CTL and target are stained 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 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. Other projects focus on the large multi-protein complexes responsible for factor Xa and thrombin formation, the intrinsic tenase (factors VIIIa and IXa) and prothrombinase (factors Va and Xa). Finally, all of the proteases generated during the haemostatic response must eventually be inhibited to avoid thrombosis. We have a long-standing interest in how serpins antithrombin, heparin cofactor II, protein C inhibitor and protease nexin-1 are regulated by cofactors such as heparin. We have solved several crystal structures of relevant complexes, including all of the antithrombin-heparin-protease complexes, and now have a detailed and complete description of how heparin regulates serpin function. The importance of serpins is highlighted by the association of deficiency with disease, often caused by missense mutations leading to the accumulation of ‘polymers’ within the endoplasmic reticulum of secretory cells. We recently solved two crystal structures of polymers that showed distinct large-scale domain swaps, and have demonstrated that the intermolecular swapping of the 30 C-terminal residues is the molecular basis of serpin polymerization within living cells.
Mechanisms of Myeloid Leukaemogenesis and Leukaemia Stem Cell Biology

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.

We utilise a combination of functional and genomic assays in complementary mouse models and human primary cells to study normal HSC biology and how this is subverted in LSC and leukaemogenesis. An evolving paradigm in myeloid malignancies is transcriptional dysregulation and many of the mutations involved in myeloid leukaemogenesis involve transcriptional and epigenetic regulators. Ongoing projects within the group look at aberrant epigenetic regulation at chromatin via the bromodomain and extra terminal (BET) proteins in acute myeloid leukaemia (AML), at transcriptional dysregulation downstream of the AML-associated fusion genes MOZ-TIF2, NUP98-HOXA9 and MLL fusions, at the HMG-box gene SOX4, a critical AML target gene and at functions of epigenetic regulators such as CBP in HSC and LSC function. In addition, we are interested in the induction and evolution of myeloid preleukaemic disorders such as chronic myeloid leukaemia (CML) and myeloproliferative neoplasms (MPN) and are generating mouse models and studies in human cells to outline disease mechanisms and identify therapeutic targets.

Our long-term aim is to improve biological understanding of leukaemogenesis, to identify rational targets for therapeutic intervention and to design novel therapeutics to improve the outcomes in myeloid malignancies.


*joint senior authors
Our aims are twofold: to characterize molecular mechanisms governing human renal tubular homeostasis (particularly acid-base balance) and to dissect functions of urinary proteins.

Intact distal nephron α-intercalated functions (secretion of protons in to 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. The transporters responsible, and their regulatory pathways, are complex and incompletely understood. We have used rare single-gene disorders where α-IC function is inadequate, imparting severely detrimental effects on the kidney’s ability to maintain normal body fluid pH. The clinical consequences are metabolic acidosis, rickets and calcium deposition in the kidney. Recessively inherited syndromes present with very severe changes in early childhood, and sensorineural hearing loss is often associated.

Having described mutations in three genes: 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 initially showed that the latter two also participate in normal inner ear function, and discovered four novel subunit isoforms (C2, G3, d2, e2). We have gone on to functional characterization, and shown that essential membrane target-ing motifs for AE1 reside in its C-terminal tail; that AE1 is regulated by GAPDH and interacts with the sodium pump. Conversely, we showed that binding of the glycolytic enzyme PFK-1 is essential for normal proton pump function, as is phosphorylation by PKA.

We have catalogued the human urinary exosomal proteome and demonstrated that these urinary microvesicles are important innate immune effectors, maintaining urinary tract sterility. The most abundant urinary protein, uromodulin, is mutated in another dominant renal disease, FIHN. We have molecularly and clinically characterized a novel UMOD mutant, and continue with clinical and laboratory studies of other tubulopathies.

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Viral Immune Evasion

We are interested in viral evasion of the immune system. As the ultimate intracellular parasites, viruses target the host cellular machinery to enable their replication and avoid elimination. Using functional genetic and proteomic technologies we identify novel cellular receptors manipulated by viruses, understand why these receptors are targeted and elucidate the mechanisms used by viruses to manipulate the cellular immunoreceptors.

Why is the study of viral evasion mechanisms of interest? Understanding the mechanisms used by viruses to manipulate cellular processes provides unique insights into fundamental cell biological pathways, teaches us about viral pathogenesis and offers novel therapeutic approaches, for instance by targeting the newly identified receptor.

Viral regulation of cell surface receptors – new approaches: Cell surface receptors are modulated by all intracellular pathogens. Our work on viral evasion of the MHC class I antigen presentation pathway fuelled an interest in how ubiquitin regulates immunoreceptor turnover. We identified the K3 and K5 viral ubiquitin E3 ligases which ubiquitinate and degrade cell surface MHC I via the endolysosomal pathway. We recently developed non-biased methods to identify cell surface receptors up- or downregulated by viruses. Using SILAC-based proteomics we can compare the relative abundance of >600 plasma membrane proteins, and identify those receptors whose expression is altered by viruses. We have identified novel amino acid transporters regulated by HIV, and drug transporters regulated by HCMV.

Defining the mechanism of action of these novel receptors: Using genetic, biochemical and cell biological approaches we then determine how newly identified cell surface proteins are compromised by intracellular pathogens. For example, our siRNA screens identified novel E3 ligases, such as TRC8, involved in receptor regulation as well as their physiological substrates. We use traditional biochemical as well as mutagenesis-based genetic screens to identify the critical pathway components required for immunoreceptor regulation.

By downregulating critical cell surface receptors, CMV prevents infected dendritic cells from trafficking to draining lymph nodes.
One in twenty-five of the Northern European population carry the Z allele of $\alpha_1$-antitrypsin (342Glu→Lys). Homozygotes for this mutation retain $\alpha_1$-antitrypsin within hepatocytes as inclusion bodies that are associated with neonatal hepatitis, juvenile cirrhosis and hepatocellular carcinoma. We have shown that Z $\alpha_1$-antitrypsin is retained within hepatocytes by the formation of ordered polymers in which the reactive centre loop of one molecule inserts into $\beta$-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 $\alpha_1$-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 small molecule screens to identify compounds that can bind to, and prevent the polymerisation of, mutant $\alpha_1$-antitrypsin in vitro and in vivo. More recently, we have used human induced pluripotent stem cells derived from skin fibroblasts to develop hepatocyte-like cells that recapitulate the intracellular polymers that characterise $\alpha_1$-antitrypsin deficiency. We then used zinc finger nuclease technology to correct the genetic defect and so produce hepatocyte-like cells that secrete wild-type $\alpha_1$-antitrypsin. This takes us closer to a cell based therapy for $\alpha_1$-antitrypsin deficiency and the serpinopathies.


Immunostaining of polymeric $\alpha_1$-antitrypsin (green) or all forms of $\alpha_1$-antitrypsin (red) in human iPS cell-derived hepatocytes from individuals with $\alpha_1$-antitrypsin deficiency and controls (from Rashid et al, J Clin Invest 2010).
Molecular Cell Biology of Post-Golgi Membrane Traffic Pathways

Lysosomes are small membrane bound organelles ~0.5 μm diameter, which are full of proteases and other hydrolytic enzymes as well as internal membranes. They function late in the endocytic pathway that takes up macromolecules from the cell surface, by fusing with endosomes, but also play a key role in phagocytosis, autophagy 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 late endocytic organelles is the membrane protein VAMP7. This is targeted to the late endocytic pathway 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. The function of VAMP7 is regulated by interaction with Varp (Vps9 and ankyrin repeat containing protein). We are also studying the role of different protein machineries including the ESCRT proteins and HOPS (homotypic fusion and vacuole protein sorting) 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 down-regulation from the cell surface by viruses. Our group maintains an active interest in diseases of membrane traffic, including the work of Rhys Roberts on Charcot-Marie-Tooth Disease.

Electron microscopic tomography of a high pressure frozen HeLa cell showing fusion pores between late endocytic organelles. A, a micrograph from the reconstructed volume data set showing a plane of section containing a fusion pore. B, the reconstructed 3D volume showing a second fusion pore. C, a rendered surface model of the 3D data set revealing the fusion pores 'en face'.


*equal last authors
The Role of Endoplasmic Reticulum Stress in Disease

Proteins destined for secretion or for insertion into the cell membrane are first folded within the endoplasmic reticulum. The process of protein folding can become defective in many pathological states such as hypoxia, malignancy and some forms of diabetes. When the level of misfolded proteins within the endoplasmic reticulum increases, the cell is said to experience "endoplasmic reticulum stress".

We wish to understand the cellular consequences of endoplasmic reticulum stress, in particular its effects on tissue growth and cell survival. In doing so we hope to identify targets for the development of novel therapies. During endoplasmic reticulum stress, protein biosynthesis is initially inhibited by phosphorylation of the translation initiation factor eIF2α by the stress-sensing kinase PERK. Subsequent dephosphorylation of eIF2α by the phosphatase GADD34 restores protein translation thereafter. We discovered that this recovery of translation could itself contribute to the toxic effects of endoplasmic reticulum stress. This raises the exciting possibility that modulation of eIF2α phosphorylation may provide a useful target for the development of novel drugs to protect tissues from cell death.

Cellular stresses frequently impair cell cycle progression, which can impair tissue growth. Using mammalian cell biology and Drosophila genetics we recently described a novel G2 cell cycle check point initiated by translation attenuation during endoplasmic reticulum stress. This too provides potential targets for the development of new therapies.
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 haematopoietic stem and progenitor cells 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. We have recently further defined the region 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. The role of other cytokines in these processes is also being investigated. Furthermore, we have also found evidence that the regulation of HSC generation is influenced by the developing sympathetic nervous system, thus providing a functional link between these two systems in the mouse embryo. We are now in the process of adding an additional level to our expression studies by identifying miRNAs that are essential for developmental haematopoiesis.

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Haematopoietic stem cells are located in the middle region of the midgestation dorsal aorta.
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. The protein coats that surround transport vesicle possess both a self-assembly function, which results in polymeric lattice formation and a cargo recognition function. The latter is mediated by the direct binding of coat components to determinants in the cytosolic portions of trans-membrane cargo, most commonly used being short linear motifs. In clathrin-coated vesicles (CCVs) the most commonly used motifs are recognised by clathrin adaptors: YxxΦ and ExxxLL recognised by AP complexes, FxNPxY recognised by PTB containing proteins and poly-ubiquitination modifications recognised by epsins and GGAs. SNAREs are membrane-embedded proteins, which provide specificity and energy to transport vesicle:organelle fusion events. Appropriate SNAREs must also be actively sorted into transport vesicles to allow the vesicles to fuse with their desired target organelle and also to return SNAREs that are required for subsequent vesicle transport events to their correct location. These recognition events, which occur in parallel with standard cargo selection, are mainly mediated by direct and highly specific recognition of the folded regions of SNAREs. In CCV-mediated transport we have elucidated the molecular mechanisms by which a variety of SNAREs (Vti1b, VAMP7, VAMPs3&8) are transported by the clathrin adaptors (epsinR, Hrb and CALM) respectively. Vesicle coat components as well as proteins that control transport vesicle:organelle and organelle:organelle fusion through SNARE regulation and membrane tethering are recruited to appropriate membranes through their binding to membrane-inserted small G-proteins and membrane phospholipids as well as by their interactions with various transmembrane proteins.

In collaboration with various groups both within and outside the CIMR we are taking an integrated structural/functional approach to studying such interactions from a number of transport vesicle and organelle biogenesis events.
Familial Intellectual Disability: From Genes to Disease

We aim to understand how genetic abnormalities cause severe intellectual impairment. We have recruited >1000 families with moderate to severe intellectual disability in the iGOLD Genetic of Learning Disability Study and have identified many genes on the X chromosome that cause disease using an exome sequencing and detailed array comparative genomic hybridization approach (aCGH). We are now taking a whole exome approach and also testing the contribution of non-coding variants to disease.

We are continuing to quantify the genetic contribution to disease by testing whether genetic abnormalities make a significant impact on the poor intellectual outcome of babies born less than 24 weeks gestation, or who are stillborn or result in neonatal death.

Current estimates are that defects in >1500 genes are sufficient to cause severe cognitive impairment and the future challenge is to understand the unifying pathways and processes that are disrupted that cause disease.

We are working on defining in detail the clinical consequences of mutations in patients and to understand the phenotypic effects of loss of function mutations in neuronal cell models of disease. In collaboration with Professor Paul Fletcher, Wellcome Trust Senior Clinical Fellow, we are interested in using functional MRI to define subtle abnormalities of brain morphology and in collaboration with Dr Roger Barker, Department of Neuroscience, we are working on human fetal brain tissue to understand the role of disease genes within human primary neurons. Our ultimate aim is to be able to translate these findings into better diagnostic tools for families with intellectual disability and to consider unifying cellular phenotypes that can be used in developing therapeutic agents that will ameliorate the disease.

A 6kb deletion upstream of the CUL4B transcripts segregated with disease and resulted in loss of CUL4B expression in affected individuals.


Noor, A. et al. (2010). Disruption at the PTCHD1 Locus on Xp22.11 in Autism spectrum disorder and intellectual disability. Sci Transl Med 2, 49–68.

Protein Crystallography and Pathogenesis

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 new protein structures. 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.

One focus of recent structural work has been on members of the serpin family, most of which undergo an extraordinary conformational change on cleavage by proteases. The structures of two hormone-binding globulins show how they harness this conformational change to deliver thyroxine and cortisol to their sites of action. Our work on angiotensinogen, the source of the hormone angiotensin, has shed new light on how blood pressure is modulated. We also have an interest in enzymes mutated in inherited metabolic diseases. The structure of galactocerebrosidase is helping to understand how mutations in this enzyme lead to Krabbe disease.

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. In a collaboration with the developers of the modelling program Rosetta, we have been excited to find that the combination of molecular replacement and advanced modelling can solve structures that elude previous methods.

Schematic illustration of the methods (including our program Phaser) used to solve the crystal structure of angiotensinogen, by averaging electron density over multiple crystal forms.
Molecular Cellular Pathology of Axonal Degeneration

Our research is focused on the hereditary spastic paraplegias (HSPs), genetic conditions in which there is a distal degeneration of the longest axons of the motor pathway in the spinal cord. These conditions provide an excellent opportunity to understand molecular mechanisms crucial for axonal function, potentially of relevance to more common neurological diseases.

We want to understand the normal functions of HSP proteins and how these functions are disrupted to cause axonopathy. Many of the disease proteins function in membrane traffic processes, especially at the endoplasmic reticulum and at endosomes. Our work concentrates on understanding the functions of this membrane traffic subgroup of HSP proteins and is based on several related themes:

1. Understanding the functions of spastin. This is crucial to understanding the pathogenesis of HSP, since mutations in the spastin gene are the most frequent cause of the disease, and since the spastin protein is at the hub of an interacting network of HSP proteins. Spastin is a microtubule severing protein and our work has shown that it is recruited to membrane traffic sites, where it couples microtubule regulation to membrane modelling processes. Spastin functions at the early secretory pathway, where it is involved in endoplasmic reticulum morphogenesis. It also functions at endosomes. We are unravelling the role of spastin at these locations, using a variety of cell biological and in vivo approaches.

2. Understanding the role of HSP proteins in BMP signalling. We are especially interested to determine whether a group of HSP proteins cause HSP by disrupting Bone Morphogenetic Protein (BMP) signalling in the axon, by affecting membrane traffic of BMP receptors. If so, targeting this pathway could open the possibility of new therapeutic approaches for the HSPs.

The microtubule severing enzyme spastin regulates endosomal tubulation. Image shows increased tubulation of an endosomal compartment (labelled with SNX1) in a HeLa cell depleted of spastin by siRNA knockdown.
Stimulus Secretion Coupling in Enteroendocrine Cells

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. As enteroendocrine cells lie scattered throughout the intestinal epithelium we have made a number of transgenic mice expressing marker proteins under the control of specific hormone promoters to aid their identification and manipulation. Tagging with fluorescent markers allows the purification of specific enteroendocrine subpopulations for expression analysis. Surprisingly, we have found cells expressing a number of hormones concomitantly, challenging the traditional classification of enteroendocrine cells based on cell morphology and limited immunohistochemical characterisation. Fluorescent markers also allow the identification of enteroendocrine cells in mixed epithelial cultures, enabling the use of single-cell techniques, like patch-clamping and live cell fluorescent imaging, to study stimulus-secretion coupling mechanisms. Whilst we have, in collaboration with Dr Fiona Gribble’s lab, identified electrogenic sodium-coupled glucose uptake via SGLT-1 as a major contributor to carbohydrate sensing, we are less sure about the lipid sensing machinery of enteroendocrine cells. Ingested lipids are, however, at least as good a stimulus as glucose for the release of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotrophic polypeptide (GIP), two hormones which between them are believed to account for the stimulation of >50% of insulin released after a meal. One current focus of the lab is thus the investigation of potential lipid sensing mechanisms of GLP-1 and GIP releasing cells with the aim to identify potential targets to manipulate hormone release in the treatment of type 2 diabetes and obesity.

A second interest of our group is in the understanding of electrophysiological mechanisms underlying pain perception. In collaboration with the group of Professor Geoff Woods, we characterise mutations affecting channel genes, as exemplified by the voltage-gated sodium channel gene SCN9A, mutations of which can give rise to hypersensitivity or complete oblivion to painful stimuli.

Eleftheria Diakogiannaki
Catherine Moss

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Full4Health


Coated Vesicle Adaptors

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 of two major components, clathrin and adaptor protein (AP) complexes, as well as other less abundant proteins.

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 CCVs 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. Top hits include several subunits of the vacuolar ATPase, and we are investigating the role of V-ATPase in CCV formation. We are also making use of a novel system that we developed, called a knocksideways, to investigate the consequences of rapidly inactivating CCV machinery in cultured cells, and we are in the process of generating a knocksideways mouse model.

Although for over 10 years it has been assumed that there are four AP complexes, we recently discovered a fifth AP complex. We are currently characterizing the AP-5 pathway, and how mutations affecting this pathway might lead to hereditary spastic paraplegia. In addition, we are investigating how the HIV-1-encoded protein Nef hijacks adaptor-mediated trafficking to downregulate the cell surface proteins MHC Class I and CD4.

The “knocksideways” system reroutes much of the AP-2 adaptor complex (red, left) to mitochondria (green) just 6 seconds after adding a small molecule (red, middle).
Aggregate-prone Intracellular Proteins and Disease – from Biology to Therapeutic Strategies

Intracellular protein aggregation is a feature of many late-onset neurodegenerative diseases, including Huntington's disease (HD) and the muscle disease oculopharyngeal muscular dystrophy (OPMD). Most of these mutant proteins cause disease via toxic gain-of-function mechanisms. Therefore, the factors regulating their clearance are crucial for understanding disease pathogenesis and for developing rational therapeutic strategies.

The two major intracellular protein degradation pathways are the ubiquitin-proteasome system and (macro)autophagy.

David Rubinsztein's laboratory studies the relevance of autophagy in neurodegenerative disease, and the basic cell biology of this important catabolic process. He aims to further the understanding of the pathogenesis of Huntington's disease and oculopharyngeal muscular dystrophy, and to develop rational therapeutic strategies for these conditions. He has identified FDA-approved drugs that may have benefit in both diseases, since he has demonstrated their efficacies and protective mechanisms in a range of cell and animal models.

Over the last two years, the highlights of his work include:

1. Characterising early steps in autophagosome biogenesis, and showing that the plasma membrane contributes to autophagosome precursors.
2. Showing that lysosomal positioning affects both autophagosome biogenesis and autophagosome-lysosome fusion, and that this is a strategy that can influence toxicity of aggregate prone proteins that cause diseases like Huntington's disease.
3. Demonstrating that mutations that cause forms of Parkinson's disease and the degenerative epilepsy, Lafora disease, inhibit autophagy.
4. Showing that nitric oxide accumulation, which occurs in many neurodegenerative diseases, impairs autophagy, and that inhibition of nitric oxide formation alleviates the aggregation and toxicity of mutant huntingtin in cell culture and in vivo.
5. Demonstrating that cystamine alleviates the toxicity of the mutation causing OPMD in cells and in mice.


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Tau Consortium

Christopher Rudd

T-cell signalling and immune function

Professor Rudd’s research focuses on deciphering the signal transduction pathways in T-cells, and their connection to immune responses and various immune disorders. My laboratory was the first to discover the CD4 and CD8-p56^Lck (Lck) complexes, initiators of the phosphorylation and activation cascade in T-cells. We are presently interested in the identity of downstream substrates, in particular, complexes responsible for the ‘inside-out’ pathway for adhesion and the movement of T-cells in lymph nodes. These events are needed for T-cell migration to sites of inflammation and interaction with antigen presenting cells. Two mediators, adhesion- and degranulation-promoting adapter protein (ADAP) and src kinase-associated phosphoprotein 1 (SKAP1) control LFA-1 activation, while SKAP1 binding to RapL controls the ‘slowing’ of T-cells in lymph nodes for interactions with dendritic cells. ADAP and SKAP1 also regulate the NFkb and ERK pathways as well as infection by the human immunodeficiency virus (HIV-1). We are interested in the targeting of these pathways in the development of new drugs for the treatment of infection and cancer.

We are also interested in the signalling events responsible for the function of co-receptors such as CD28, ICOS, CTLA-4 and PD-1. These co-receptors qualitatively change immune responses, and have been successfully targeted in the treatment of auto-immune disorders and cancer. We identified CD28 binding to the adaptor Grb2 in the activation of the transcription factor NFkB, while the CD28 binding to PI 3K activates glycogen synthase kinase (GSK3) for optimal cytolytic T-cell (CTL) function. We have also proposed a new model ‘reverse stop signal model’ to explain CTLA-4 dampening of immune responses and protection against the development of autoimmunity. CTLA-4 activates T-cell motility and limits T-cell-dendritic cell interactions. Our laboratory uses a variety of approaches from basic biochemistry to cellular immunology and the generation of models of immunodeficiency and infection.

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Wellcome Trust


Upper panel: T-cell receptor signalling pathway for activation of LFA-1 on T-cells.
Lower panel: motifs within the cytoplasmic tail of CD28 bind various signalling proteins.
Molecular Mechanisms of Neurodegeneration

My laboratory focuses on understanding the molecular mechanisms underlying neurodegenerative diseases, using molecular genetics, animal modelling and biophysical methods. The presenilin complex performs the intra-membranous cleavage of the amyloid precursor protein to generate the neurotoxic, aggregation-prone Abeta peptide. Using a series of biophysical tools including negative stain electron microscopy, mass spectrometry, FLIM-FRET and analytical ultracentrifugation, we have generated a model of the presenilin complex and demonstrated how the binding of small molecule inhibitors and substrates induces a conformational change in the complex. Ongoing work now seeks to improve the resolution of this model. In a separate series of experiments we have also investigated how mutations in the FUS gene cause motor neuron disease, we have generated a model in C.elegans. In this model, mutations cause paralysis, the severity of which directly mimics the severity of the human disease associated with that mutation. We have shown that this arises because of aggregation of the mutant FUS protein, and preliminary evidence suggests that the disease phenotype can be reversed by small molecule inhibitors of aggregation.

Katie Cox
Roger Dodd
Yi Li
Stephen Lu
Beth McDonald
William Meadows
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Protein localization within eukaryotic cells is essential for normal cellular physiology. The mechanisms that govern the localization of membrane proteins within the post-Golgi endocytic system control diverse processes such as; nutrient uptake, signaling receptor downregulation, synaptic transmission, the response to infection and generation of immunity. There is a growing awareness and appreciation of the importance of correct endosomal protein sorting in various neurodegenerative disorders.

In my lab we study the functioning of the endosome-to-Golgi retrieval pathway and have extensively characterized the role of the retromer complex in that pathway. Retromer is a conserved protein complex that localizes to endosomes to sort membrane proteins into nascent tubules. The retromer complex can be functionally dissected into two subcomplexes; a cargo-binding complex comprising a heterotrimer of VPS35-VPS29-VPS26 proteins and the sorting nexin dimer of Snx1 or Snx2 with Snx5 and Snx6.

We have recently demonstrated the role that the small GTPase, Rab7a, plays in regulating the membrane association of the cargo-selective retromer complex. In addition to Rab7a, the TBC1D5 protein also interacts with the cargo-selective retromer complex by direct binding to VPS29. As a member of the Rab GDP-activating protein (GAP) family, TBC1D5 operates antagonistically to Rab7a. Therefore, Rab7a and TBC1D5 ensure that the cargo-selective retromer complex mediates the sorting of membrane proteins through a dynamic cycle of association and dissociation of the complex with the membrane.

Attempts to identify proteins that interact with the retromer complex and contribute to the efficiency of endosomal protein sorting are on-going and comprise a number of complementary techniques including; native immunoprecipitation to identify proteins associated with retromer and functional genomics using high-throughput siRNA screening technologies to identify candidate genes required for endosome-to-Golgi retrieval.

As a result of these efforts, we have recently reported the role of the retromer complex in mediating the recruitment of the endosomal WASH complex. One of the components of the WASH complex is a protein called Strumpellin that is mutated in Hereditary Spastic Paraplegia (HSP) – a neuronal degenerative disorder. Loss of Strumpellin function results in dysregulation of endosomal tubules suggesting that defective regulation of endosomal membrane dynamics may contribute to the pathology of HSP.
Symeon Siniossoglou

Linking Phospholipid Metabolism to Membrane and Organelle Function

Lipids are 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. Defects in lipid metabolism or signalling can lead to a large number of disorders such as metabolic syndrome or cancer.

The aim of our laboratory is to understand how cells maintain lipid and membrane homeostasis during growth and development. Our current studies focus on a fundamental step in lipid metabolism, the dephosphorylation of phosphatidic acid (PA) to diacylglycerol (DAG) that is catalyzed by a conserved family of lipid phosphatases, lipins. DAG generated by lipins is used for the biosynthesis of (a) membrane phospholipids and (b) triglyceride stored in lipid droplets. Consistent with these essential metabolic functions, lipins are important regulators of both organelle biogenesis and fat storage in many eukaryotic cells.

Recent work from our group led to the identification of key regulators of the yeast lipin Pah1p and a model on how these cooperate to recruit Pah1p onto membranes for DAG production. We are currently expanding these studies to both mouse and human fat cells (adipocytes) that express lipin 1, 2 and 3 and investigate their roles both during adipocyte differentiation and lipogenesis. Unexpectedly, lipins also translocate into the nucleus where they regulate gene expression. We are using a combination of genetics and gene expression profiling approaches to identify the nuclear targets of lipins and uncover the function of these lipid phosphatases into the nucleus.

Hiroshi Sembongi

Funding: Medical Research Council


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: 5 μm). Loss of the lipin Pah1 causes nuclear/ER membrane expansion in yeast (lower panel, arrows point to the expanding nucleus in green, bar: 1 μm).
Immune Regulation, Autoimmune Disease and Infection

We aim to discover how genetically determined variation in immune regulation balances the risks of autoimmune disease and infection. Regulation of the B cell immune response is a major interest. We have investigated the function of inhibitory receptors such as 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 immune dysregulation (see Figure) and 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 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. We have recently discovered a regulatory T cell which specifically regulates the germinal centre and may have autoimmune implications. 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 activation, lymphoid development 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). 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. We are also using genetics to identify novel pathways for investigation. Examples include our initiation of the European Vasculitis Genetics Consortium which has just completed the first genome-wide association study in ANCA-associated vasculitis, and a novel analysis of the inflammatory bowel disease GWAS which has identified genetic variants associated with clinical course rather than diagnosis, and defined their functional implications in humans using the Cambridge BioResource, and in mouse models.

These programmes together allow us to interrogate mouse and human biology in an integrated fashion, increasing our capacity to probe immunity and disease and to translate basic biological findings to the clinic.
John Todd

Identification of Molecular and Cellular Mechanisms in Autoimmune Disease

Our aim is to further characterise the molecular basis for the autoimmune inflammatory disease type 1 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 immunological studies. Our major effort now is to correlate susceptibility genotypes with biomarkers and phenotypes e.g. we have correlated flow cytometric phenotypes of T lymphocytes with disease-predisposing genotypes of the IL-2RA (CD25) gene. This is a first step towards identifying disease precursors that could be used in future therapeutic studies to stratify patients. To achieve this we have helped build a local biobank of volunteers and patients in whom we can study the effects of disease-associated genotypes and environmental factors (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 laboratory of Linda Wicker, 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 International
National Institutes of Health (USA)
NIHR Cambridge Biomedical Research Centre
Medical Research Council
European Union FP7


The Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory

The Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory (JDRF/WT DIL) has two Principal Investigators and is composed of four integrated research efforts: John Todd (human genetics and immunology), Linda Wicker (mouse modelling, human immunology), Chris Wallace (statistics) and Frank Waldron-Lynch (clinical). In the last ten years under programmatic funding we have discovered and defined several mouse and human susceptibility loci for type 1 diabetes. In the last five years we have been correlating the presence of the identified susceptibility alleles with their functions to determine which molecules 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 and their possible implications for new, mechanism-based therapeutic strategies. A key approach is the collection of local healthy volunteers and patients (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). 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 Peakman, Tim Tree, David Dunger and Polly Bingley. Investigations of therapeutic strategies in type 1 diabetes are supported by a collaborative project funded by the European Union’s 7th Framework Programme (FP7), Natural immunomodulators as novel immunotherapies for type 1 diabetes (NAIMIT).

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 and Laura Esposito.

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Genetic and Functional Relationships between Polymorphic 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 large 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.

Frequencies of unique KIR haplotypes with variable gene copy number. Inset charts: frequencies of centromeric and telomeric haplotype structures (Figure: J Traherne).
Identification of Molecular and Cellular Mechanisms in Autoimmune Disease

Our group, as part of the Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory (DIL), 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 nonobese diabetic (NOD) mice. Some T1D-associated genes and molecular pathways are shared by humans and mice as exemplified by the CTLA-4 and IL-2 pathways. Both CTLA-4 and IL-2 are required for the function of FOXP3+CD25+CD4+ regulatory T cells, a T cell subset that dampens the immune response and is less functional in T1D patients and NOD mice. FOXP3+CD25+CD4+ regulatory T cells are a therapeutic target in T1D and the subject of intense investigation by many laboratories, including the DIL.

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. Genotypes at T1D-causal genes are correlated with phenotypes ranging from protein expression of 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 of CD25 on naïve CD4+ T cells (see Figure). The variant of the gene encoding CD25 that increases the likelihood of developing T1D and multiple sclerosis is correlated with an increased frequency of CD25+ naïve CD4+ T cells. In the susceptible genotype, the frequency of CD25+ naïve CD4+ T cells is influenced by both age and sex. We are currently investigating this poorly characterised subpopulation of naïve CD4+ T cells and testing the hypothesis that CD25 expression decreases the activation threshold thereby making it more likely that naïve CD4+ T cells with affinity to self antigens will differentiate into pathogenic effector cells.

Using multicolour flow cytometry and blood samples from Cambridge BioResource donors, we have correlated an increased frequency of CD25+ naïve CD4+ T cells (outlined in red on the figure) with susceptibility to type 1 diabetes and multiple sclerosis.
The Study of Mendelian Disorders of Neurogenesis and Pain

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

We have shown that “autosomal recessive primary microcephaly” (MCPH for short) is a disorder of neurogenic mitosis in the embryonic and foetal developing brain. After birth the MCPH brain is small, but architecturally normal, and that the phenotype is mental retardation – but not physical retardation. The MCPH proteins are highly expressed in the neuro-epithelium lining the interior of the brain, and from which the majority of neurones arise in foetal life. Our initial focus was to find the MCPH genes, now we are trying to find what these genes do and how perturbation of this process leads to a small human brain. As all MCPH genes to date are centrosomal components we are studying their effects on mitosis, cytokinesis, cell polarity and the centriole and centrosome cycle. We have recently found that most of the MCPH genes form a complex. Completely unexpectedly this complex is involved in daughter centriole attachment and maturation on the mother centriole — an apparently fundamental process in animal cells. Why defects of centriole maturation in humans should manifest only as a brain of reduced size is now our “big question”. Another strand of our work is the evolution of the human brain and whether the MCPH genes have contributed to the recent threefold increase in size.

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

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

Magnified image of mouse E13 cerebral cortex neuroepithelium showing Wdr62 (red) in apical mitotic precursors (nuclei in blue/DAPI). Strong Wdr62 expression is seen in apical neural precursor cells undergoing mitosis with a pair of centrosomes (green) either side of a metaphase plate.
Core Scientific Facilities at CIMR

The above are all core staff funded as part of CIMR’s Wellcome Trust Strategic Award.
The MRC Mitochondrial Biology Unit evolved from the former MRC Dunn Human Nutrition Unit. Its formation by the MRC recognises growing evidence for the involvement of mitochondria and their dysfunction in an ever-increasing range of human diseases most notably in neuromuscular and neurodegenerative 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 ten 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, mitochondrial genetics and biogenesis of mitochondria in relation to mitochondrial disease (Ian Holt, Michal Minczuk and Antonella Spinazzola), and to aspects of apoptosis and generation of reactive oxygen species in relation to ageing (Michael Murphy). A bioinformatics group (Alan Robinson) has developed modelling an in silico model of the mitochondrion. The goal is to develop models for the dynamics and control of the metabolic and bioenergetic pathways, and to use them to analyse various human pathologies. A proteomics group (John Walker and Ian Fearnley) is using modern mass spectrometry to characterise proteins involved in respiration, in signalling in the mitochondrion, in mtDNA replication and organelle biogenesis. 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, so as to exploit our fundamental knowledge to generate new therapies.

Currently, the MRC Mitochondrial Biology Unit has a staff of 105 including 49 PhD students.
CIMR Affiliated Principal Investigators

Genetics, Genomics and Vaccine Studies in Leishmaniasis

The major highlight of the research based at CIMR during 2009–2011 has been a genome-wide association study (GWAS) of visceral leishmaniasis undertaken as part of the Wellcome Trust Case Control Consortium Phase Two (WTCCC2). This involved the analysis of discovery and replication case-control samples from India, and families from north-eastern Brazil (with Shyam Sundar, India; Selma Jeronimo, Brazil; Mary Wilson, USA). The HLA-DRB1-DQA1 locus was the only region to show strong evidence of association (P=1.47×10^{-9} at rs9271252; 2.14×10^{-9} at rs9271255) in the Indian discovery dataset. Replication occurred within India (P=5.85×10^{-5} at rs9271255) and Brazil (P=7.41×10^{-6} at rs9271252); P_{combined}=5.55×10^{-16} across three studies. The protective allele at SNP rs9271252 (and at rs9271255; r^2=1) tagged three DRB1 allele groups at the two digit level: *15, *16 and *01. These findings are of relevance to our further analysis of immune responses to 12 novel vaccine candidates for leishmaniasis that we have analysed in exposed donors (recovered cases, skin-test positive asymptomatics) from Brazil and India. Congenic mice bearing the HLA DRB1 risk and protective alleles are under construction with genOway to help us further understand the mechanisms by which these HLA class II molecules control disease pathogenesis and response to vaccination.

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The Molecular Pathogenesis of Alzheimer’s and Related Neurodegenerative Diseases

My laboratory uses Drosophila melanogaster, Caenorhabditis elegans and prokaryotic systems to study specific protein aggregates that have been implicated in proteinopathies such as Alzheimer’s disease, tauopathies, Parkinson’s disease and Familial Encephalopathy with Neuroserpin Inclusion bodies.

We use invertebrate model organisms to link the biophysical properties of particular proteins, and their aggregates, with whole-organism phenotypes such as reduced longevity and locomotor abnormalities.

One of the strengths of these systems is the power of the genetic toolkits that are available for studying the biological pathways that underpin disease phenotypes. Alzheimer’s disease appears to be initiated by the aggregation of a peptide called Aβ. We have created a fly model of Alzheimer’s disease by expressing this toxic peptide in the insects’ brains. We have sought to modify the consequent longevity and behavioural phenotypes by a range of genetic manipulations and have discovered modifiers of Aβ toxicity in the fly. Similarly in the worm we can compare the network of genes that mediate the toxicity of Aβ with the orthologous network of genes implicated by human genome wide association studies in Alzheimer’s disease. Analogous experiments have been performed on proteins involved in a range of neurodegenerative disorders.

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**Genetic, Molecular and Physiological Basis of Human Obesity**

We use a number of complementary genetic strategies including whole exome sequencing to study a cohort of over 4000 patients with severe early onset obesity in collaboration with the Wellcome Trust Sanger Institute. Through these approaches we are discovering mutations in novel obesity genes whose function is studied using a number of molecular and cellular approaches. As many of these proteins modulate hypothalamic neural circuits involved in the regulation of appetite, we are developing the use of patient specific neural cell lines derived from inducible pluripotent stem cells (obtained from fibroblasts), as a model system for investigating molecular mechanisms and for drug discovery. As part of our parallel programme of translational research, we undertake physiological studies in patients with monogenic obesity syndromes to examine the role of the relevant molecules in eating behaviour, energy expenditure and peripheral metabolism. Our overall aim is to make a major contribution to the design of pharmacological, nutritional and behavioural interventions to benefit patients with severe obesity.

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**Genetic and Functional Mechanisms of Susceptibility to Infection**

Genetic variants in the human genome may confer susceptibility to or resistance from infectious diseases. To discover such variants and to understand underlying fundamental mechanisms we use methods of human genetics, including genome-wide association studies (GWAS) and exome sequencing, cellular models of infection as well as methods of molecular biology. We study patients with primary immunodeficiencies caused by Mendelian mutations that suffer from severe and/or recurrent infections, in particular from mycobacterial and viral infections. We also study patients that suffer from pulmonary tuberculosis, a common infectious disease and a global medical problem. Our objective is to understand biological pathways involved in protection from infection and, eventually, to find new diagnostic approaches and novel targets for therapeutic intervention.

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Sadaf Farooqi


Sergey Nejentsev


I have a long-standing interest in the aetiology and pathophysiology of human metabolic and endocrine disease and how such information might be used to improve diagnosis, prognostication, therapy and prevention.

My two principle areas of research are obesity and insulin resistance. We use a wide range of human genetic and physiological approaches, accompanied by studies in cellular and animal disease models to better understand the biological causes of extreme forms of obesity, insulin resistance and lipodystrophy and also the mechanisms whereby more widespread genetic variants predispose to common forms of disease. Our long-term aim is that better understanding of the pathways that control human energy balance, adipocyte biology and insulin sensitivity will, ultimately, lead to clinical benefits.

Our research is supported by the MRC Centre for Obesity and Related Metabolic Diseases (MRC CORD), the Wellcome Trust, the NIHR Cambridge Biomedical Research Centre and the EU.

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Proteins that fail to attain or maintain their structure reduce fitness in part through toxic gain of function mechanisms referred to as “proteotoxicity”. The latter conspicuously affects poorly-renewable tissues of long-lived organisms in which the threat of protein misfolding can exert its deleterious consequences over extended periods of time. Protein misfolding is compartment-specific and its extent is influenced by the burden of newly-synthesized unfolded proteins presented to a given compartment (cytosol, endoplasmic reticulum, mitochondria) and by the protein folding environment in that compartment. The latter is influenced by structural elements operating within and on the compartment and by its metabolic state. Both parameters are regulated by complex homeostatic pathways, constituting what has been termed heuristically a proteostasis network, in which compartment-specific unfolded protein responses (UPR) are important.

Interesting reciprocal links have been uncovered between protein folding homeostasis and metabolism: Defects in handling unfolded protein load and proteotoxic features of rare mutant proteins have revealed the importance of proteostasis to the function of tissues such as the endocrine pancreas, liver and fat that figure heavily in metabolic control. Less well understood, but of potentially considerable importance, are the emerging links between intermediary metabolism and the protein folding environment in the various compartments of the eukaryotic cell. Our research aims to uncover the molecular basis of the aforementioned reciprocal links.

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Andrew Peden

**Constitutive secretion** is a fundamental, conserved process that delivers newly synthesised proteins to the extracellular environment and is key to many important physiological processes such as antibody secretion. Hypersecretion of antibodies is associated with many immune-derived diseases such as Amyloidosis, Macroglobulinemia and Monoclonal Gammapathy of undetermined significance and may also have a role in auto-immune diseases such as Systemic Lupus Erythematosus. Elevated levels of circulating antibodies can cause severe pathology and lead to conditions such as Cryoglobulinemia and hyperviscosity syndrome. Thus, having the ability to modulate the levels of circulating antibodies has significant therapeutic potential. We hope that by studying the secretory pathway and determining the machinery required for antibody secretion we will not only provide new insights into a fundamental cellular process, but also identify new druggable targets for the treatment of these diseases.

My research has three main aims:

1. To understand the role of SNAREs in constitutive secretion.
2. To identify and characterise novel machinery required for post-Golgi trafficking and antibody secretion.
3. To develop novel inhibitors of antibody secretion.

Moving to the Department of Biomedical Science at the University of Sheffield to take up the post of Lecturer.
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).

Wellcome Trust/MRC 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 Paul Lehner) offers 6 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 research charities to individual principal investigators. They 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. We also host the University of Cambridge/Sanger Institute Wellcome Trust PhD Programme for Clinicians that funds 7 clinical fellows per annum for 5 years. This scheme is administered from the CIMR although the faculty is drawn from the whole of the School of Clinical Medicine and the wider University of Cambridge.

The Director of the four year non-clinical PhD programmes and the Wellcome Trust clinical PhD programme is Professor David Lomas, the Director for Graduate Studies within the Institute is Dr Folma Buss and the Programme Administrator is Sonia Lyne.

Postgraduate Opportunities in the Institute

Prof. Sheena Radford
University of Leeds
External examiner for
CIMR 1+3 MRes/PhD Programme 2009–11

Sonia Lyne

CIMR 4 Yr PhD Students, 2011 intake
The annual CIMR Research Retreat was held on 21–22 March 2011. This year it was the turn of the postdoctoral fellows and graduate students to present to members of the Institute. The presentations reflected the diverse nature of ongoing research within the building. We also had excellent presentations on antibody engineering from Sir Greg Winter and on chromosomal instability by Ashok Venkitaraman. We continued our tradition of inviting a member of the MRC Mitochondrial Biology Unit to talk at the Retreat and were delighted to hear from Ian Holt about his work on mitochondrial myopathies. The presentations from members of the Institute were of a very high standard and the judges awarded the prize for the best presentation from a postdoctoral fellow to Dr Janet Deane (Prof Randy Read’s group) now a PI herself, with the runner-up being Dr Jenny Lumb (Dr Evan Reid’s group). The prize for the best presentation from a graduate student went to Miss Hemma Brandstätter (Dr Folma Buss’s group) with the runner-up being Mr David Gordon (Dr Andrew Peden’s group). The poster prizes were given to Dr Xin Smith (postdoctoral fellow in Prof Chris Rudd’s group) and jointly to Miss Sally Thomas and Miss Elke Malzer (graduate students with Dr Stefan Marciniak).

David Lomas
Deputy Director
It is a privilege for me to introduce this section of the Report to acknowledge the work of all the support staff in what has been another busy and productive year. All staff endeavour to provide a support service to our scientists in an efficient and effective and customer focussed manner so that the scientific community remains satisfied with the value of the services provided.

As the Institute’s Administrator I have responsibility for overseeing the Administration’s individual units and for providing advice and guidance on a wide variety of administrative issues to the Director, Institute committees, the scientists, and staff. In this period of reduced funding opportunities, of particular importance is ensuring that the grant application process is followed appropriately with particular emphasis on costings to ensure that sufficient funds will be available to meet the needs of the research, whilst remaining within the limits set by the grant awarding bodies. I also have direct operational management responsibility for the Human Resources Unit. The service includes providing advice on all aspects of employment issues including work permits, adhering to HR best practice, and initiating appointments/extensions/termination of employment for employees.

Since the last Report we have experienced the lowest turnover of administrative staff since the Institute was opened. However, there was one significant managerial change. We were very happy to welcome Neil Kent to the team in August 2011. He leads the Accounts and Purchasing Unit and replacing Susan Reeder who retired having completed 12 years service. Neil has joined us from Cambridge Assessment, a department of the University, where he worked for nine years and qualified as a CIMA Management Accountant.

The team supports scientists by undertaking daily accounts work including the processing of purchase orders and expense claims, dealing with invoice queries, managing accounts receivable and providing information and advice regarding the financial position of grants. Training and development is key to offering a good service and most of the team are currently studying to aid their professional development.

Jonathan Wilson, continues to lead the IT Unit, has responsibility for the Institute’s IT facilities, including the provision of a support service to both the scientific and administrative staff. His team manages the data network and audio-visual facilities within the Institute, and maintains the Intranet and Web site. Over the next 5 years the IT Unit will invest £300k into renewing the Institute’s internal network, data centre and communal computing facilities. In 2010 the IT Unit modernised the facilities in the Sackler lecture theatre to provide state of the art digital presentation. The generation of scientific data within CIMR is now doubling annually and to
meet the challenge of data storage and back-up, the IT Unit is developing an off-site data replication system. The website presence has been revamped but there is always more we can do to communicate our services and facilities.

The Laboratory and Facilities team remains under the direction of Dave Cheesman. As with the Accounts and Purchasing Unit, various members of the team have undertaken courses leading to professional accreditation. This team is responsible for the provision of building-wide services such as cleaning, catering, security, media preparation and glass-washing, and for the CIMR communal laboratories. The shared facilities provide essential equipment for use by the Research Staff and include dark room services, centrifugation, phosphor imaging, and shared areas such as Tissue Culture Labs and Containment Level 2 suites. Due to the nature of the service provided by this unit, there is a great deal of overlap with the Building Services Unit.

Ray Woodstock manages the Building Services Unit which has recently expanded to include the Custodian function. The Unit provides the day-to-day maintenance of the building, including numerous small projects such as minor building modifications for new equipment and redecorating of the public areas. The Unit is also involved with major projects which have recently included cladding and external insulation improvements, lift refurbishment and the replacing of the building’s heating and cooling control system. Planned projects for the next year include replacing of the floor covering in all the public areas, and installing new cycle sheds.

Sarah Smith
CIMR Administrator

CIMR Support Organisational Chart
Total expenditure on grants has continued to increase over the last two years, from £20.0m in 2008/9 to £21.4m in 2010/11, a rise of 7%.

Overall Wellcome Trust support is approximately 60%, as it has been for the last 5 years. One-third of non-Wellcome Trust grants are funded by the MRC.
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 directly proportional to the space occupied in the building.

**Recurrent Costs for the CIMR**

August 2009–July 2010

- £191k
- £342k
- £137k
- £864k

August 2010–July 2011

- £256k
- £414k
- £220k
- £858k

**Recurrent Costs for the Wellcome Trust/MRC Building & CIMR**

August 2009–July 2010

- £191k
- £353k
- £1,258k
- £864k

August 2010–July 2011

- £256k
- £341k
- £1,304k
- £858k
Over the last four years the Clinical School with National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) funding has been able to establish several critical core facilities that enable translational medical research across the main research themes on campus (see BRC website, http://cambridge-brc.org.uk/), including many researchers in the Cambridge Institute for Medical Research.

1 The Cambridge BioResource (http://www.cambridgebioresource.org.uk/) allows researchers to recall volunteers for their studies based on disease-associated genotypes and phenotypes. This resource, with the renewal of the Cambridge Biomedical Research Centre to 2017, will now include patients from several clinics in the hospital. Moreover, we have just been awarded additional funding by NIHR to roll out the BioResource nationally for patients and populations.

2 The Cell Phenotyping Hub. This is a centralised flow cytometry and microscopy facility for phenotypic and functional analyses of human blood and tissue samples. The facility has state of the art equipment and is closely aligned to the Cambridge BioResource, for example in gene-to-phenotype analyses of immune-mediated diseases, such as lupus and type 1 diabetes.

3 The Eastern Sequence and Informatics Hub (EASIH) provides facility and expertise in next-generation sequencing and bioinformatics. Major projects include exome and human microbial pathogen sequencing, as well as the translation of high throughput sequencing into the Clinical Regional Genetics Laboratory, for example, in HLA tissue typing. Also housed in Clinical Biochemistry are facilities for core biomedical assays (Core Biochemical Assay Laboratory: http://www.cuh.org.uk/research/researchers/starting/facilities/cbal/core_biochemical_assay.html) and microarray gene expression (http://cambridge-brc.org.uk/new/infrastructure-infrastructure-laboratoryfacilities.htm).

4 The BRC BioRepository (NIHR BRC-MRC BioRepository, F & G Block, Level 2, Addenbrooke’s Hospital) has been established with the MRC Epidemiology Unit, to provide smart, automated sample (DNA, plasma, serum) storage facilities of BRC- and MRC-associated samples.
Honours, Awards & Personal Fellowships

Principal Investigators:

David Clayton: Wellcome Trust Principal Research Fellowship, renewed December 2010; Honorary Chair, Department of Epidemiology and Population Health, Medical Statistics Unit, London School of Hygiene and Tropical Medicine

Janet Deane: Royal Society University Research Fellowship, October 2011

Sadaf Farooqi (Affiliated): Professorship in the University of Cambridge, October 2011

Andres Floto: BUPA Foundation Researcher of the Year award 2010

Bertie Göttgens: 2010 McCulloch & Till Award by the International Society for Hematology and Stem Cells; Professorship in the University of Cambridge, October 2011

Tony Green: Elected Distinguished Visiting Professor Cancer Science Institute, Singapore, 2009–10; Elected Newton Abraham Visiting Professorship, University of Oxford, 2011

Fiona Gribble: Minkowski Prize, EASD 2010; University of Cambridge Readership, October 2010

James Huntington: ISTH 2011 Wright-Schulte Memorial Lecture; Professorship in the University of Cambridge, October 2011

David Lomas: Patron, Alpha-1 Awareness; Visiting Professor, University of Florida and Cleveland Clinic

Stefan Marciniak: MRC Senior Clinical Research Fellowship, March 2012

Sergey Nezhentsev (Affiliated): Wellcome Trust Senior Research Fellowship in Basic Biomedical Science, June 2011

Katrin Ottersbach: British Society for Haematology Early Stage Investigator Fellowship; Leukaemia & Lymphoma Research Bennett Senior Fellowship, September 2011

David Owen: Wellcome Trust Principal Research Fellowship, October 2010

Randy Read: William A Bridger Lectureship in Biochemistry, University of Alberta, Edmonton, Canada, 2010

David Rubinstein: Wellcome Trust Principal Research Fellowship, March 2012

Christopher Rudd: Wellcome Trust Principal Research Fellowship, extended December 2010

Peter St George-Hyslop: Fellow of the Society of Biology

John Todd: David Rumbough Award for Scientific Excellence from the JDRF

Geoff Woods: Professorship in the University of Cambridge, October 2011

Fellowship Award, March 2011

Geoffrey Hesketh (Luzio): Canadian Institute of Health Research Fellowship, August 2011

Nick Matheson (Lehner): Wellcome Trust Clinical Research Training Fellowship, April 2011

Anna Petrunkina Harrison: Extraordinary Professorship (‘Ausserplanmaessige Professeur’), University of Veterinary Medicine, Hanover, 2011

Rhys Roberts (Luzio): Wellcome-Beit Prize/Wellcome Trust Intermediate Clinical Fellowship, June 2011

Chris Wallace (DIL): Wellcome Trust Career Development Fellowship, February 2010

Lena Wartosch (Luzio): FEBS Long-term Fellowship, April 2010; EMBO Fellowship, April 2011

Michael Weekes (Lehner): Wellcome Trust Intermediate Clinical Fellowship, July 2011

Aiwu Zhou (Read): BHF Senior Basic Science Research Fellowship, January 2011

Other Information

Research Scientists:

Mark Dawson (Hunty): Wellcome-Beit Prize/Wellcome Trust Intermediate Clinical Fellowship, 2010

Jyoti Evans (Green): Kay Kendall Leukaemia Fund Junior Clinical Research Fellowship, April 2011

Shaun Flint (Smith): ACT Clinical
Editorial Boards of Journals

David Clayton: Annals of Human Genetics

Andres Floto: PLoS ONE

Bertie Götgens: Experimental Hematology (Associate Editor)

Fiona Gribble: British Journal of Pharmacology; Biochemical Journal

Gillian Griffiths: Journal of Cell Biology; Traffic; Current Opinions in Cell Biology; Biomed Central Biology; Centrosome

James Huntington: Journal of Biological Chemistry; Biochemical Journal

Brian Huntly: Experimental Hematology

David Lomas: American Journal of Respiratory Cell and Molecular Biology; Journal of Chronic Obstructive Pulmonary Disease (COPD); Clinical Medicine

Paul Luzio: Traffic

Stefan Marciniak: World Journal of Diabetes

Randy Read: Acta Crystallographica Section D

Margaret Robinson: Traffic

David Rubinsztein: Autophagy (Associate Editor); Human Molecular Genetics; Journal of Applied Biomedicine; PLoS ONE (Academic Editor); Cell Death and Differentiation

Christopher Rudd: Current Biology; Immunology; International Journal of Biochemistry; Proceedings National Academy of Science (PNAS); PLoS ONE; Frontiers in Bioscience; European Journal of Immunology; Self/Non-Self; Seminars in Immunopathology; Frontiers in T Cell Biology

Peter St George-Hyslop: Neurodegenerative Diseases; Molecular Neurodegeneration; American Journal of Alzheimer’s Disease

Symeon Siniossoglou: Journal of Biological Chemistry

John Todd: Expert Reviews in Molecular Medicine; Human Molecular Genetics

John Trowsdale: European Journal of Immunology; Tissue Antigens; Human Immunology

Linda Wicker: Journal of Experimental Medicine (Advisory Editor)

Staff Affiliations

Folma Buss: Cell Biological Committee of the Biochemical Society

David Clayton: MRC ASTRAL Trail Steering Committee; SNP Steering Group, Cancer Research UK; Council of the International Biometrics Society; GeneLibrary Ireland Scientific Advisory Board

Andres Floto: European Cystic Fibrosis Society Nontuberculous Mycobacteria (NTM) Group (Chair); ECFS–CF Foundation Guidelines Committee for NTM Infection (Co-chair)

Bertie Götgens: International Society for Hematology and Stem Cells (Director); BBSRC – Pool of experts/ member of core grant committees

Tony Green: Membership of National/ International Bodies: Academy of Medical Science; American Society of Haematology; American Association of Physicians; Association of Physicians; British Society for Haematology; British Association for Cancer Research; European Haematology Association; European Haematology Association Scientific Program Committee; International Society for Experimental Haematology; 1942 Club; Selected Committees/ Research Administration: Head, University of Cambridge Department of Haematology; Chairman: Addenbrooke’s Hospital Haematology Senior Staff Group; Scientific Advisers to the Kay Kendall Leukaemia Fund (2004–); Member: European School of Haematology Executive Committee (2002–); NCRI Myeloproliferative Disorder Study Group (1997–); American Society of Hematology, Scientific Committee for Hematopoietic Cytokines and Factors (2008–); Scientific Advisory Board, Hemato–Linné Stem Cell Programme; European Haematology Association Board (2009–); Clinical Research Fellow Committee (2009–)
Fiona Gribsb: 2010– SAB member for OXION – Ion Channels and Disease Initiative, Universities of Oxford, Cambridge, London and MRC Harwell; 2011 – Aeres Visiting Committee, Dijon, France; External SAB Roche, Basel; EFSD/Amylin Grants Committee; WT/NIH PhD Studentship grant panel member

Gillian Griffiths: Wellcome Trust Sir Henry Wellcome Postdoctoral Fellowship Committee; EMBO Membership Committee

Brian Huntly: CRUK Discovery Committee (2006–); LRF Medical and Scientific Advisory Panel (2009–); European Hematology Association, Membership Committee, (2006–); European Hematology Association, Member of the Scientific Advisory Committee for the 15th Annual European Hematology Association meeting, Barcelona 2010; Invited Faculty member, Faculty of 1000, (2009–)

Fiona Karet: University WiSETI steering group (2007–); Wellcome Trust Clinical Interview Committee (2006–2011); Academy of Medical Sciences Clinical Research Champion (2007–); UK Renal Association Executive and Chair of Research Committee (2010–); UK Kidney Research Consortium lead: monogenics clinical study group (2009–); Kidney Research UK Trustee (2011–); Salt wasting alkaloses Rare Renal Disease Group lead (2011); Medical Education England ‘Shape of Medical Training’ Steering Group (2011–)

Paul Lehner: Wellcome Trust Expert Review Group: ‘Immune System in Health and Disease’ (Chair); Wellcome Trust 4 Yr PhD Programme in Infection and Immunity (Director); Trustee British Society of Immunology

David Lomas: British Lung Foundation Grants Committee (Chair); MRC Population and Systems Medicine Board (Chair); British Lung Foundation (Trustee); Academy of Medical Sciences Sectional Committee; Alpha-1 Foundation (US) Grants Committee (Chair); GSK Respiratory CEDD (Centre of Excellence in Drug Discovery) (Board member); Alpha-one Antitrypsin Laurell Training Award (ALTA); Wellcome Trust Clinical PhD Programme (Director); Wellcome Trust/MRC 4 Yr PhD Programme, CIRM (Director); BRC Fellowships and Capacity Building (Theme Lead); Cambridge University Clinical Research Society (Senior Treasurer & Patron); External Advisory Committee, HRB PhD Scholars Programme (Ireland); MRC PhD Studentship skills portfolio advisory group (member)

Paul Luzio: MRC Molecular & Cellular Board (Chair) (until March 2012); MRC Strategy Board (member) (until March 2012)

Stefan Marciniak: Fellow of the Royal College of Physicians; Fellow of St Catherine’s College, Cambridge

Lucy Raymond: Action Medical Research Grants Committee

Randy Read: wwPDB X-ray Validation Task Force (Chair); PDB-Europe Scientific Advisory Committee (Chair); CCP4 Executive Committee (member)

Evan Reid: Scientific Advisory Board of American Spastic Paraplegia Foundation (member); Cell Biology Theme Panel of Biochemical Society (member)

Margaret Robinson: Wellcome Trust Cell and Developmental Biology Expert Review Group (member)


Peter St George-Hyslop: Alzheimer Research Trust Scientific Advisory Board, Institut du Cerveau et de la Moelle Epiniere de France, Agence Nationale de la Recherche, Department of Health, Ministerial Advisory Group on Dementia, Deutsches Zentrum Fur Neurodegenerative Erkrankungen, Scientific Advisory Board, GlaxoSmithKline Neuroscience

John Todd: Type 1 Diabetes Genetics Consortium Steering Committee; Cambridge Computational Biology Institute Management Committee, University of Cambridge; Wellcome Trust Case Control Consortium Management Committee; NIHR Cambridge Biomedical Research Centre Cambridge BioResource Management Committee; Institute of Metabolic Science-Metabolic Research Laboratory Strategy Committee; Professorial Pay Committee, Clinical School, University of Cambridge; Scientific Advisory Board of NIHR Biomedical Research Centre Core Biochemical Assay Lab; Juvenile Diabetes Research Foundation UK Scientific Advisory Committee; Senior Academic Promotions
Committee, Clinical School, University of Cambridge; Council of School, Clinical School, University of Cambridge; Board of Electors, Professorship of Statistics in Biomedicine, University of Cambridge; Planning Steering Group, Clinical School, University of Cambridge; Scientific Advisory Board of NIHR Cambridge Biomedical Research Centre Cambridge BioResource; Management Committee (Chairman) of the MRC–NIHR Cambridge Biomedical Research Centre, University of Cambridge Eastern Sequence and Informatics Hub; Cambridge University Hospitals NHS Foundation Trust Biomedical Research Centre Executive Committee; Scientific Advisory Board of the Centre for Dermatology and Genetic Medicine, Medical Sciences Institute, Dundee; Member of the Advisory Committee for the Regius Professorship of Physic; Board of Electors, Genzyme Professorship of Experimental Medicine, University of Cambridge

Linda Wicker: Type 1 Diabetes Repository Advisory Committee, National Institutes of Health (Chair and member) (2002–)

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, David Owen, Margaret Robinson, David Ron, David Rubinsztein


Davies, J. E., Rose, C., Sarkar, S. and Rubinsztein, D. C. (2010). Cystamine suppresses polyalanine toxicity in a mouse model of oculopharyngeal...


*equal first authorship;
†equal contributions


Stinchcombe, J. C., Salio, M., Cerundolo, V., Pende, D., Arico, M. and Griffiths, G. M. (2011), Centriole polarization to the immunological synapse directs secretion from cytolytic cells of both the innate and adaptive immune systems. BMC Biol 9, 45.


The Wellcome Trust/MRC Building

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 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.

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

2. This procedure shall apply also for re-appointments.

Directors (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.

Regulations approved by the Faculty Board of Clinical Medicine, University of Cambridge

(These regulations are currently under review, pending approval by the Faculty Board of Clinical Medicine)
A new “knocksideways” system, in which a coat protein, AP-2 (in red), gets rerouted to mitochondria in cells expressing a “Mitotrap” construct (green), while clathrin (blue) does not get rerouted. This rerouting occurs within seconds of addition of a small molecule, and causes the rerouted protein to be unavailable for its normal role and therefore non-functional.

(Illustration courtesy of Margaret Robinson)