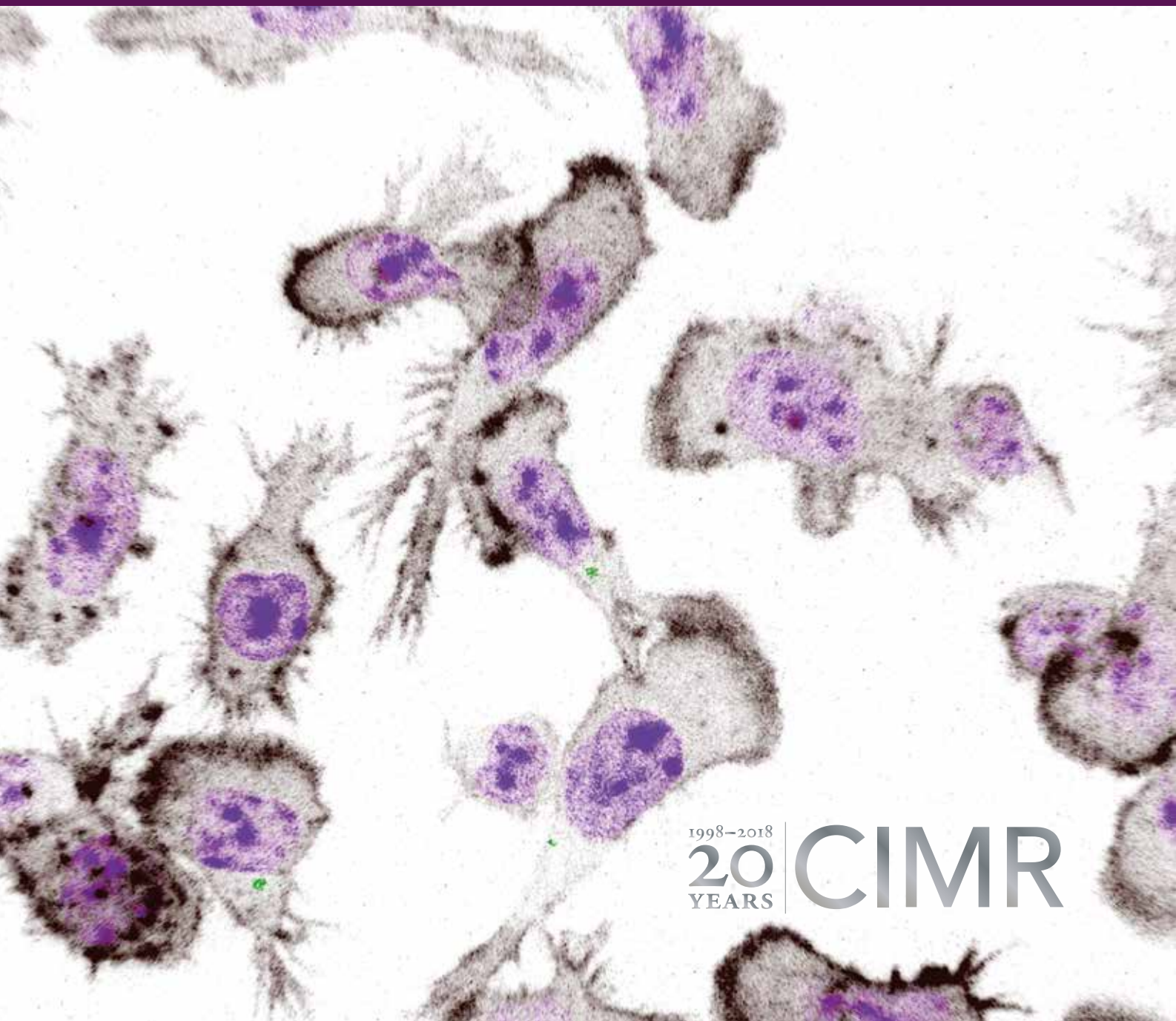
UNIVERSITY OF CAMBRIDGE
School of Clinical Medicine

Cambridge Institute for Medical Research

ANNIVERSARY REPORT 2018



1998–2018 20 YEARS CIMR

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A confocal microscopy image of cytotoxic T lymphocytes (actin, grey; nuclei, purple; centrosomes, green) migrating to seek out target cells. Image by Yukako Asano, Griffiths lab.

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Reid lab (p4)
Warren and Ron labs (p9)
Buss lab (p13)
Owen lab (p16)
Huntington lab (p17)

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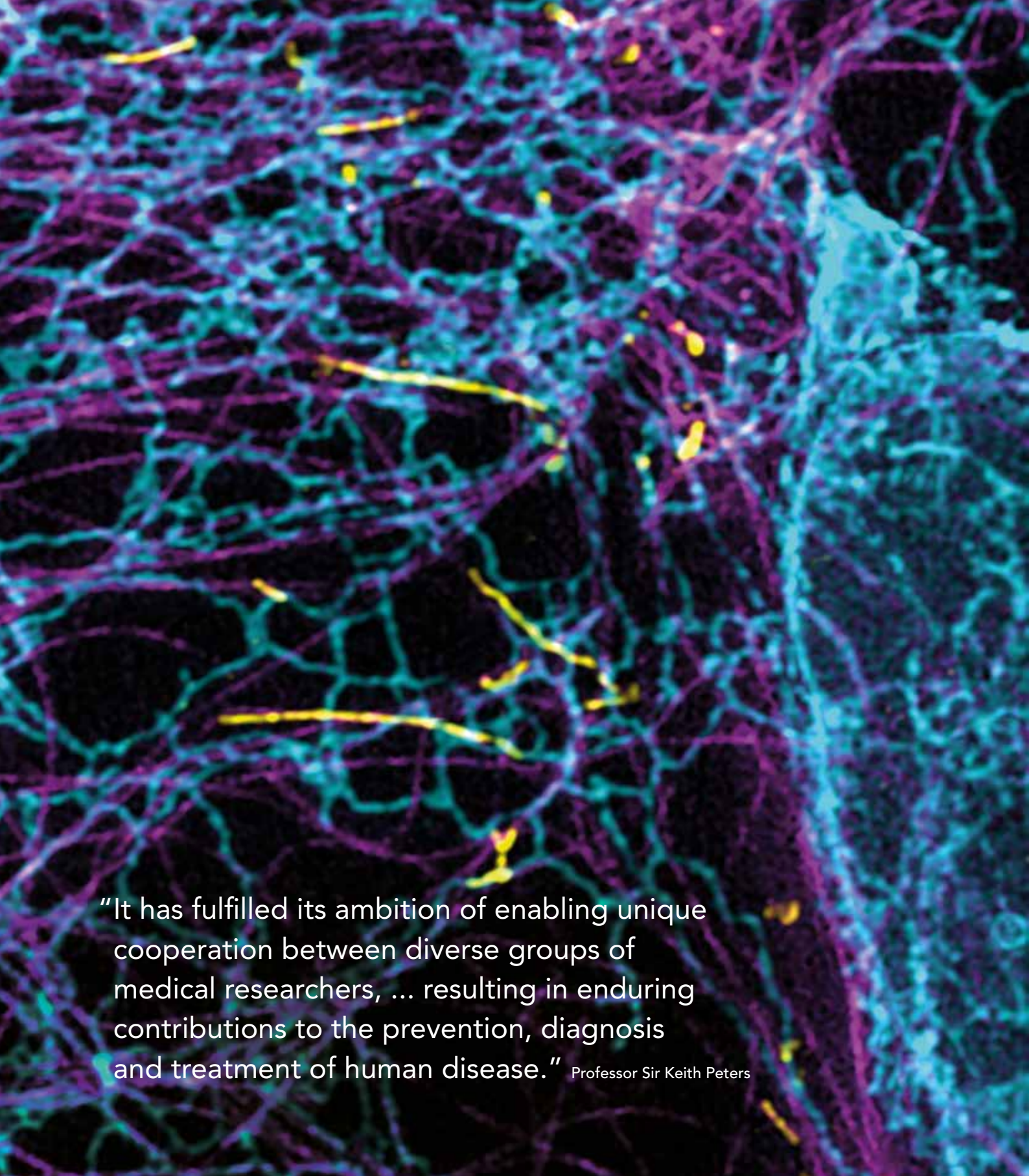
1998–2018 20 YEARS CIMR
CAMBRIDGE INSTITUTE FOR MEDICAL RESEARCH



"It has fulfilled its ambition of enabling unique cooperation between diverse groups of medical researchers, ... resulting in enduring contributions to the prevention, diagnosis and treatment of human disease." Professor Sir Keith Peters

Contents

Introduction

FROM THE DIRECTORS

PROFESSOR JENNIE BLACKWELL (DIRECTOR, 1998–2002)

Planning the birth of CIMR was a ten-year project – four years of writing proposals to secure the capital funds for the building, four years of design and build, and two years of occupancy before we held the official opening. During this time, another 12 separate proposals were submitted to secure the funds for the core facilities. We were blazing a trail at the time, as there was no mechanism by which we could acquire one large infrastructure grant, even from the Wellcome Trust. Our experience I believe encouraged the Trust to put such mechanisms in place, which has been vital to CIMR's continued success in acquiring infrastructure support across the years. Our vision was to create an institute that brought basic scientists alongside clinician scientists to apply the power of modern technologies to understanding the molecular mechanisms of disease. How could we achieve this with an apparently disparate group of 45 Principal Investigators, whose research fell broadly within the areas of human genetics, immunology, cell biology, developmental biology, oncology and structural biology? Where were the collaborations? Where were the FRSs? We boldly told our funders that the very process of bringing basic scientists and clinician scientists into the same building would foster the synergies, as I believe it has. As to the FRSs – we would grow our own – and indeed we did!

PROFESSOR PAUL LUZIO (DIRECTOR, 2002–2012, AND HEAD OF THE CIMR, 2017–2018)

In 1998, moving into the new laboratories in the nascent CIMR was an exciting moment, with the real prospect not only of doing excellent science but helping the CIMR become a flagship in the UK for interdisciplinary research at the interface of basic and clinical science. The institute's focus has always been to do excellent science and really understand the molecular and cellular basis of disease, as well as to develop young scientists into the research leaders that many have become. We have had wonderful colleagues throughout and some really exciting collaborations have developed here. From the beginning there has been a truly collegiate ethos, with principal investigators working together to bring in competitive funding to improve and develop our core scientific facilities – notably microscopy, flow cytometry and proteomics – which are used by all our research groups. The translational successes, not least the establishment of the spin-out company X01 with its novel approach to anti-coagulation therapy, have been a real bonus. I believe they reflect Marie Curie's wise words when she wrote, "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 the science, and then there is always the chance that a scientific discovery may become, like radium, a benefit for humanity".

PROFESSOR GILLIAN GRIFFITHS (DIRECTOR, 2012–2017)

By 2012, CIMR was not only well established as a leading international institute, but had spawned many others: its successes had led to a number of its original Principal Investigators moving on to found specialized research centres on the Biomedical Campus (see page 12). A long-term focus had always been cell biology, and there was an exciting opportunity to build on these strengths when I became Director. With the enormous advances that have taken place over the previous decade in genome sequencing, establishing the genetic basis of disease, our community is presented with an even greater challenge: to understand how these changes generate disease-causing defects within cells. CIMR is well placed to address this challenge: our focus on fundamental cell biology makes it possible to understand these processes from structural interactions to high-resolution imaging in specialized cells. Our unique partnership between basic and clinical research is a vital component of this strategy, and has led to many scientific successes. The original research vision has delivered in spades and, by 2017, a total of 13 FRSs had been grown by CIMR (page 30). But perhaps one of the most rewarding aspects of being Director was the ability to recruit new early career researchers to sustain the success of a very vibrant and collegiate community.

Retrospective

KEITH PETERS

AS I CONTEMPLATED WHETHER TO ACCEPT THE INVITATION TO SUCCEED SIR JOHN BUTTERFIELD IN 1987 AS REGIUS PROFESSOR OF PHYSIC ONE OF MY FIRST ACTS WAS TO CONSULT THE WELLCOME TRUST TO GAUGE ITS INTEREST IN THE CLINICAL SCHOOL.

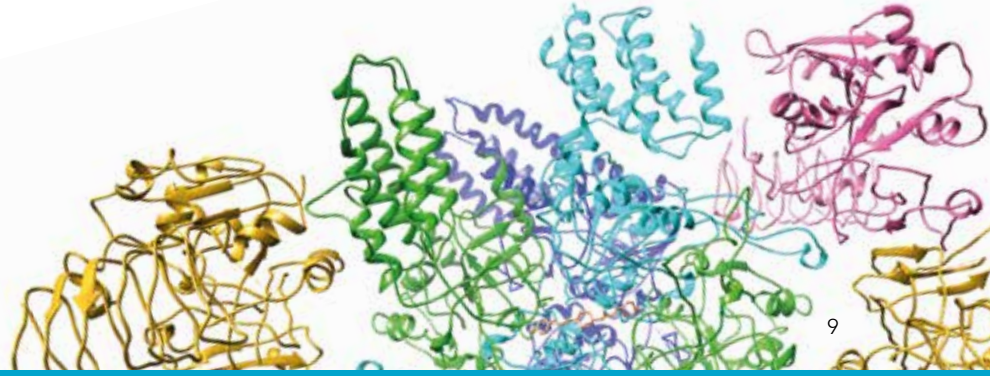
In particular, I wanted to ascertain whether the Trust might contribute to the building of a laboratory promoting the kind of clinical science that characterised the Royal Postgraduate Medical School at the Hammersmith Hospital where I had worked for the previous 18 years. A recurring theme of Hammersmith research was the in-depth study of highly selected and rare patients, often defined by emerging technologies, in whom elucidation of disease mechanisms led to insights into more common diseases. Bed-to-bench and bench to bedside research – as it is commonly termed – needs good beds and good benches, and synergy between them. This was what I hoped to expand in Cambridge.

The Trust was encouraging and I sensed that a proposal which built on Cambridge's strengths in subjects such as immunology, haematology and endocrinology, with the necessary added value of a number of new key researchers, would be sympathetically received. But it was to be more than a decade before this proposal was realised. I will not detail the hurdles that we faced but a few are worth mentioning. First we needed the new laboratory to be close to the MRC Laboratory of Molecular Biology (LMB) to promote collaboration and take advantage of its unique strengths in molecular and cellular biology. But we also needed to be close to the hospital wards and clinic. The best site was the LMB car park. There were severe planning constraints and the City planners were hostile to any development that promoted increased traffic and, in particular, included a multi-storey car park! When planning permission was eventually obtained, it was vital to build a big enough building to take maximum advantage of the footprint. However it was clear that we would not secure sufficient funding from the Trust for a building which did that. Luckily the MRC came to the rescue for its Secretary, Sir Dai Rees, had been persuaded of the need to co-locate the MRC Dunn Nutrition Unit to the Addenbrooke's campus. We also experienced something of a Catch-22 in that a number of potential recruits would only be prepared

to commit to the School if they had assurance that they would be in the new building; but without that commitment, the case to the Trust became less compelling. However in due course we were able to secure the appointment of a number of key figures including: Jennie Blackwell to the Professorship in Molecular Parasitology (endowed by Glaxo-Wellcome through the support of Richard Sykes); Martin Bobrow, a pioneer of medical genetics; and Bruce Ponder in cancer genetics. Jennie was to become the first Director of CIMR and played a vital role in its development.

A challenging issue, which has echoes today, was that some at the Trust felt that our proposal was for what was disparagingly referred to as a research hotel, lacking a compelling and unifying research theme. Our response was that we envisaged a unique mix of laboratory and clinician scientists who together would exploit the rapid developments in molecular and cell biology to elucidate human biology and pathology. Eventually, and with particular help from David Gordon at the Trust, we were successful. The development of what became CIMR can now be seen as a key event in the evolution of the Clinical School and in the establishment of the Cambridge Biomedical Campus. Notable successes include research in: oncology, and endocrinology and metabolism, now respectively in separate research institutes; and immunology and infection, shortly to move to a new institute (see page 12). But most importantly it has fulfilled its ambition of enabling unique cooperation between diverse groups of medical researchers, some of whom care directly for patients, resulting in enduring contributions to the prevention, diagnosis and treatment of human disease, which are elaborated in this excellent brochure.

Professor Sir Keith Peters
(Regius Professor of Physic and Head of the School of Clinical Medicine, University of Cambridge, 1987–2005)



The CIM
AT A GLANCE

SCIENTIFIC IMPACT IN 2017

127 publications*

*(20% in Nature, Cell, Science, eLife family journals)

147 seminars in 25 countries

TRANSLATION

>20 current collaborations with industry

FIRST SPIN-OUT COMPANY SOLD*

*XO1 Ltd acquired by Janssen Pharmaceuticals in 2015

>£21 MILLION funding for spin-outs* in 2017

*Series A funding for Z Factor Ltd and ApcinteX Ltd

131 research scientists

31 students

25 group leaders
– 40% clinically active
– >30% female PIs

7 Fellows of the Royal Society

13 Fellows of the Academy of Medical Sciences

10 Wellcome Trust Fellows

5 EMBO members

AN INTERNATIONAL RESEARCH COMMUNITY

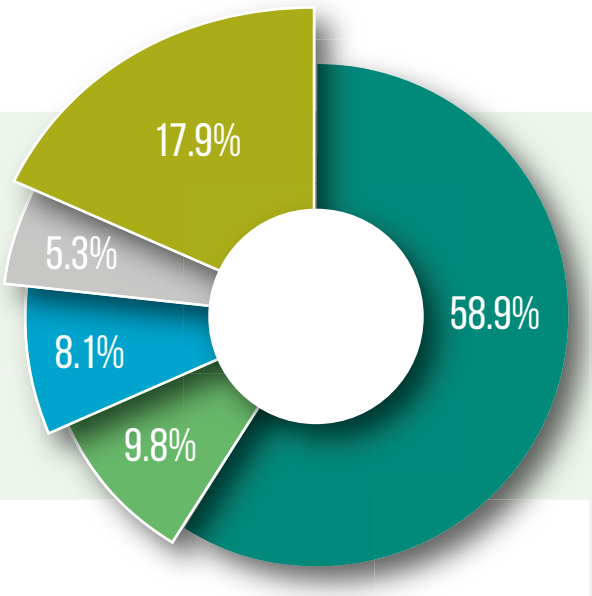
28 nationalities across 5 continents …

1/3 group leaders from outside UK

1/2 staff and students from outside UK

1/3 staff and students from other EU countries

R today



OUR FUNDING

Total value of grants held in the CIMR in 2017 was £114 million

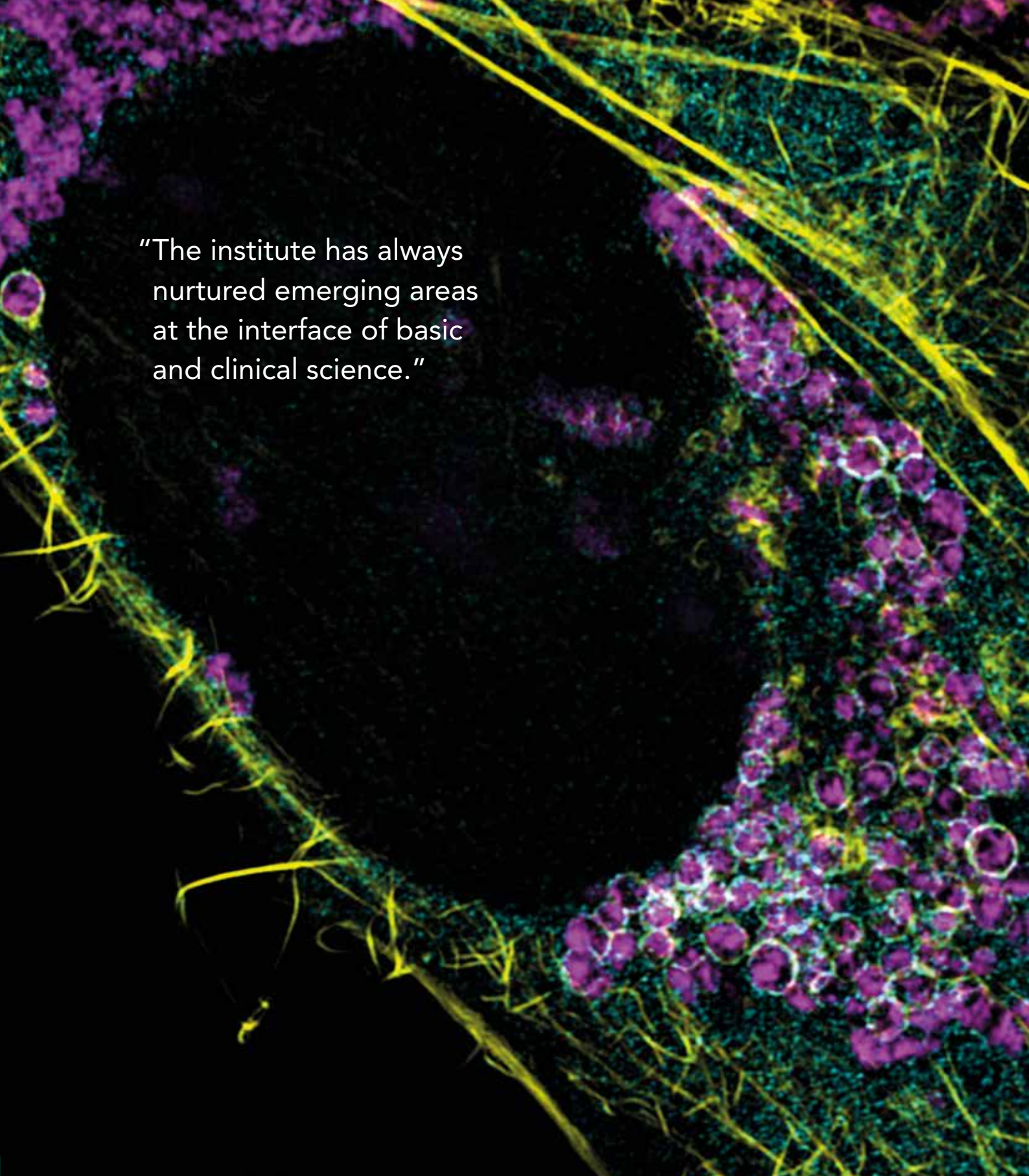
- Wellcome Trust
- Medical Research Council
- Alzheimer's Research UK
- Bloodwise
- Other

CIMR as a springboard for new institutes

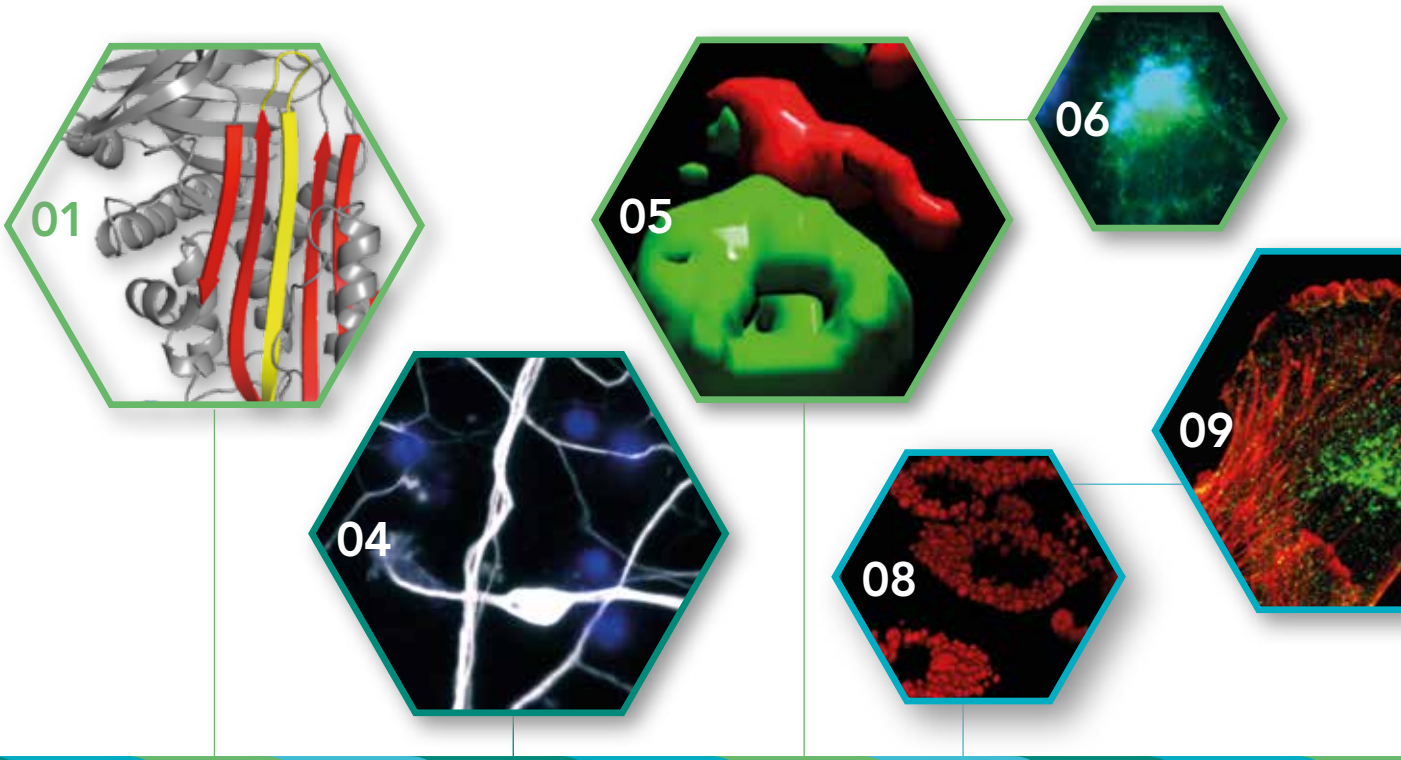
WHEN IT WAS FIRST ESTABLISHED IN 1998, THE CIMR SIGNIFICANTLY INCREASED THE CAPACITY FOR RESEARCH IN THE CLINICAL SCHOOL (WITH A 50% INCREASED RESEARCH LABORATORY SPACE). TWENTY YEARS LATER, WITH SO MANY NEW RESEARCH BUILDINGS ON THE CAMPUS, THAT SEEMS EXTRAORDINARY.

In addition to its focus on the molecular mechanisms of disease and core strengths in fundamental cell biology, the institute has always nurtured emerging areas at the interface of basic and clinical science. This ethos has helped several CIMR PIs and other senior researchers to move on to establish and lead pioneering new research institutes that are part of the Clinical School today. While at the CIMR, these PIs made numerous outstanding research advances in their respective fields. Their contributions have been an essential component of our research history and of growth of the Cambridge Biomedical Campus. The schematic below depicts a selection of key CIMR alumni, their current location, and the new institutes they helped establish and/or in which they now lead research groups.

YEAR INSTITUTE OPENED	CAMBRIDGE INSTITUTE	CIMR ALUMNI
2001	Hutchison/MRC Research Centre	Ashok Venkitaraman
2007	CRUK Cambridge Institute	Bruce Ponder, Carlos Caldas, Maike de la Roche, Doug Winton
2007	Institute of Metabolic Sciences	Stephen O'Rahilly, Tony Coll, Krishna Chatterjee, Sadaf Farooqi, Fiona Gribble, Mark Gurnell, Kevin Moreau, Frank Reimann, Giles Yeo
2008	Anne McClaren Laboratory for Regenerative Medicine	Roger Pedersen, Ludovic Vallier (now Stem Cell Institute)
2012	Cambridge Stem Cell Institute	Tony Green, Bertie Göttgens, Brian Huntly, Anna Philpott
2018	The Cambridge Institute for Therapeutic Immunology and Infectious Disease	Ken Smith, Menna Clatworthy, James Lee, Paul Lyons, Nick Matheson, Eoin McKinney, Chris Wallace



"The institute has always nurtured emerging areas at the interface of basic and clinical science."



20 YEARS

OF DISCOVERIES AT THE CIMR

by current investigators

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2000

01 Structure of serpin-protease inhibitory complex

02 A proton pump that is mutated in kidney disease

2002

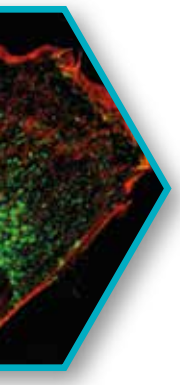
03 Structure of the AP2 adaptor complex

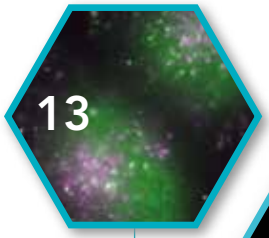
04 A motor protein that can cause spastic paraplegia

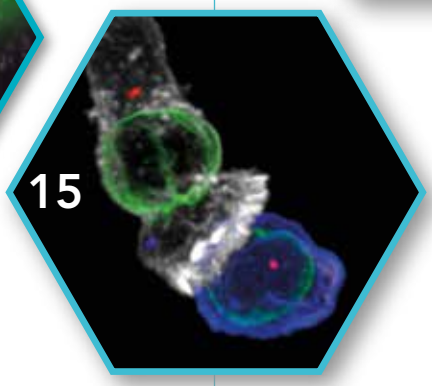
2004

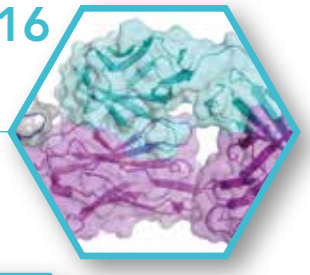
05 Autophagy protection against toxicity of neurodegenerative disease proteins

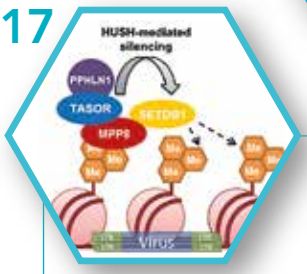
06 Retromer function in mammalian cells

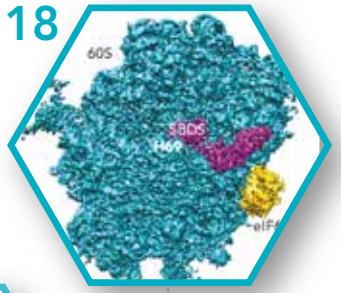












08 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018

2005

07 Endosome-lysosome kissing and fusion

08 Coupling of phospholipid biosynthesis to nuclear membrane growth

09 Functional characterization of a myosin cargo adaptor complex

2006

10 A gene controlling all pain

2007

11 Phaser programme for solving molecular structures

2009

12 >18 novel genes that cause intellectual disability

2011

13 A fifth adaptor complex, implicated in hereditary spastic paraplegia

2013

14 A marker of latent HCMV infection

15 Immune synapse use of ciliary signalling

16 Patent for a new anticoagulant and first spin-out company

2015

17 The HUSH complex in retrovirus silencing

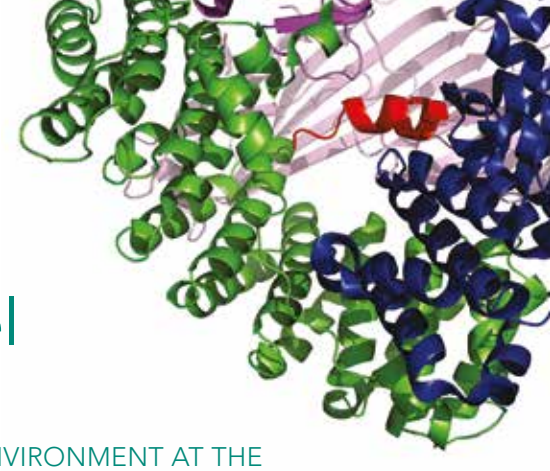
18 A key quality control step in ribosome assembly

2017

19 Chaperone function in sensing unfolded proteins

2018

20 A phase transition underpinning neurodegenerative disease



A research environment where outstanding scientists can excel

HERE FOUR CIMR GROUP LEADERS DISCUSS HOW THE RESEARCH ENVIRONMENT AT THE CIMR TODAY SETS ITS RESEARCHERS TO TACKLE CHALLENGES IN BIOMEDICAL RESEARCH.

MARGARET ROBINSON (Professor of Molecular Cell Biology, Wellcome Trust Principal Research Fellow) has been at the CIMR since its opening.

What have been key contributing factors to the institute's success during the past two decades?
There's no question that the combination of basic and clinical scientists has been key. Another factor is the focus on cell biology, which was there to begin with but has become even stronger. This means that when a clinician finds a particular gene, there is often an expert cell biologist at the institute. Conversely, when a cell biologist finds an unexpected connection with a particular disease, there is often an expert clinician already here. So there are now many in-house examples of using cell biology to understand disease mechanisms and vice versa.

How have the institute and the campus evolved in that time?
During the past 20 years, the interactions between MDs and PhDs at the CIMR have become even stronger. I was probably one of the most diehard of all the basic scientists, and was convinced that most of the cellular machinery we were working on was so fundamental that anybody with mutations wouldn't be sick, they'd be dead. Of course I was wrong, and we've been incredibly fortunate that when, for instance, we found that mutations in either AP-4 or AP-5 cause hereditary spastic paraplegia, Evan Reid just happened to be across the corridor.

HAYLEY SHARPE (Wellcome Trust Henry Dale Fellow) started her lab in 2016 after a postdoc at Genentech in the US.

What attracted you to set up your lab at the CIMR?
CIMR appealed for several reasons. The diversity of research matched well with my background in basic cell biology, cell signalling and disease genetics. It is a particularly collaborative and friendly institute, which is reflected in the number of co-authored publications. Finally, although it might be perceived as risky to rely on external money for your salary, it provides the opportunity to focus almost entirely on research. We have really benefited from the well-managed core facilities and wide range of expertise among colleagues, especially in bringing new techniques into the lab.

As a researcher who did a postdoc in Genentech, what have been your priorities in setting up a new academic lab?
A key guiding principle I have acquired is the fundamental importance of the basic research that underpins all drug discovery efforts. Indeed, one of the major challenges for translational research is the lack of reproducibility of basic research, which can be for a number of reasons. My priorities are to shed light on an understudied area of biology, using unbiased approaches and novel tools. I work in a research area that industry has historically ignored, which could be a good focus for an academic lab and has the potential to reveal future drug targets.

DAVID RON (Professor of Cellular Pathophysiology and Clinical Biochemistry, Wellcome Trust Principal Research Fellow) joined the institute in 2014.

What have been the strengths of the CIMR for your research?

The CIMR provides a broad tent for disease-orientated research with its mix of active clinicians (which I am not) and a rich environment of basic researchers employing cutting edge techniques. This provides unique opportunities for cross-fertilization and collaboration. The high quality of the science and the high standards that are self-imposed by our community of researchers were further important attractions.

This mix, while maintaining a focus on cellular phenomena, is a hard balance to strike and I think CIMR does a particularly good job at it. Finally, and no less important is the collegial atmosphere and the excellence of our support facilities and dedication of our support staff.

What challenges would you like to see met by the CIMR in the next decade?

The biggest challenge for any successful organization is maintaining its success and this inevitably means having a pipeline of new researchers to replace the leavers and creating an environment in which successful researchers re-invent themselves. Cambridge and CIMR are great places to do science and as an Institute we need to leverage that to get the very best people. But recruitment also entails getting the best graduate students and I feel that expansion of the CIMR PhD programme should be a priority.

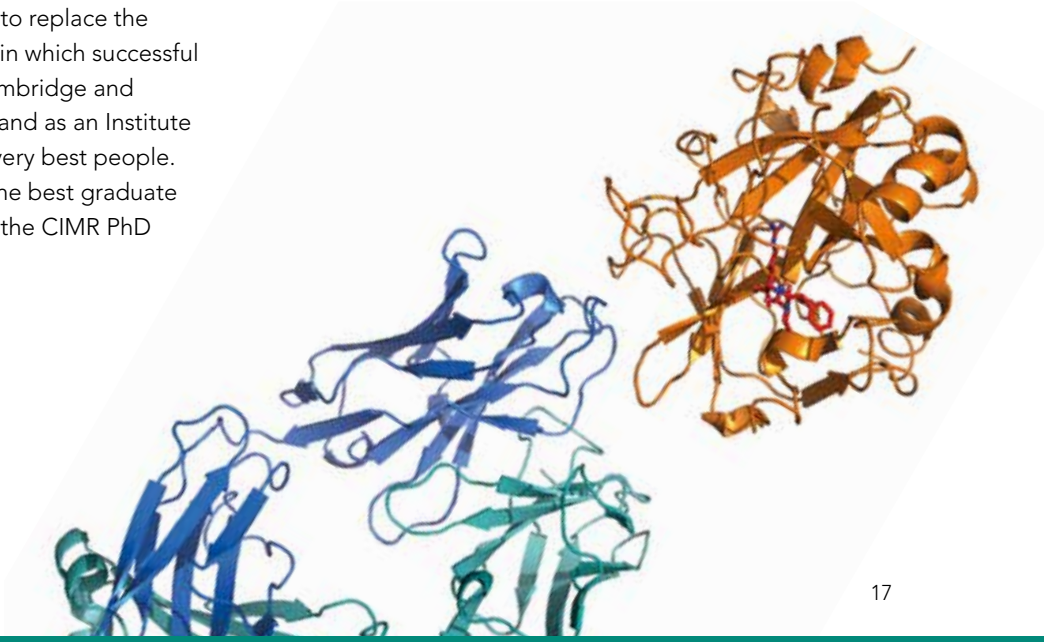
JAMES NATHAN (Wellcome Trust Senior Research Clinical Fellow) started his group in 2014.

As a clinician scientist who was previously at Harvard, what attracted you to set up your first lab at the CIMR?

I wanted to establish my group in an institute with a focus on fundamental research, where clinicians and scientists closely interact – the CIMR was the obvious choice. I also wanted to establish my group in an institute with renowned expertise in protein homeostasis. Working alongside the groups of David Ron, David Rubinsztein and Paul Lehner was a strong attraction.

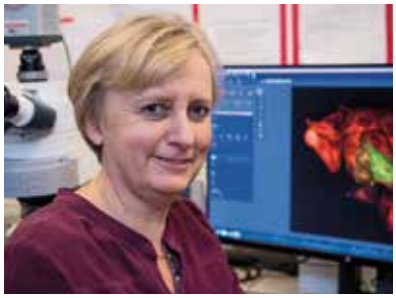
How does the research environment at the CIMR help new PIs?

The Institute's excellent facilities allowed my group to quickly establish projects, and the support from the core departments such as flow cytometry and proteomics were key to this. However, on reflection, I think the most important aspect has been the ability to openly discuss projects and science with my colleagues. This really helps you develop your scientific themes. It's equally important for members of my group, who know that that they can easily discuss experimental approaches with other labs to help drive projects forward.



FOLMA BUSS

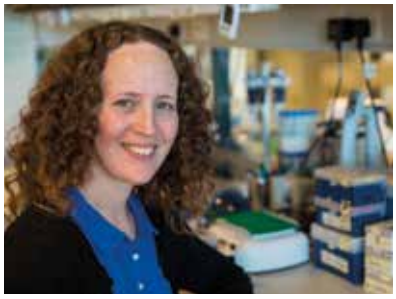
Myosin motor proteins in health and disease



Motor proteins use energy derived from ATP hydrolysis to organize cellular compartments and control intracellular transport along cytoskeletal tracks; defects in these fundamental transport processes are linked to a wide range of disorders including deafness, cardiomyopathy, neurodegeneration and cancer. Research in our lab is focused on the cellular function of myosin motors that generate force and move cargo along actin tracks. We are using a variety of cellular, molecular and biochemical approaches to determine how a motor recognizes and selects its cargo, and how motor activity and cargo attachment are coordinated. Much of our research has focused on myosins of class I and also class VI, a unique highly specialized class of myosin motors that move in the reverse direction along actin filaments. Our overall aim is to determine: the role(s) of these myosins and their cargo adaptors in cell signalling, cargo transport and autophagy; and why dysfunction is linked to neurodegenerative disorders such as Alzheimer's, Parkinson's and motor neuron disease.

JANET DEANE

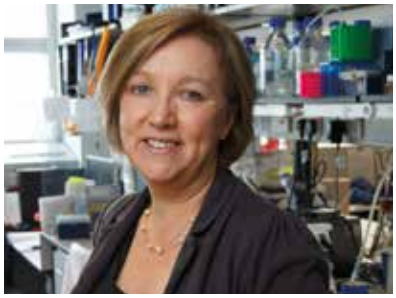
Pathogenesis of rare inherited lipid disorders



Lipids are required for forming cellular membranes and represent a potent energy source. What is less well understood is the essential role of some specialized lipids in cell signalling pathways. Sphingolipids play critical roles in regulating cell growth, cell death and inflammation. Our lab studies the molecular mechanisms of sphingolipid metabolism and the compartment of the cell where these lipids are processed, the lysosome. Defects in the processing of sphingolipids result in a range of disorders including neurodegenerative diseases, metabolic diseases and cancers. We have a particular focus on a rare neurodegenerative disorder, Krabbe disease, which primarily affects infant children. It is caused by deficiencies in the enzyme galactocerebrosidase (GALC), which is essential for lipid recycling and thereby maintenance of the lipid-rich myelin sheath that protects nerve cells. We have determined the molecular mechanisms underlying the pathogenesis of a series of disease-causing mutations in GALC, and also provided structural insights into how GALC binds its activator SapA. These insights into sphingolipid metabolism are highlighting new avenues for therapeutic development.

GILLIAN GRIFFITHS

Controlling T cell serial killing

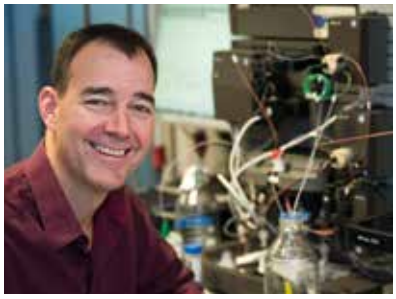


Cytotoxic T cells (CTLs) of the immune system recognise and destroy virally infected and cancerous cells with remarkable efficiency and precision. Understanding the cell biological mechanisms that control these events is key to finding ways to improve therapies for cancer and autoimmune disease. We use an integrated approach that includes cutting-edge high-resolution 4D imaging to provide remarkable insights into the subcellular events that control formation of the immune synapse. By comparing synapse formation with parallel biological systems – particularly ciliogenesis in non-immune cells – we are able to uncover the cell biology of polarized toxic granule secretion during killing. Important discoveries that have emerged from our recent research are: that centrosome docking at the immune synapse via the distal appendages of the mother centriole delivers secretory granules; and that this is mediated by localized actin dynamics and phosphoinositide remodelling.

We also use genetic approaches, including studies on primary immunodeficiencies and genetic screens including the immunophenotyping (3i) consortium (http://www.immunophenotype.org/).

JIM HUNTINGTON

Mechanisms of blood coagulation



Blood clotting is a complex and tightly controlled process, with dysregulation resulting in bleeding or thrombosis. My lab aims to develop a structural understanding of this regulation, with the hope of improving therapies for the prevention and treatment of diseases such as haemophilia, deep vein thrombosis, heart attack and stroke. Our basic research centres on the two molecular engines of clot formation, the intrinsic Xase complex and the prothrombinase complex that produces thrombin. Haemophilia is caused by deficiencies in Xase components, and thrombosis is caused by excessive thrombin formation. Work is ongoing to determine the structures of human prothrombinase and the homologous Xase complex in the presence of their substrates using crystallography and single-particle cryo-electron microscopy.

Our previous collaboration with Trevor Baglin (Addenbrooke's Hospital, Cambridge) led to a new class antithrombotic agent (ichorcumab; through spin-out XO1 Ltd), which is now in clinical development at Janssen Pharmaceuticals. We have also founded ApcinteX, Rebalance Therapeutics, SuperX and Z Factor to develop treatments for haemophilia, thrombosis and α1-antitrypsin deficiency.

FIONA KARET

Mechanisms of kidney tubule homeostasis

My group's goal is to understand renal tubular function and its associated diseases, many of which are inherited and most of which are rare but confer a major health burden on both patients and providers. We have completed a large body of work concerning molecular pathophysiology of inherited acidoses and tubulopathies, which can result in kidney failure. Our current focus has three strands. First, we aim to reverse malfunction of specific renal tubular proteins that normally mediate 'housekeeping' or homeostasis by the kidney. Second, we study human urinary exosomes, for which we have demonstrated an essential antibacterial role, and potential roles as disease biomarkers. Third, we are using biomaterial technology, in collaboration with the Department of Chemistry, to develop a whole blood potassium sensor that could be suitable for patient home use.

These projects run in parallel with clinical studies of patients with rare renal disorders as well as related inherited and heritable conditions, for whom I have clinical responsibility in my multidisciplinary Renal Genetics and Tubular Disorders clinic.

DELPHINE LARRIEU

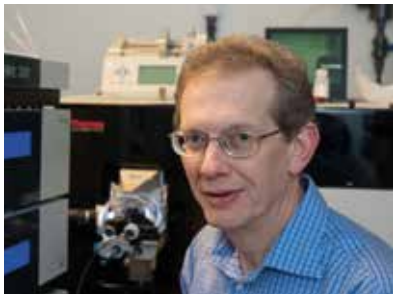
Nuclear envelope regulation and links with disease

The nuclear envelope (NE) lies at the interface between the nucleus and the cytoskeleton, and regulates NE integrity and cell homeostasis. NE defects are associated with a broad range of diseases including premature ageing disorders such as Hutchinson Gilford Progeria Syndrome (HGPS), as well as with physiological ageing.

Our main goal is to identify and characterize new pathways that can modulate NE function. Initially, we will focus on the N-acetyltransferase 10 (NAT10) as a new regulatory node in NE control. We will explore further how NAT10 functions in normal and ageing cells, and how its inhibition improves chromatin structure and nuclear shape and reduces DNA damage. In addition, we will screen for new candidates involved in NE control, and test the relevance of these new regulatory pathways *in vivo* in specific mouse models that recapitulate human syndromes associated with NE defects. Our work will thus improve our understanding of NE regulation and identify druggable targets that might yield novel therapies for NE-associated diseases.

PAUL LEHNER

Viral silencing and immune evasion pathways



Studying how viruses manipulate host cells to enable viral replication and evade immune recognition provides insight into both viral function and cellular regulation. Our group integrates human genetic screens with advanced proteomics to uncover mechanisms mediating these processes – an approach that can also identify therapeutic ways of targeting these pathways.

Our application of genome-wide forward genetic screens has identified novel cellular pathways used to control viruses. We discovered the 'Human Silencing Hub' (HUSH), an epigenetic transcriptional repressor complex which silences newly integrated retroviruses such as HIV, as well as endogenous retrotransposons.The application of functional quantitative proteomic approaches allows a systematic unbiased quantification of cell surface and intracellular receptors, and provides an unprecedented overview of cellular receptors manipulated by viruses. We can now compare the relative abundance of >1200 plasma membrane proteins and create a temporal cell surface map of receptors that are altered upon infection with viruses or in tumours.

PAUL LUZIO

Membrane traffic in the late endocytic pathway

Endocytosed macromolecules are degraded in endolysosomes, providing a recycling system that is essential for cellular health and metabolism, as well as both susceptibility and resistance to infection.

Our goal is to understand the coordinated fusion and fission events of the regenerative cycle that links endolysosomes and lysosomes. Lysosomes are small membrane-bound organelles that are full of other hydrolytic enzymes and function late in the endocytic, phagocytic and autophagic pathways. In the endocytic pathway, lysosomes kiss and fuse with late endosomes to form active, acidic endolysosomes; these digest endocytosed macromolecules and can signal to the nucleus, but they are transient compartments from which neutral, 'enzyme-storage' lysosomes are regenerated. We study the roles of membrane traffic machinery in this pathway. This includes the ESCRT (endosomal sorting complex required for transport), HOPS (homotypic fusion and vacuole protein sorting) and SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complexes, as well as ion channels, the proton pumping V-ATPase and the multifunctional protein VARP (Vps9 and ankyrin repeat containing protein).

STEFAN MARCINIAK

Endoplasmic reticulum stress in disease

We are interested in cellular stress in health and in disease, particularly the detection of misfolded proteins in the endoplasmic reticulum (ER); this 'ER stress' is essential for cell growth and survival. ER stress triggers phosphorylation of the protein translation initiation factor eIF2α and consequently activates an integrated stress response (ISR). We described the first invertebrate eIF2α phosphatase (or PPP1R15 enzyme), and revealed that G-actin is a conserved component of this holoenzyme, thereby making the ISR sensitive to actin dynamics. Through collaborations with the Ron and Read labs, we now understand the structural basis of the PPP1R15-actin interaction.

Another focus is on how changes in α1-antitrypsin, a protein secreted by the liver that protects the lung from inflammatory damage, can affect the ER. We find that accumulation of mutant α1-antitrypsin polymers leads to fragmentation of the ER, but that these fragments remain functionally connected by SNARE-mediated vesicular transport. We are developing tools to measure this protein-folding environment, and thereby understand the mechanism of ER dysfunction.

PATRICK MAXWELL

Oxygen sensing and renal diseases

All multicellular animals have a powerful ability to adapt to changes in oxygenation. This response system operates in all mammalian cell types, orchestrated by the master regulator hypoxia-inducible factor (HIF), which alters gene expression to modulate diverse processes including blood vessel growth and metabolism. HIF also contributes to a range of diseases, most notably clear cell renal cell carcinoma (CCRCC), the most common form of kidney cancer. The HIF pathway is constitutively activated in the majority of CCRCC through inactivation of the von Hippel Lindau (VHL) gene, which we discovered encodes part of an E3 ubiquitin ligase complex that targets HIF-α through recognition of specific hydroxylated prolyl residues.

Our current foci are on understanding the role of cellular oxygen sensing in the immune response, and on understanding how altered mitochondrial function contributes to kidney disease. To investigate these we are using integrated approaches, which include identifying humans with rare mutations that cause altered oxygen sensing and kidney diseases, studying genetically modified mice and extensive cell culture approaches.

JAMES NATHAN

Protein degradation, oxygen sensing and metabolism

A fundamental requirement for cell survival is the ability to respond to the local oxygen and nutrient environment, for example through rapid changes in protein homeostasis. We aim to gain improved understanding of these pathways, and thereby provide potential new therapeutic targets for cancers and inflammatory disease.

Central to this process are the hypoxia inducible transcription factors (HIFs), which are usually rapidly ubiquitinated and degraded by the proteasome when oxygen is abundant. However, HIFs can be stabilised and activated even in aerobic conditions, and we have adopted near-haploid and CRISPR/Cas9 human forward-genetic screens to identify genes required for this. This has uncovered a novel regulatory pathway for oxygen sensing, centred on the 2-oxoglutarate dehydrogenase complex (OGDHC) – a mitochondrial enzyme required for respiration. These findings highlight an intricate relationship between mitochondrial metabolism, lipoic acid and oxygen sensing enzymes. Understanding the role of key metabolites in this pathway under physiological contexts is a current focus of our studies.

DAVID OWEN

Transport vesicle and organelle biogenesis

Transmembrane proteins are moved between organelles in transport vesicles, a process that is essential for eukaryotic cells and leads to a wide range of pathophysiological effects when disrupted. We combine structural and functional analyses to dissect the mechanisms that control this process.

The protein coats that surround transport vesicles have self-assembly and membrane deformation properties that are important for vesicle formation. Cargo selection is mediated by the direct binding of coat components to the cytosolic portions of transmembrane cargo. We have uncovered the molecular mechanisms behind these recognition processes for a number of different vesicle coats. Another focus is on SNAREs, membrane-embedded proteins that provide specificity and energy to transport vesicle:organelle fusion events. We have proposed that appropriate SNAREs must be actively sorted into transport vesicles to allow the vesicles to fuse with their desired target organelle, and have gone on to demonstrate how these recognition processes occur in different vesicle coats in parallel to standard cargo recognition mechanisms.

LUCY RAYMOND

The genetic basis of rare diseases and intellectual disability

The research aim of the group is to increase our understanding of intellectual disability and related rare diseases in children and young people. We are studying >2000 families and individuals with intellectual disability to both identify novel genes that cause this genetically heterogeneous disease and translate new strategies for improved clinical care using a combination of exome and whole genome analysis.

We are using the NIHR Bioresource for Rare Diseases and the East of England Genomic Medicine Centre to develop a national programme to deliver whole genome sequence on cases with intellectual disability and related rare diseases. In 2014, we launched the IMAGINE ID study to assess the mental health and neurodevelopmental impact of genomic disorders. For some novel disease-causing genes, we continue to perform highly specialized phenotypic assessments to understand the resulting pathophysiology. This requires design of new assessment tools and has led to a more profound understanding of children with specific mutations.

RANDY READ

Innovations in protein structure discovery

The three-dimensional structure of a protein provides an essential framework for understanding its biochemistry. We focus both on extending the scope of the methods used to determine structures of proteins and other macromolecules, and on applying those methods to proteins involved in disease. Our group has solved diverse protein structures, with implications for their roles in different processes and diseases. This has included: members of the serpin family important for blood clotting; globulins that affect hormone delivery; angiotensinogen in the control of blood pressure; enzymes mutated in inherited metabolic diseases; and galactocerebrosidase and iduronate sulphatase implicated in the neurodegenerative Krabbe disease and Hunter syndrome, respectively.

In developing methods for protein crystallography, we focus on improvements to maximum likelihood methods through our program Phaser. By accounting better for the effects of errors, these new methods can solve structures that evaded earlier approaches. Excitingly, we are finding that some of the powerful approaches we have developed for crystallography can also be adapted to cryo-EM.

EVAN REID

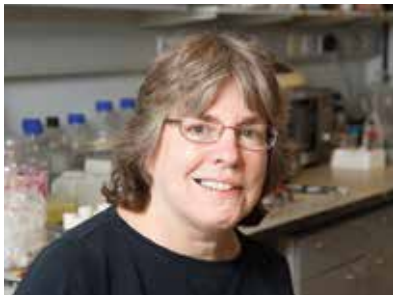
Unravelling the molecular pathology of axon death

We focus on understanding cell biological mechanisms required for axonal health and thereby nervous system function by studying the molecular pathology of the hereditary spastic paraplegias (HSPs). These are human genetic conditions in which axons develop selective distal degeneration, so identifying the genes involved enables us to target with precision proteins that are vital in keeping axons alive. We primarily focus on the functions of spastin, a protein encoded by the gene most commonly mutated in HSP.

Through our work on spastin, we have discovered a cellular pathway that links groups of HSP proteins involved in endoplasmic reticulum shaping and endosomal tubule fission to a common feature of lysosome dysfunction. We propose that this is the key underlying pathology in most genetic subtypes of HSP. We are now investigating the mechanisms by which lysosome dysfunction could cause axonal degeneration in HSP, with the aim of identifying tractable therapeutic targets.

MARGARET ROBINSON

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 depend on coat proteins. Our research focuses on adaptors, major components of the vesicle coat that select which proteins get packaged into a vesicle and which get left behind.

To look for novel adaptors and other trafficking machinery, we have been using several approaches, including subcellular proteomics, genome-wide siRNA library screening and a 'knocksideways' approach that we developed for rapid inactivation of proteins of interest. Current studies in the lab include the generation of a knocksideways mouse model, genome editing and insertional mutagenesis to identify additional trafficking machinery, and characterisation of a new vesicle tethering complex. Although much of our work is on vesicles coated by the clathrin coat protein, we are also studying two non-clathrin-associated adaptors, AP-4 and AP-5, which are implicated in hereditary spastic paraplegia, as well as the ancient TSET protein complex.

DAVID RON

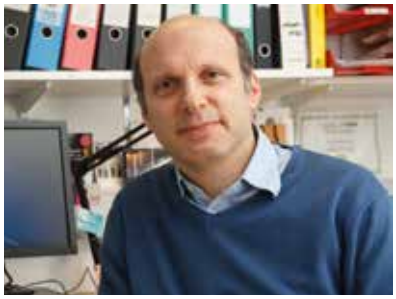
Protein folding homeostasis

Cells have mechanisms in place to ensure correct folding of proteins, but must also adapt rapidly to the presence of unfolded/misfolded proteins. If the burden of misfolded proteins increases beyond the corrective capacity of the cell, this can lead to proteotoxicity. The accumulative deleterious effects of proteotoxicity are believed to contribute to important diseases of ageing, affecting metabolism, endocrine function and the nervous system, amongst others.

Adjusting protein folding capacity to match the rate of secreted protein synthesis is a particular challenge in the endoplasmic reticulum (ER), the entry point of the secretory pathway. Eukaryotes have thus evolved signalling pathways that detect unfolded protein ER stress, and elicit rectifying responses. This unfolded protein response (UPR) modifies gene expression at the transcriptional, post-transcriptional and translational level, and is the focus of our lab. Our long-term goal is to elucidate a detailed molecular understanding of protein folding homeostasis in the secretory pathway and to exploit this for potential therapeutic benefit.

DAVID RUBINSZTEIN

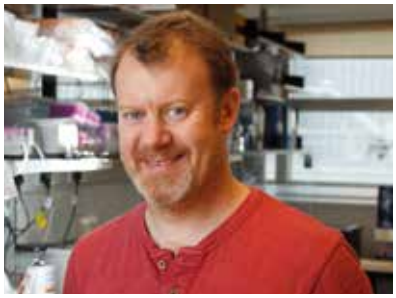
Autophagy and neurodegeneration



Intracellular protein misfolding and aggregation are features of many late-onset neurodegenerative diseases. These include Alzheimer's disease, Parkinson's disease, tauopathies and polyglutamine expansion diseases such as Huntington's disease. Currently, there are no effective strategies that slow or prevent neurodegeneration. We are currently employing a range of approaches to address this issue, including biochemistry and cell biology, as well as studies in zebrafish and mouse models. The mutations causing Huntington's disease and many proteinopathies often confer toxic aggregation of the specific protein, and disease severity frequently correlates with changes in protein levels. We have discovered that autophagy, a bulk degradation process that mediates the clearance of long-lived proteins and organelles, regulates the levels of such aggregate-prone proteins. We are characterizing the early membrane remodelling events that drive autophagy and aim to understand how autophagy compromise can have pathological consequences. We are pursuing our findings that the toxicity of these proteins can be alleviated by enhancing their removal by autophagy, in the hope of identifying safe and effective therapeutic strategies.

MATTHEW SEAMAN

Retromer-mediated endosomal protein sorting

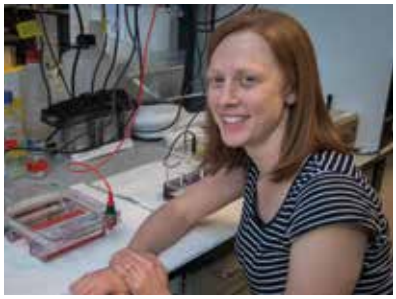


The controlled movement of proteins between organelles, through vesicle traffic, is essential for normal cell function. The retromer complex is a conserved and vital component of the cellular machinery that controls sorting and trafficking at endosomes into both endosome-to-Golgi retrieval and endosome-to-cell surface recycling pathways. My lab aims to determine the mechanisms by which retromer, and other endosomal protein-sorting proteins mediate these processes, and how this is implicated in disease.

Retromer selects membrane protein cargo for retrieval or recycling through the action of the retromer cargo-selective complex (CSC) – a trimer of VPS35, VPS29 and VPS26. My lab has shown that a mutation in VPS35 that causes Parkinson's disease (PD) impairs the association of the retromer CSC with the actin regulatory WASH complex, leading to defects in the localization of cargo. We are also investigating how retromer and novel components of the endosome-to-Golgi retrieval pathway control the sorting and localization of the amyloid precursor protein (APP), and its implications for Alzheimer's disease (AD).

HAYLEY SHARPE

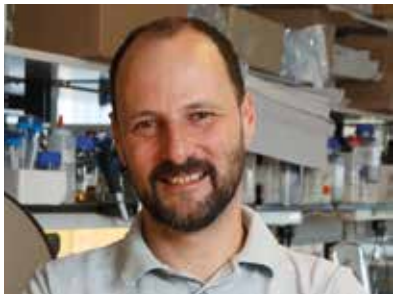
Receptor tyrosine phosphatase signalling



Reversible post-translational modifications serve as switches for protein activity and influence fundamental cellular processes. Our focus is on tyrosine phosphorylation, which is controlled by the antagonistic actions of protein tyrosine kinases and protein tyrosine phosphatases (PTPs). Dysregulation of this balance is associated with numerous diseases as well as developmental abnormalities. Our main objectives are to understand mechanisms of cell signalling that are mediated by the membrane-associated receptor PTPs (RPTPs), by identifying their physiological roles, substrates and principles of regulation. One of our research focuses is PTPRK, a receptor tyrosine phosphatase previously implicated in cell adhesion and transforming growth factor ß signalling. We aim to identify relevant substrates and physiological functions of PTPRK in primary culture systems using phosphoproteomics and biochemistry. Cancer genomics studies indicate that PTPRK is mutated or deleted in several human cancers and that some gastrointestinal cancers harbour oncogenic PTPRK–RSPO3 gene fusions. Understanding how PTPRK expression is regulated could therefore provide a therapeutic opportunity in this subset of cancers.

SYMEON SINIOSSOGLOU

Lipid metabolism in membranes and organelles

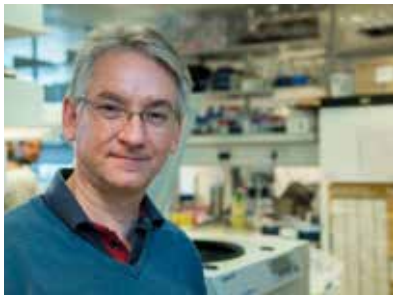


Cells use lipids as building blocks to form membranes and as storage molecules to preserve energy for later use. Membrane is required for organelle biogenesis, cell growth and division while the ability to store energy in lipid droplets is essential for survival during nutritional or environmental stress. Controlling lipid partitioning between membranes and storage is important not only physiologically, but also because disrupting the balance of stored versus mobilized lipid leads to serious metabolic disorders, such as type 2 diabetes, nonalcoholic fatty liver disease and obesity.

Our overall aim is to understand the mechanisms by which cells control membrane lipid homeostasis. To address this, we investigate how growth and nutritional signals regulate the activity of key lipid biosynthetic enzymes in the endoplasmic reticulum (ER), the central hub for lipid synthesis in eukaryotes. Because the basic design of lipid metabolism is conserved from unicellular organisms to humans, we perform our studies in budding yeast, as a model organism that provides unique genetic tools, to inform experiments in mammalian systems.

ALAN WARREN

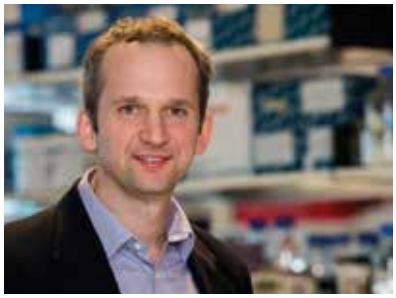
Mechanisms of eukaryotic ribosome assembly



The coordinated assembly of actively translating ribosomes is critical for protein synthesis in all cells. However, the mechanisms involved in this process still remain poorly understood. By addressing this fundamental biological problem, we aim to provide insight into the molecular basis of a new class of cancer predisposition disorders know as ribosomopathies that are associated with mutations either in the ribosomal proteins themselves or in some of the >200 assembly factors involved in ribosome biogenesis. The focus of our work is the inherited leukaemia predisposition disorder Shwachman-Diamond syndrome (SDS) that is caused by mutations in several assembly factors that function during the late cytoplasmic steps of 60S ribosomal subunit maturation. Our lab uses the latest advances in single-particle cryo-electron microscopy (cryo-EM) together with genetic and biochemical approaches to define the pathway of cytoplasmic 60S ribosomal subunit maturation and to understand how the disruption of ribosome assembly causes human developmental abnormalities and cancer predisposition.

MICHAEL WEEKES

Innate immune evasion by intracellular pathogens



Human cytomegalovirus (HCMV) is a ubiquitous herpesvirus that persistently infects the majority of the world's population. Following primary infection, HCMV establishes a latent infection under the control of a healthy immune system. However, in immunocompromised individuals, such as transplant recipients and AIDS patients, viral reactivation can cause serious disease. Our aim is thus to understand how HCMV and other intracellular pathogens evade innate immunity. To do this, we combine cutting-edge tandem-mass-tag-based multiplexed proteomics with detailed molecular studies of novel cellular targets. We recently developed the proteomic technology 'quantitative temporal viromics' (QTV), which provides a systematic quantitative analysis of temporal changes in host and viral proteins throughout the course of productive viral infection. This revealed how HCMV orchestrates the expression of >8,000 cellular proteins to manipulate immune defences, and identified novel putative antiviral restriction factors. We are now (i) employing functional proteomic secondary screens to identify important HCMV restriction factors, and (ii) determining their mechanisms of action, as well as how they are targeted by HCMV.

GEOFF WOODS

The basis of inherited painlessness

Pain is an evolutionarily conserved warning mechanism that alerts us to danger (i.e. potential tissue damage). But rare individuals – about one in a million in the UK – are born unable to feel pain. By discovering the genes mutated in these people we seek new understanding of how the human pain system develops and functions. These genes that cause painlessness nearly all have roles after development in normal pain sensing. We are now exploring the roles of these genes in chronic pain disorders.

We also study people with defined types of chronic pain (such as Complex Regional Pain syndrome, and Fibromylagia) – again seeking the genetic changes that cause or allow the pain to develop and persist. We hope that this will lead to new diagnostic tests, new classifications of pain, the ability to target existing pain therapies accurately, and completely new pain treatments. We also work closely with anesthetists, rheumatologists and neurologists to study individuals with painlessness and common pain disorders, as well as collaborating widely with nociception researchers.

Research index

Institute leadership
Professor Paul Luzio, Head of the CIMR
Professor David Rubinsztein, Deputy Director and Head of the CIMR Division for Translational Research

Previous Directors of the CIMR
Professor Gillian Griffiths (2012–2017)
Professor Paul Luzio (2002–2012)
Professor Jennie Blackwell (1998–2002)

Institute Management Committee (2017–2018)
Paul Luzio (Chair), Sarah Smith (Business and Operations Manager), David Rubinsztein, Paul Lehner, Stefan Marciniak, Alan Warren, Margaret Robinson, Janet Deane, Mike Murphy (MRC Mitochondrial Biology Unit) and Mariann Bienz (MRC LMB)

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Graduate education
Folma Buss, Head of Graduate Studies
Amanda Goldsmith, PhD Administrator

Scientific strategy and communications
Alison Schuldt

Fellows of the Royal Society (alumni and current PIs)

Year of election	Fellow	CIMR PI dates
2001	Bruce Ponder	1998–2007
2002	Robin Carrell	1998–2003
2003	Stephen O'Rahilly	1998–2007
2004	Martin Bobrow	1998–2005
	Peter St George-Hyslop	2007–present
2009	John Todd	1998–2017
2012	Margaret Robinson	1998–present
2013	Gillian Griffiths	2007–present
2014	Randy Read	1998–present
	David Ron	2014–present
2017	Krishna Chatterjee	1998–2007
	David Owen	2000–present
	David Rubinsztein	1998–present

Wellcome Trust Principal Research Fellows (current PIs)
Gillian Griffiths, Paul Lehner, David Owen, Randy Read, Margaret Robinson and David Ron

Fellows of the Academy of Medical Sciences (current PIs)
Gillian Griffiths, Jim Huntington, Fiona Karet, Paul Lehner, Paul Luzio, Patrick Maxwell, David Owen, Margaret Robinson, David Ron, David Rubinsztein, Peter St George-Hyslop, Alan Warren and Geoff Woods

EMBO members (current PIs)
Gillian Griffiths, David Owen, Margaret Robinson, David Ron and David Rubinsztein

The CIMR postgraduate student community in 2017

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