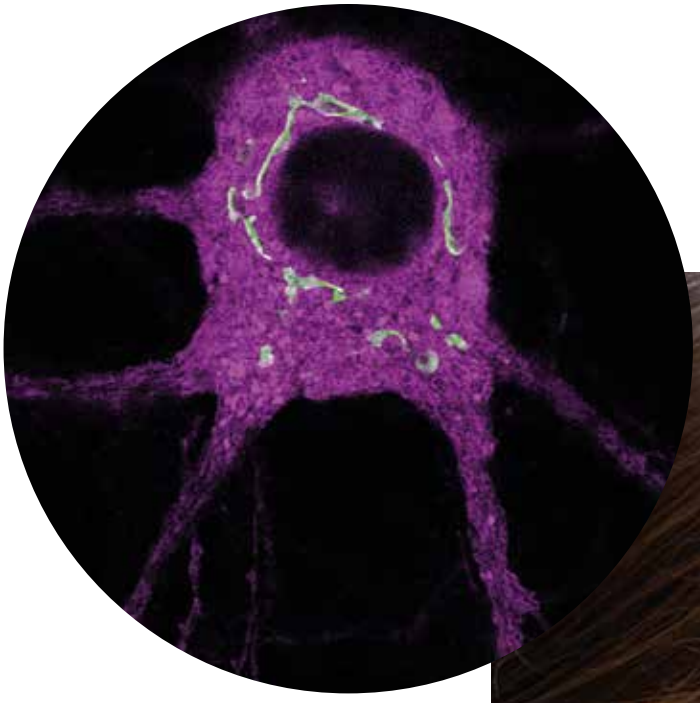
CIMR
Cambridge Institute for Medical Research

UNIVERSITY OF CAMBRIDGE
School of Clinical Medicine



CIMR Report 2024

Transforming our understanding of human disease

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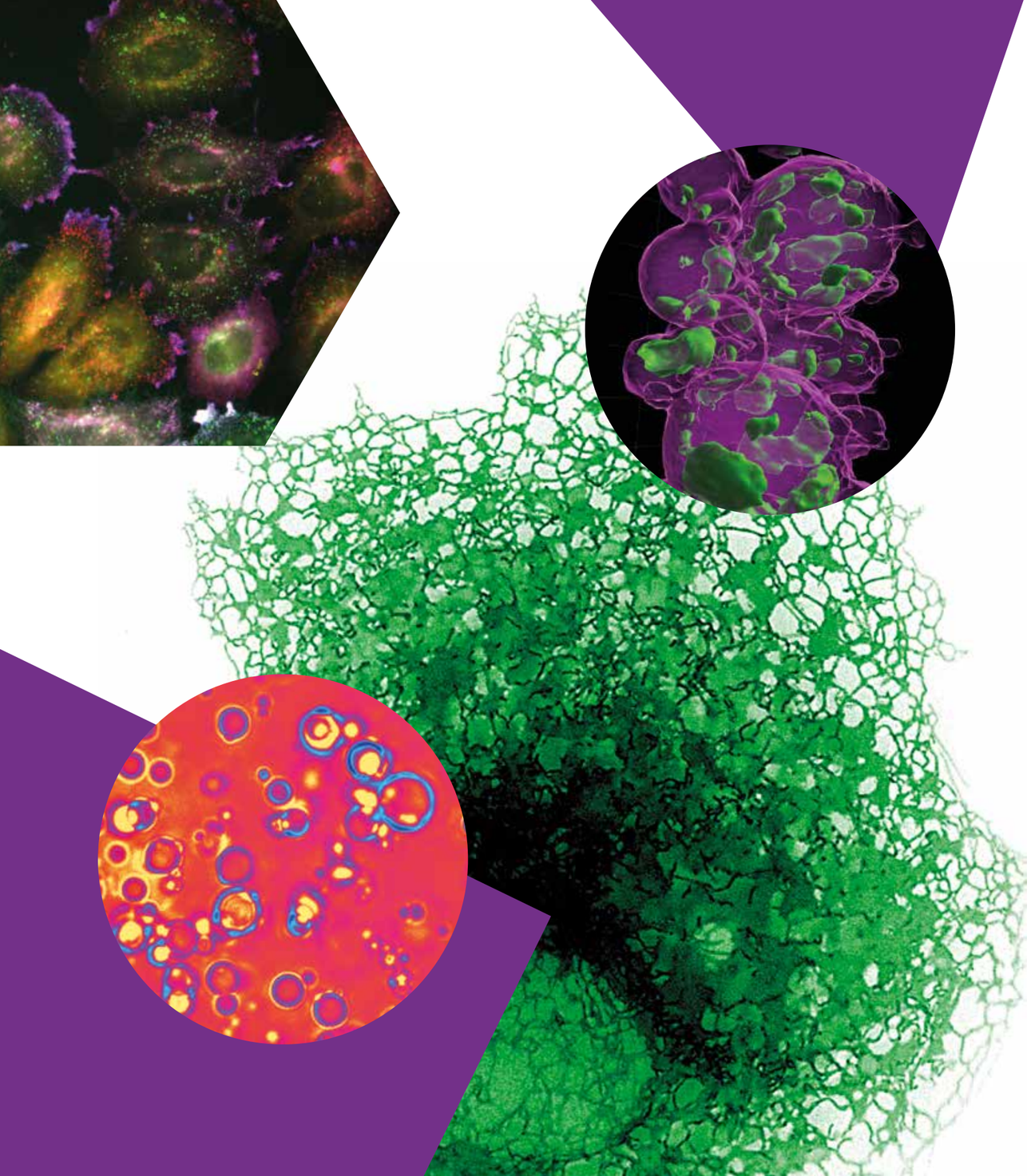

CIMR Report 2024

Molecules, Mechanism, Medicine –
from small details to big discoveries

CIMR
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for Medical Research

Contents

"The idea that scientific discoveries are made by a solitary genius working alone in a lab is much more myth than reality. Discoveries come from great teams working in a supportive and positive environment, where everyone's contributions are valued and celebrated. I'm hugely grateful to everyone who makes CIMR such an extraordinary place to work. "

Introduction

from Professor Julian Rayner, Director of CIMR

Research never stands still – new discoveries, new technologies and new ideas are always changing what can be done. This is one of the things that makes science so exciting; the sense that knowledge and opportunities are always expanding and that the approaches we can employ today are very often ones that we simply couldn't have dreamed were possible even ten years ago.

The same is true for research institutes. CIMR has an incredibly storied history and discoveries made in our labs have quite literally rewritten cell biology textbooks, created new understanding of disease, and led to new treatments. However, CIMR can't stay still – we need new technologies, new ideas and new leaders to stay at the cutting-edge of research. Keeping that sense of momentum and renewal, in an ever-changing funding and organisational environment, is one of our core challenges.

I'm delighted therefore that this report provides several significant examples of renewal and growth over the last two years. Three new Principal Investigators, Melissa Gammons, Janin Lautenschläger and Jonny Nixon-Abell, have recently joined CIMR supported by prestigious fellowships and have established new research labs. We have been lucky enough to receive several substantial equipment grants, which combined with critical support from the School of Clinical Medicine have enabled us to refresh key equipment in our microscopy and flow cytometry core facilities. Finally, this year we will be welcoming the first group of students on our new MPhil programme on Molecular Mechanisms of Disease, which will significantly increase the number of graduate students carrying out research in CIMR labs.

Each of these initiatives have required an enormous amount of work from multiple people, and people are of course at the heart of all we do – it is the extraordinarily talented and committed people across the whole institute, from the support teams to the labs, that make CIMR the most genuinely collaborative and supportive place that I've ever had the privilege to work. Attracting great people from all backgrounds is something that we think deeply about, and in the following pages you'll also read about initiatives in these areas, such as recruiting outstanding apprentices and giving them opportunities to develop their careers, and a range of approaches we take to provide experience and mentorship for students from backgrounds under-represented in research.

It has been another fantastic two years – thank you to everyone who works in and supports CIMR, for all that you do.

News highlights

CIMR WELCOMES THREE NEW PRINCIPAL INVESTIGATORS

Three new Principal Investigators have set up their laboratories at CIMR over the past year, all supported by highly competitive fellowships. Dr Janin Lautenschläger & Dr Jonathon Nixon-Abell were both postdoctoral fellows in Prof St George-Hyslop's group here at CIMR, while Dr Melissa Gammons joins us after carrying out a period as a postdoctoral fellow in Dr Mariann Bienz's lab at the MRC Laboratory of Molecular Biology. Both Dr Gammons & Dr Nixon-Abell are recipients of a Wellcome Career Development Award, while Dr Lautenschläger holds a Dorothy Hodgkin Research Fellowship from the Royal Society.

LAUNCH OF NEW MPHIL PROGRAMME

CIMR, together with our close colleagues at the MRC Mitochondrial Biology Unit (MBU), have launched a new one-year MPhil in "The Molecular Mechanisms of Human Disease". It combines extensive research projects with taught content that covers disease diagnosis and identification, lab-based mechanistic studies using cutting-edge technologies, and how understanding mechanisms can lead to the development of new therapeutics. The course is co-led by Prof Folma Buss, Dr David Gershlick and Prof Matthew Seaman from CIMR along with Prof Mike Murphy from MRC-MBU.

"We're thrilled to introduce the new MPhil programme, specifically designed to equip graduate students with essential practical research skills and a strong theoretical foundation in the molecular mechanisms underlying health and disease. We offer a unique opportunity to engage with leading experts at CIMR and MBU, preparing students to contribute meaningfully to groundbreaking research." David Gershlick

NEW CUTTING-EDGE EQUIPMENT FOR CORE FACILITIES

Thanks to a major equipment grant from the Medical Research Council and support from the School of Clinical Medicine, the Microscopy Facility has purchased two new Zeiss confocal microscopes. The LSM980 with Airyscan2 detector significantly increases the resolution for both live and fixed sample microscopy, a Dynamics Profiler enabling measurements of molecular concentration and flow in living samples, and a 730nm laser for use with near infra-red fluorophores. The LSM980 with FCS has spectral detection, plus new functions that allow users to tailor image capture based on features identified through image analysis.

Funding from the Biotechnology and Biological Sciences Research Council has allowed purchase of a new Bigfoot spectral cell sorter in our Flow Cytometry Facility. Equipped with seven lasers, five scatter and small particle and 60 fluorescence detectors, this cutting-edge machine radically increases the range of colours that can be detected, and as a result the complexity of cells that can be sorted from a single sample. The Bigfoot can also be operated with a variety of nozzle sizes to allow more gentle sorting of cells from clinical samples.

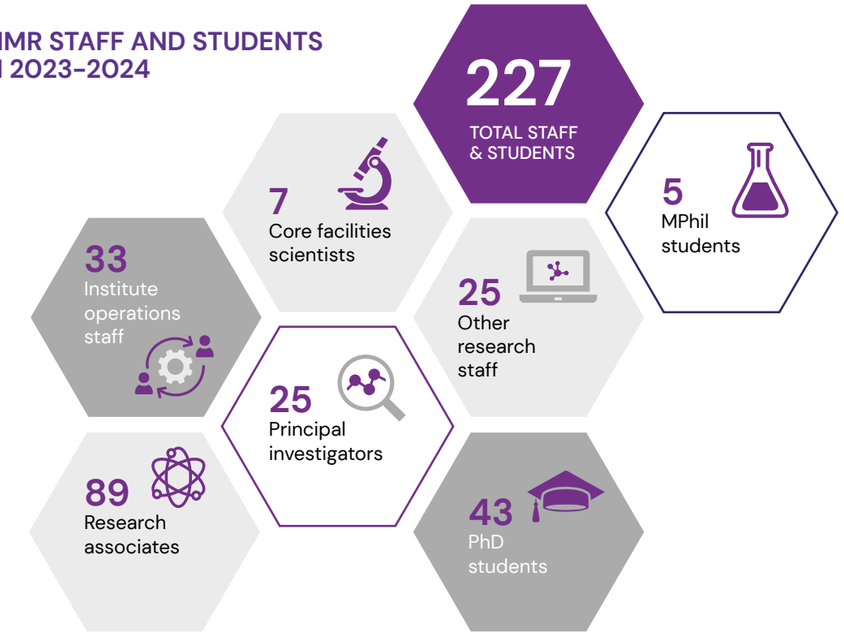
Our core facilities teams are a hugely important part of CIMR, and keeping these facilities up to date with state-of-the-art equipment is a key component of our strategy.

CIMR PI TO CO-LEAD NEW CENTRE FOR RARE RESPIRATORY DISEASES

The medical research charity LifeArc has launched four new Translational Centres for rare diseases. Worldwide, over 300 million people are living with rare diseases. Research into these diseases can be fragmented, but these new centres, which partner Universities and NHS Trusts across the UK, will provide patients with a single 'go to' centre connecting them with clinical experts and researchers. CIMR PI and consultant respiratory physician Prof Stefan Marciniak will co-lead the National Translational Centre for Rare Respiratory Diseases while Dr Jennifer Dickens, another clinician-scientist at CIMR, will contribute her significant expertise in miniaturised lung models. The centre will also create a UK-wide biobank of patient samples and models of disease, helping to facilitate development of clinical studies and hopefully new therapies.

CIMR in summary

CIMR STAFF AND STUDENTS IN 2023-2024



47%
of CIMR people from overseas

32 Nationalities

5 Continents

25 CIMR Principal Investigators

9	Women
8	Clinically trained
6	Fellows of the Royal Society
11	Fellows of the Academy of Medical Sciences
5	Members of European Molecular Biology Organisation

THE LAST 5 YEARS OF CIMR RESEARCH OUTPUTS AND IMPACT

402 RESEARCH PAPERS
over 5 years, of which 24 highly cited

23949
Citations

WIDENING PARTICIPATION:

5 Work experience schemes

42 Students engaged

20 Labs involved

60 Staff involved

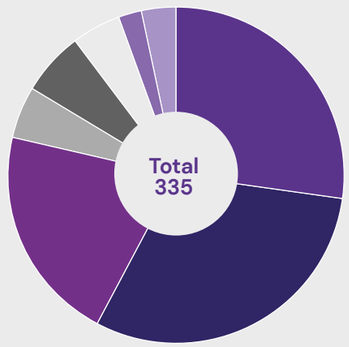
2 ONLINE
widening participation events

250
Students engaged

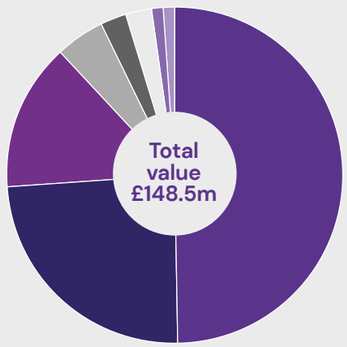
THE LAST FIVE YEARS OF FUNDED RESEARCH AT CIMR

77 Funding sources

Number of active grants



Value of active grants



KEY

- Wellcome
- UK charity (non-Wellcome)
- UK Government
- Industry
- Non-UK Charity
- EU
- UK Professional Bodies
- Non-UK Government

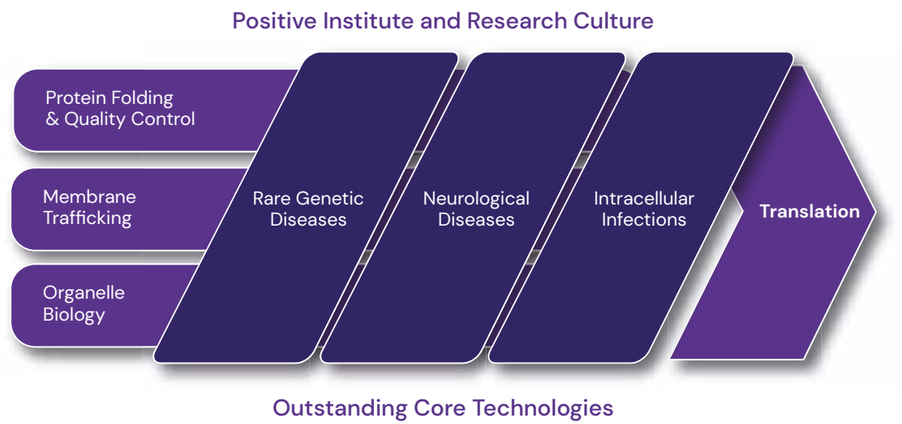
CIMR's strategy and approach

We believe that connecting the intricate details of how cells work with the big picture of human disease is the fastest route to both scientific breakthroughs and therapeutic advances. CIMR research therefore links **molecules, mechanisms and medicine** with a clear mission – to determine the molecular mechanisms of disease in order to improve human health.

Our strategy is to:

- Support collaboration between leaders in fundamental molecular discovery and clinicians with real-life expertise and understanding of disease, in a positive, diverse and vibrant research environment.
- Invest in and deploy a range of outstanding, high-quality platforms and technologies that allow us to understand cellular and disease mechanisms at high resolution.
- Focus on specific areas of disease and biology in order to maximise connections and synergy.

CIMR research is centered on fundamental pathways of cell function and the diseases that occur when these pathways are disrupted, either by mutation or infection.



We have three interlinked biological areas of focus: **protein folding and quality control, membrane trafficking** and **organelle biology**. Disruption of these core pathways through genetic changes leads to diseases that are often rare, devastating, and frequently occur in the nervous system. Numerous infectious pathogens have also evolved to infect cells by exploiting and manipulating these pathways. CIMR therefore has three disease areas of focus: **rare genetic disease, neurological disease** and **intracellular infections**. These diseases are frequently neglected and overlooked, meaning there is significant unmet patient need.

We actively encourage the **translation** of fundamental discovery into new treatments and diagnostics by leveraging the outstanding clinical and commercial environment of the Cambridge Biomedical Campus.

"Our approach is to connect the fine details and big picture of human disease, to accelerate scientific breakthroughs and advance modern medicine."

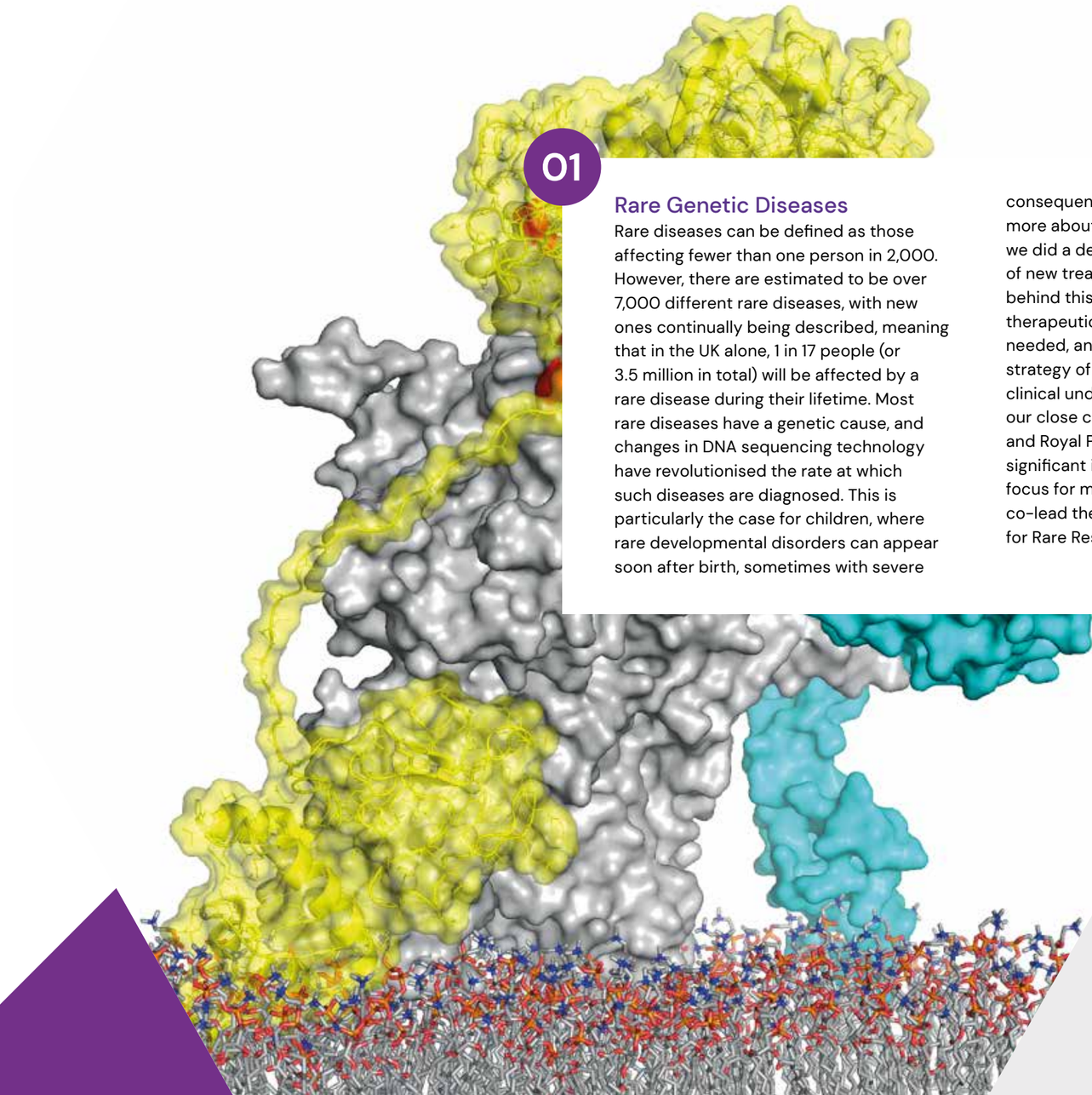
We also believe that for science and research to have the greatest impact they must be integrated with and informed by society, so we champion and seek out new innovative ways to **engage** the public and patients with our research, and **widen** the pool of people who participate in research-related careers.

Research themes

Life on Earth is built on cells, which must organise and maintain themselves in order to grow and divide - whether they are part of complex multi-cellular organisms such as humans, or single-celled organisms such as the bacteria and parasites that can infect us.

The ability of cells to maintain themselves depends on many thousands of different proteins, all of which must be produced, folded into three-dimensional structures, transported to the location (or organelle) within the cell where they function, and then destroyed when they are no longer required. CIMR hosts many world-leading experts in these fundamental processes – **protein folding and quality control**, **membrane trafficking** and **organelle biology**.

Understanding such critical and highly complex biological processes in turn helps us understand how diseases occur when these processes are altered by genetic changes or subverted by infectious pathogens. Conversely, understanding disease frequently adds to our fundamental understanding of cell biology. CIMR's strength is our ability to combine both disciplines synergistically, which increases the speed with which we can develop new treatments that benefit patients. We focus on three specific areas of disease.



01

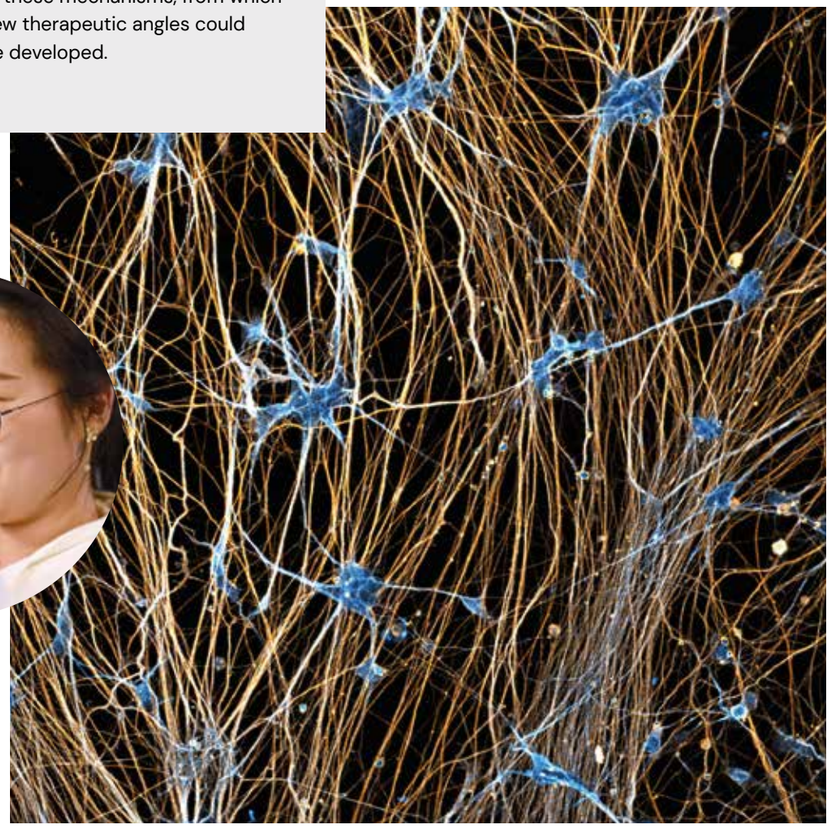
Rare Genetic Diseases

Rare diseases can be defined as those affecting fewer than one person in 2,000. However, there are estimated to be over 7,000 different rare diseases, with new ones continually being described, meaning that in the UK alone, 1 in 17 people (or 3.5 million in total) will be affected by a rare disease during their lifetime. Most rare diseases have a genetic cause, and changes in DNA sequencing technology have revolutionised the rate at which such diseases are diagnosed. This is particularly the case for children, where rare developmental disorders can appear soon after birth, sometimes with severe consequences. While we know much more about the causes of rare disease than we did a decade ago, the development of new treatments lags significantly behind this revolution in diagnosis. New therapeutic approaches are urgently needed, and this is an area where CIMR's strategy of combining biological and clinical understanding and making use of our close connections with Addenbrooke's and Royal Papworth Hospitals, can have significant impact. Rare genetic disease is a focus for many of our researchers, and we co-lead the National Translational Centre for Rare Respiratory Diseases.

02

Neurological Diseases

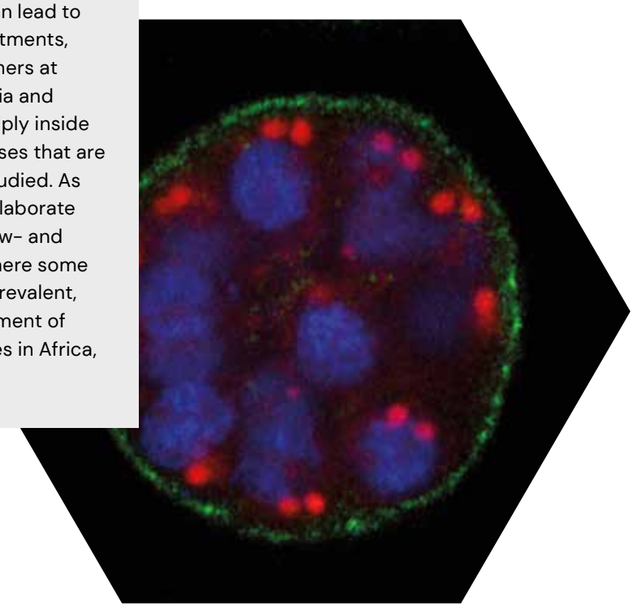
The vast and intricate connections and interactions between the billions of cells that make up the human brain influence our behaviour, our memories and our creativity - but these cells are also where devastating neurological diseases can develop. Some of these conditions are very rare, while others such as Alzheimer's and Parkinson's diseases affect hundreds of thousands of people in the UK alone. Recent clinical trials send a clear message for the first time that treatments that alleviate the suffering due to these diseases are possible. However, there is no question that a more complete understanding of the core mechanisms of neurological diseases would help the development of more effective and targeted treatments. CIMR researchers combine fundamental exploration of nerve and other brain cell function with clinical insight to deepen understanding of these mechanisms, from which new therapeutic angles could be developed.



03

Intracellular Infections

Intracellular pathogens hide within our cells in order to avoid key elements of the immune system and to use the contents of their host cells as a source of food and energy. These pathogens often use and subvert membrane trafficking pathways to gain entry into human cells, sometimes even staying within host organelles throughout their intracellular existence. Deeper understanding of the interactions that take place between pathogens and their hosts can lead to the development of new treatments, drugs and vaccines. Researchers at CIMR work on viruses, bacteria and parasites that grow and multiply inside human cells and cause diseases that are often neglected and understudied. As part of their work, several collaborate closely with researchers in low- and middle-income countries, where some of these diseases are more prevalent, thus supporting the development of research capacity in countries in Africa, Asia and South America.



Institute culture

At CIMR we believe in a positive, collaborative and sustainable culture of work and research.

Diversity is at the heart of science and the best research happens in a positive environment where ideas are shared openly and people are supported to meet their potential.

We are committed to recruiting people from diverse backgrounds with a range of experiences and perspectives. Diversifying the range of people represented in roles across CIMR is a major focus of our Widening Participation initiatives, outlined in the Public Engagement section (p22). This year we were delighted that Prof Janet Deane was awarded the Inclusive Practice award at the Student-Led Teaching Awards run by the Cambridge Students' Union. Nominated and selected by students, this award recognises staff who are exceptional or impressively proactive in ensuring that their work is inclusive of all students in terms of race, disability or gender.

CIMR aims to support people at all career levels through mentoring and a wide range of training opportunities. These are not only focused on those active at the bench carrying out research; our professional services staff are a vital part of the Institute and recognising and valuing their contribution is an essential part of our approach. We support the University's Apprenticeships scheme and currently employ two apprentices in the Building Services team and in HR.

CIMR encourages a sense of community through our Institute seminars and research retreat, as well as social events from summer barbeques to international baking days.

Sustainability plays an increasingly important role at the University of Cambridge, and we have an active Green Committee who work to ensure that both research and the running of the building are carried out as sustainably as possible.

IMAGES
L-R: HR apprentice Macy Driver; Facilities apprentice Lawrence Fitch; CIMR Green Committee, chaired by Prof Weekes

"The postgraduate student community at CIMR is supportive, friendly and inclusive. The Student Committee organises a wide range of social, academic and welfare events for CIMR students and research assistants to make sure that you are well supported and that your time here is a lot of fun!"

Philanthropy

At CIMR we are fortunate to receive generous donations from individual philanthropists. Such donors often have a personal connection to the research they are supporting, and several recent donations focus on under-funded rare diseases, which, although individually rare, together affect 1 in 17 people in the UK.

One of our donors, Hazel Satchell, explains:

"The relatively low numbers of people affected by all the various rare diseases do not warrant pharmaceutical companies investing in research into the individual diseases. Understandably, from a commercial perspective, they are much more likely to choose higher profile diseases affecting larger numbers.

I am affected by Hereditary Spastic Paraplegia SPG7, diagnosed some 8 years ago, and, being over 70, I feel time is ticking away to find a therapeutic answer to this cruel disease. To have a connection with CIMR and the honour to have the opportunity to influence scientific research is the most satisfying use of our money. Suddenly material things do not really matter any more, and the ray of hope that our donations may bring to us and others in the future is massive. It is also rewarding for us to be able to support the career development of extremely bright PhD students who are bringing their skills and knowledge to bear on this valuable and ground breaking research."

CIMR extends gratitude to all our philanthropic partners for their generous support. In particular, we would like to thank David Soanes for funding the Michael House PhD Studentship based in Prof Deane's lab, PSMC5 Foundation for supporting research in Prof Rubinsztein's lab and RxCelerate for their contribution to a Master's student based in Prof Huntington's lab.

Prof Reid says:

"I was absolutely delighted to receive such a generous donation, which is funding an innovative PhD project being undertaken by Isabelle Hall in my lab. Not only is this project supporting Isabelle's work, but it has also catalysed a new collaboration between my lab and Professor Patrick Chinnery's lab in the Mitochondrial Biology Unit. I am very much looking forward to seeing the project progress."

"I'm grateful for the opportunity this donation has provided to investigate an under-studied neurodegenerative condition and to work closely in alliance with the people most affected by it."

Isabelle Hall, PhD student

Public engagement

Public engagement brings scientists into direct contact with a range of public audiences through interactive events.

It is built on two-way communication for mutual benefit, introducing audiences to complex scientific concepts and research discoveries, while providing scientists with the opportunity to hear directly from the patients and members of the public that their research will impact.

The focus of our public engagement over the past two years has been on widening participation programmes which aim to diversify the talent pool entering scientific careers. In collaboration with the MRC MBU and St Catharine's College, we run the Inspiring Scientists at CIMR & MBU programme. Over the last three years, we have hosted groups of 12 sixth form students from across Cambridgeshire and East Anglia for a week, during which they gained insight into the world of biomedical research. Students carried out a short research project in a lab, received advice and mentoring on how to apply to study at Cambridge, and learned about life in college.

"It was amazing! The work was super interesting and there was a lovely community."

"I saw a side to science that I'd hadn't seen before. I wasn't expecting everything to be so technological... I enjoyed seeing all the different types of technology used."

"The researchers were really nice and welcoming, I expected working in a lab to be serious and strict."

We also host students on the Aspiring Scientists Training Programme. Coordinated by the Gurdon Institute but involving several University departments and Institutes, this week-long residential programme for sixth-form students from diverse backgrounds across the UK is another valuable contribution to widening participation.

Prof Janet Deane also co-leads the Experience Postgrad Life Sciences Programme, which provides two-month long fully funded summer research placements in labs across the School of Clinical Medicine and School of Biological Sciences, with several students hosted at CIMR.

As well as these focused programmes, our researchers take a range of hands-on activities to events such as the Cambridge Festival, Big Biology Day and RareFest, and visit schools and community groups. This enables us to connect more widely with various audiences including patients, families and school children.

"Thank you for this experience, it was so impactful and I'm grateful for the chance to see how research life is like, as well as university life. This truly is the most effective way to show people just how important STEM careers are."

Training

Training the next generation of researchers is a core focus of CIMR's strategy.

There are currently 43 PhD students carrying out research at CIMR and from autumn 2024 our graduate student numbers will be boosted further by students enrolled in our new MPhil course. We also host a vibrant community of postdoctoral researchers, who during their time at CIMR take the critical first steps in the transition from formal study to research independence.

Our graduates and early-career researchers go on to a wide range of careers including medicine, education, and policy, but many are now running their own groups in the UK and overseas. Dr Xiaoting Wu, a former PhD student in Prof Rubinsztein's lab, is now an Assistant Professor at the Ichan School of Medicine at Mount Sinai in New York; Dr Jonas Albarnaz, a post-doc from Prof Michael Weekes' lab left in 2023 to set up his own lab at the Pirbright Institute, and Dr Chris Hill was awarded a Wellcome Henry Dale Fellowship following his PhD in Prof Janet Deane's lab, and now runs his own lab at the University of York.

CIMR alumini who have gone onto careers in industry include Massimo Sammito, a recent post-doc in the Read lab now working at Astra Zeneca, and Rachel Watkins from the Reid lab who is now Director of Experimental Biology at CoSyne Therapeutics. CIMR trainees have also moved successfully into the broader science ecosystem, such as Nienke Lubben, a former PhD student in the Robinson lab who went on to qualify as a patent attorney and is currently a partner at Harrison Goddard Foote.

Dr Xiaoting Wu
a former PhD student in Prof Rubinsztein's lab, is now an Assistant Professor at the Ichan School of Medicine at Mount Sinai in New York.

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a post-doc from Michael Weekes' lab left in 2023 to set up his own lab at the Pirbright Institute.

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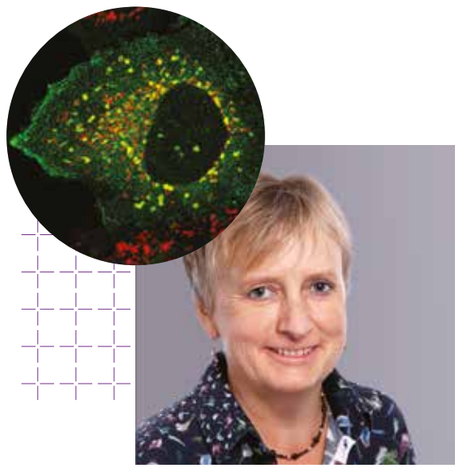
Principal investigators



Professor Folma Buss – Myosin motor proteins in health and disease

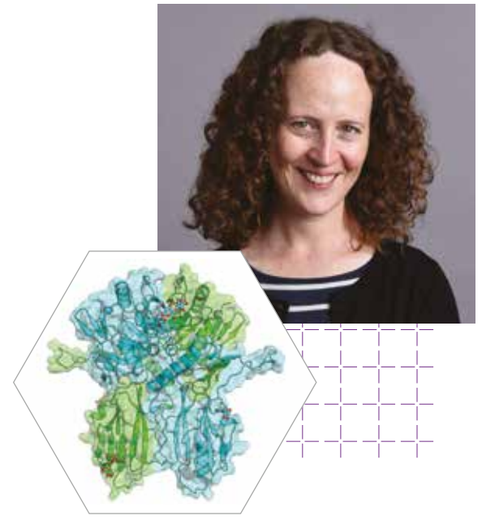
Membrane Trafficking, Organelle Biology, Intracellular Infections

In living cells dynamic processes such as muscle contraction and intracellular transport are powered by myosin motor proteins, which are nanomolecular machines that move cargo along actin tracks rather like a train running along a railway network to specific destinations. In our lab we follow the activity of myosin motors in living cells using high resolution microscopy but also use a wide variety of biochemical and biophysical techniques on isolated motors in the test tube to study their characteristic behaviour. Dysfunction of motor activity is linked to many human diseases including deafness, cancer and neurodegeneration. Therefore, a deeper understanding of how motors are switched on/off, fine-tuned and which cargo is transported, will guide our efforts to modulate myosin activity as a therapeutic strategy.

Professor Janet Deane - The role of sphingolipids in health and disease

Membrane Trafficking, Rare Genetic Diseases, Neurological Diseases

The cell surface is decorated with a diverse array of proteins and lipids that play essential roles in cell contact and signalling. An important class of lipids enriched at the cell surface are glycosphingolipids (GSLs). Imbalances in GSL levels underlie a range of severe disorders from neurodegeneration to cancer. My lab investigates the molecular mechanisms by which altered sphingolipid metabolism results in devastating neurological disease. Our work explores similarities between rare genetic neuropathologies and common neurodegenerative diseases, laying the scientific foundations for future therapies.



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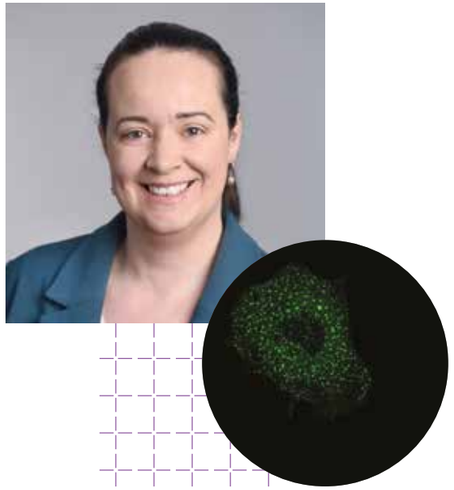


Dr Melissa Gammons – Molecular mechanisms of Wnt signalling in health and disease

Membrane Trafficking, Organelle Biology, Rare Genetic Diseases, Neurological Diseases

Cells communicate by signal transduction pathways whereby secreted molecules bind to receptors on target cells to trigger intracellular responses. It is critical for our development and homeostasis that these signals are regulated and correctly interpreted. Misregulation of these pathways is a leading cause of diseases, including rare genetic diseases, neurological disorders and cancer. We focus on Wnt signalling pathways that regulate an array of cellular processes including cell proliferation, differentiation, migration and polarity. We investigate how Wnts selectively regulate morphogenetic processes, namely migration and polarity, or cell fate decisions, such as proliferation.

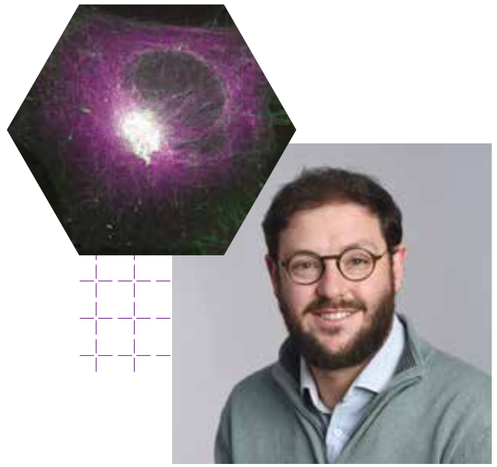
We also investigate how misregulation of Wnt signalling causes rare genetic diseases, such as the skeletal dysplasia Robinow Syndrome. By understanding how these pathways work at the molecular level, we will be able to devise more targeted therapies.

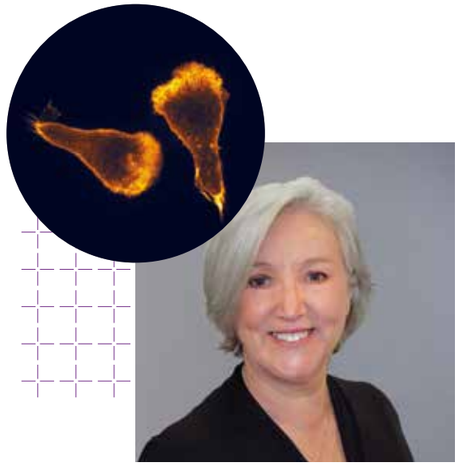
Dr David Gershlick – Characterising the secretory pathway machinery

Membrane Trafficking, Organelle Biology, Rare Genetic Diseases

The seamless operation of cellular functions depends on precise delivery and sorting of proteins and lipids within the cell. These processes are orchestrated by secretory pathways, where the Golgi apparatus plays a pivotal role. We aim to decode the complex mechanisms of protein and lipid trafficking from the Golgi to the plasma membrane. This pathway is essential for cellular homeostasis and secretion of vital molecules such as cytokines, lipoproteins, and antibodies.

Using cutting-edge techniques including super-resolved imaging, CRISPR knockout screens and genetics, and mass spectrometry, we study the molecular machinery that drives these secretory processes. Understanding these pathways allows us to explore new therapeutic avenues for conditions resulting from trafficking defects, ranging from metabolic disorders to immune deficiencies. We aim to bridge fundamental cell biology with clinical applications through a fundamental understanding of the cell.





Professor Gillian Griffiths FMedSci FRS – Control of secretion at the immunological synapse

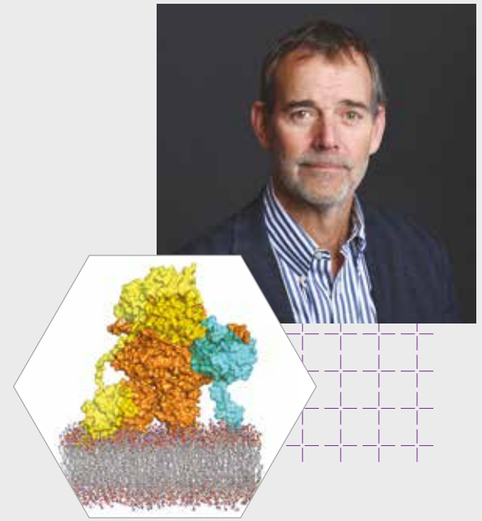
Intracellular Infections, Organelle Biology, Rare Genetic Diseases

Within every teaspoon of our blood are 5 million potential killer cells. These are remarkable little cells that circulate around our bodies recognising and destroying virally infected and cancer cells with extraordinary specificity and precision. We have discovered new genes that suggest that many different components within killer cells play a part in delivering the lethal hit. We wish to work out how each part of the killer cell contributes. We study killer cells in which the new genes are missing to see where things go wrong. We are able to film live killer cells and pinpoint what is different in each case. This is particularly important right now as new cancer therapies in medicine aimed at helping killer cells are proving very effective. By understanding exactly how killer cells work, it will be possible to devise better therapies.

Professor Jim Huntington FMedSci - Basic and translational research into haemostasis and thrombosis

Rare Genetic Diseases, Protein Folding and Quality Control

Blood must be able to flow to deliver nutrients and signals to cells throughout the body. When blood vessels rupture, clots must form quickly to limit bleeding, but overgrowth of clots can cause thrombosis. We study the structure of proteins that regulate blood clotting, and use these insights to devise therapies for disorders including haemophilia, heart attacks, stroke, and deep vein thrombosis.



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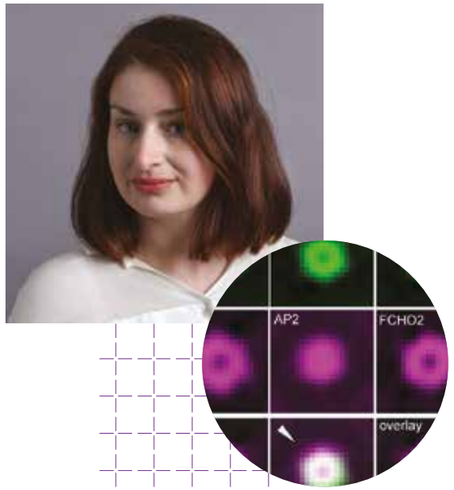


Dr Zuzana Kadlecova - Integration of NAK kinases with membrane trafficking machinery

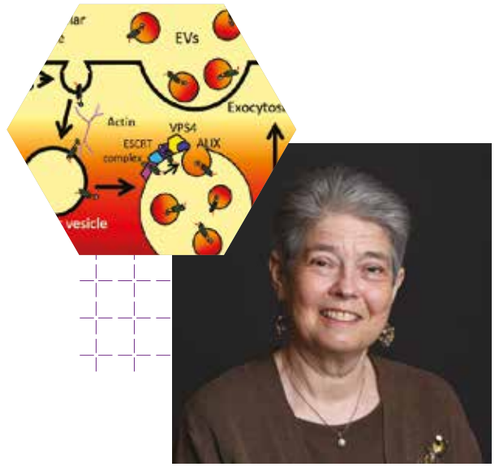
Membrane Trafficking, Neurological Diseases

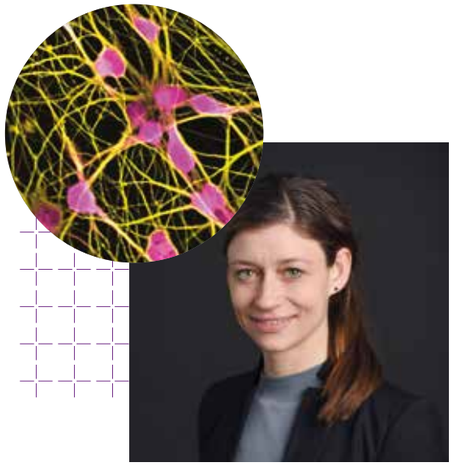
All living cells are surrounded by cell membranes. These are essential to keep the inside of the cell separate from its outside surroundings, but are also very dynamic, controlled structures to make sure that the cell remains healthy and functioning within its environment. Problems with the functioning of cell membranes can result in disease. It is therefore important to understand the complex processes which control cell membrane structure and function, and one of them is a process called endocytosis. Endocytosis is a process in which cells use plasma membrane to package and transport essential materials such as nutrients, from outside to inside. By turning over the cell membrane, endocytosis is also a key mechanism for controlling the protein content of the plasma membrane and its interactions with neighbouring cells. In the lab we are using powerful microscopes and biochemical techniques to study the proteins which control endocytosis, and how the process might go wrong in disease.

Professor Fiona Karet FMedSci - Renal tubular homeostasis in health and disease

Rare Genetic Diseases

Our kidneys are responsible for keeping many substances in the body in balance (such as salt, potassium, calcium and acid) and, when any of these goes wrong, disorders including Gitelman syndrome, hypertension or recurrent kidney stones can result. We have previously characterised the genes that are mutated in these diseases, and looked to understand their underlying function in the kidney. A related aim focuses on small packages termed ‘extracellular vesicles’ that are released by kidney cells into urine, which we have discovered kill bacteria, and may also have potential for diagnosis of kidney malfunction. We also study common inherited kidney disorders such as polycystic kidney disease in the clinic, and in a separate project are developing a handheld kit that will enable anyone, anywhere to measure their blood potassium levels, which is crucial to management of almost all forms of kidney disease as well as cardiac conditions.





Dr Janin Lautenschälger – Protein phase separation at the pre-synapse — Alpha-synuclein in health and disease

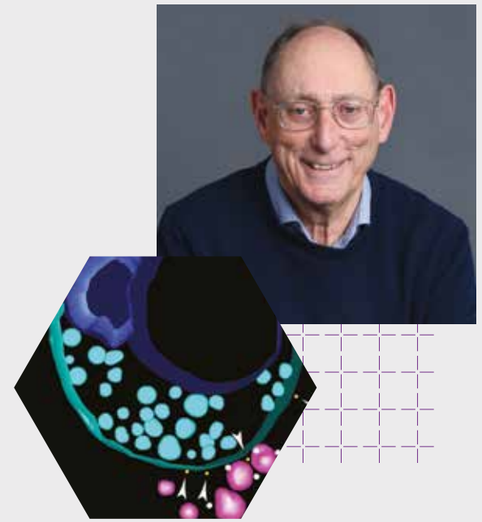
Neurological Diseases, Rare Genetic Diseases, Membrane Trafficking, Protein Folding and Quality Control

Alpha-synuclein is a presynaptic protein which is involved in the formation of protein aggregates. These are known as Lewy bodies and are the pathological hallmark of Parkinson’s disease. Recent research suggests that protein phase separation and the subsequent formation of condensates could play a critical role for the function alpha-synuclein as well as its aggregation. To gain an understanding of this phenomenon, it is essential to understand how alpha-synuclein phase separation is regulated. Combining in-vitro biochemical studies, cellular phase separation assays and super-resolution imaging in the lamprey reticulospinal giant synapse we delve into the principles of synapse compartmentalisation, studying alpha-synuclein function and dysfunction in disease.

Professor Paul Luzio FMedSci – Membrane traffic in the late endocytic pathway

Membrane Trafficking, Organelle Biology

Cells are compartmentalised by specialised organelles (little organs within each cell), and cargo including proteins is moved between these compartments by trafficking of vesicles. We aim to understand how the membrane traffic machinery moves specific proteins around the cell for their normal function and for their degradation, the latter taking place in the lysosome. This organelle is acidic and a current focus is understanding how this acidity is regulated and contributes to lysosome function. We hope our work will contribute to the understanding of many diseases, including diabetes, atherosclerosis and neurodegenerative diseases, where defects in the cell surface and/or in membrane traffic occur; and infectious diseases where microbes subvert the membrane traffic system in order to infect cells. It will also contribute to developing better ways of targeting drugs to particular sites within cells for more specific drug therapies.



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Professor Stefan Marciniak – The role of cellular stress in lung diseases

Protein Folding and Quality Control, Organelle Biology, Rare Genetic Diseases

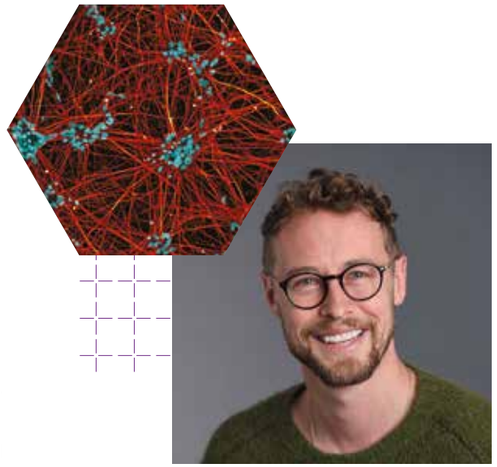
Proteins must be folded properly to function. If this becomes defective, cells experience stress and respond by clearing away these misfolded proteins for destruction. We are investigating how the response to this form of cellular stress is important in lung health and disease. Current projects in our group address a variety of lung diseases including altered endoplasmic reticulum function in alpha1-antitrypsin deficiency; multiomics analysis of new models of mesothelioma; the role of GCN2 signalling in pulmonary hypertension; and altered protein trafficking in pulmonary fibrosis.

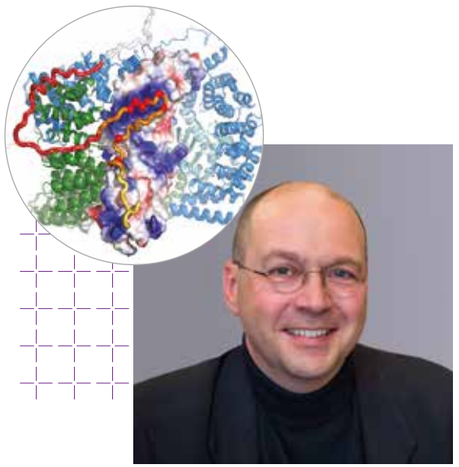
Dr Jonathon Nixon-Abell – Organelle interactions and dynamics in neurons

Organelle Biology, Neurological Diseases, Membrane Trafficking, Rare Genetic Diseases

Understanding how neurons in the brain work together to produce movement, sensation, and cognition is a central challenge in scientific research. While much attention has been focused on how neurons communicate with one another, there is an equally important and lesser understood network of communication that happens within individual neurons. This communication occurs between organelles and plays a crucial role in enabling neurons to function and share information.

We have shown that disruption of these organellar communication pathways can lead to numerous neurological disorders, such as Alzheimer's, Parkinson's and motor neuron disease. We focus on identifying the cellular machinery and mechanisms responsible for orchestrating communication between organelles. Our goal is to unravel how these factors enable neurons to function properly and understand what goes awry during neurodegenerative disease.





Professor David Owen – Structural biology of transport vesicle and organelle biogenesis

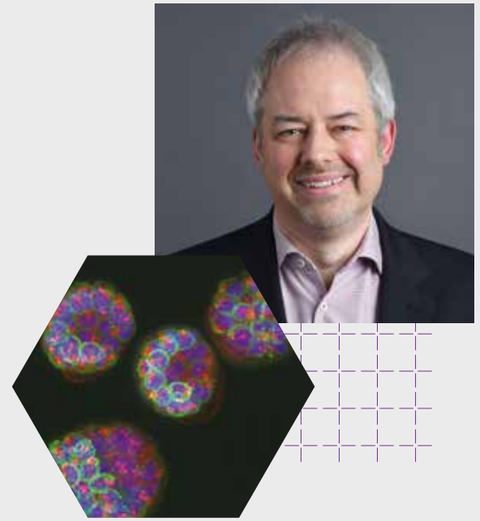
Membrane Trafficking, Organelle Biology

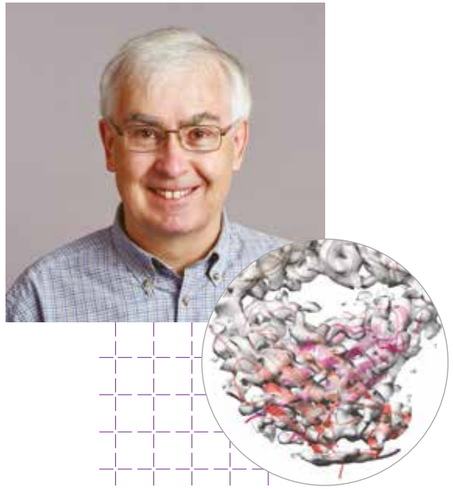
Transmembrane proteins are moved between the membrane-bound organelles of a cell in transport vesicles and tubules. These carriers are formed by complex, carefully orchestrated processes involving many protein components: we investigate how. We determine atomic resolution structures of protein complexes and assemblies, which then guide the generation of mutations for testing *in vitro* and *in cell*. Understanding how and when vesicles/tubules are formed and how this is related to organelle function and identity is key to understanding the cell. These formation processes go awry in many disease states, while pathogens, including bacteria and viruses, subvert them to infect host cells.

Professor Julian Rayner FMedSci – The molecular mechanisms of malaria infection

Organelle Biology, Intracellular Infections

Malaria remains a devastating, global health concern, with more than 200 million cases every year, and nearly half a million deaths, primarily in young children (source: World Health Organisation). Our focus is on understanding the molecular details of the interactions between malaria-causing Plasmodium parasites and the human red blood cells which they multiply inside. We use genetic, biochemical and cell biological tools to identify the proteins used by the parasites to recognise and invade human red blood cells, a process that is essential for parasite survival and also central to the disease complications of malaria. Understanding this rapid and complex process helps us to identify parasite proteins that could be targeted by new vaccines or drugs to prevent or treat infection. We work closely with scientists in countries where malaria is endemic, and are committed to helping support their work.





Professor Randy J Read FRS - Methods for structural biology

Protein Folding and Quality Control

The three-dimensional structure of a protein can be determined primarily using two techniques termed X ray crystallography and cryo-electron microscopy. This information provides vital insights into how a protein functions and how it is controlled by other factors in the cell. Our goal is to develop new improvements to these techniques, including the use of new software and computer modelling approaches, to allow more challenging structures to be elucidated. The techniques we are developing contribute to understanding the structures of proteins that affect disease development.

Professor Evan Reid - Unravelling the molecular pathway of axon death

Rare Genetic Diseases, Neurological Diseases, Membrane Trafficking, Organelle Biology

Hereditary spastic paraplegias (HSPs) are a subtype of motor neuron disease in which affected people develop progressive leg paralysis because some of the longest neuronal connections ('axons') degenerate. HSPs are caused by mutations in specific genes, most commonly in the gene that codes for the spastin protein. Our aim is to understand how spastin and other HSP proteins normally work and how this goes wrong in HSPs. We are currently focusing on a role of HSP proteins in regulating the trafficking and transport systems in human neurons and how this affects functioning of specific subcellular organelles. This detailed understanding should inform rational treatment approaches for hereditary spastic paraplegias and perhaps other similar neurological conditions.

Professor Margaret Robinson FMedSci FRS - Coated vesicle adaptors

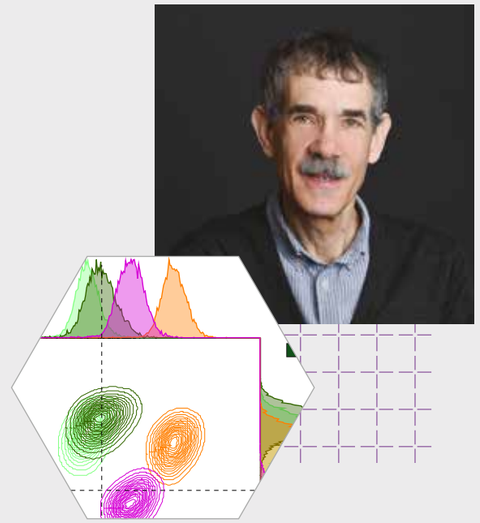
Membrane Trafficking, Rare Genetic Diseases

Cells are divided into special compartments called organelles. Normal cell function requires the constant movement of factors between these compartments, and this is mediated by the cellular transport machinery. Protein and other cargo are packaged into small membrane-bound packages called vesicles for transport, and labelled for delivery to a particular destination. Our research focus is on the role of the 'adaptor' proteins that regulate the formation of specific transport vesicles, determining which proteins get bundled into a particular vesicle and where it is targeted to in the cell. Understanding the function and control of adaptor proteins has broad implications in development and in certain diseases such as the hereditary spastic paraplegias that can be caused by mutations in adaptor proteins.

Professor David Ron MD FMedSci FRS – Protein folding homeostasis in the endoplasmic reticulum

Protein Folding and Quality Control, Organelle Biology

Proteins must fold into their correct three-dimensional structure to function properly and cells are adept at detecting and responding to incorrect protein folding. Secreted proteins and membrane proteins – which are often of medical importance – fold in a particular compartment, the endoplasmic reticulum, where misfolded proteins trigger an 'unfolded protein response' that contributes to their extraction and destruction. Our research focuses on the control of this process and the implications of this for protein folding diseases and ageing. We are also investigating emerging connections between the regulation of protein folding and metabolism in the pancreas, liver and fat. Our hope is that better understanding of protein folding and surveillance might provide opportunities for new therapies.



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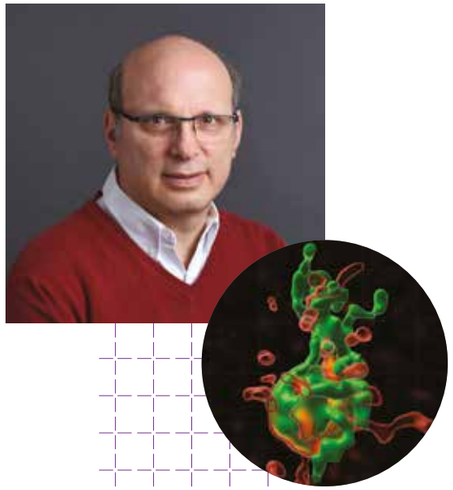


Professor David Rubinsztein FMedSci FRS - Autophagy and neurodegeneration

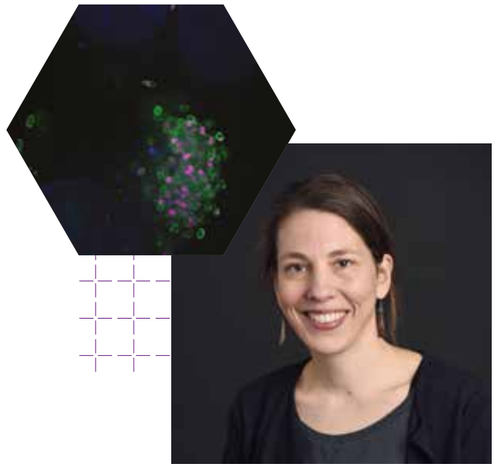
Protein Folding and Quality Control, Membrane Trafficking and Organelle Biology, Neurological Diseases, Rare Genetic Diseases

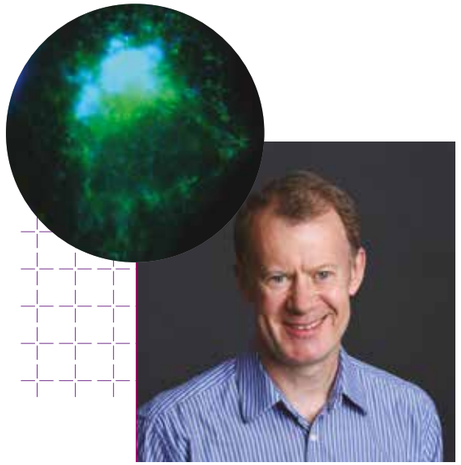
Neurodegenerative diseases, such as Alzheimer's, Parkinson's and Huntington's Disease, are associated with the accumulation of particular proteins that form clumps because they are not folded properly. Our research goal is to understand the links between these diseases and autophagy – the bulk recycling process that degrades proteins and particular parts of the cell. We currently focus on understanding how autophagy is regulated using several cell and animal models; and possible ways to ramp up this process in order to remove toxic proteins and avoid the development of neurodegenerative disease.

Dr Jeanne Salje – The cell biology of obligate intracellular bacteria

Intracellular Infections, Organelle Biology

Obligate intracellular bacteria have evolved to live in intimate proximity with eukaryotic host cells without being destroyed by them. By studying this interface, we can gain fundamental insights into the biology of prokaryotic and eukaryotic cells, and the interactions between them. Obligate intracellular bacteria are also clinically important, causing numerous human and animal diseases. My lab studies their fundamental biology, with a particular focus on *Orientia tsutsugamushi* which causes scrub typhus, a life-threatening human disease that is endemic in many parts of Asia. Our research ranges from genomics and bacterial physiology to the intracellular infection cycle and mechanisms of pathogenesis. Through our long-standing work in Southeast Asia, we aim to apply new scientific insights into *O tsutsugamushi* to the development of improved diagnostics and treatments for scrub typhus.





Professor Matthew Seaman - The molecular mechanisms of endosome-to-Golgi retrieval

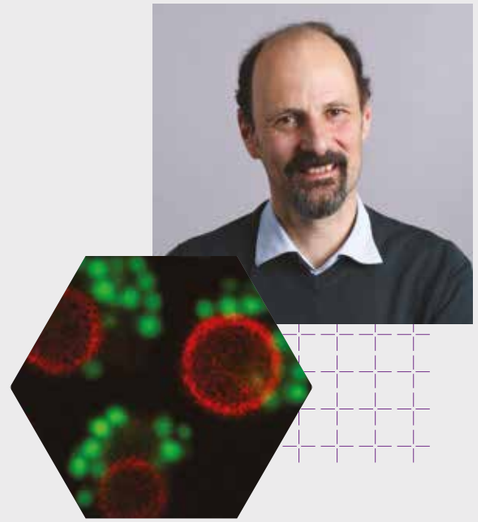
Membrane Trafficking, Organelle Biology

Cells are divided up into specialised compartments called organelles, each surrounded by membrane. This provides control by segregating different biological processes. Communication between these compartments is also a vital part of cell function, and this is achieved by the transport of small parcels of membrane. We focus on understanding a particular transport pathway that occurs between two organelles – endosomes and the Golgi. We have recently identified 90 genes that control this and, by characterising their functions, we hope to provide new insights into this transport pathway. This has broad implications, as this pathway has been linked both to neurodegenerative diseases including Alzheimer's, and to bacterial and viral infections.

Dr Symeon Siniossoglou - Linking phospholipid metabolism to membrane and organelle function

Organelle Biology

Cells use lipids as building blocks to form their membranes and as storage molecules to preserve energy for later use. Membranes separate cells from the environment, and continuous membrane synthesis is required for cell growth and proliferation, while the ability to store energy in the form of triacylglycerol (or fat) in lipid droplets is essential for survival during nutritional or environmental stress. Our aim is to understand how different lipids are made, and the mechanisms by which cells partition them between membranes for growth or lipid droplets for energy storage. This understanding is vital as disruption of the balanced use and processing of lipids in cells can result in several pathologies and is at the heart of the current obesity epidemic.



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Professor Alan J Warren FMedSci – Mechanisms of ribosome assembly

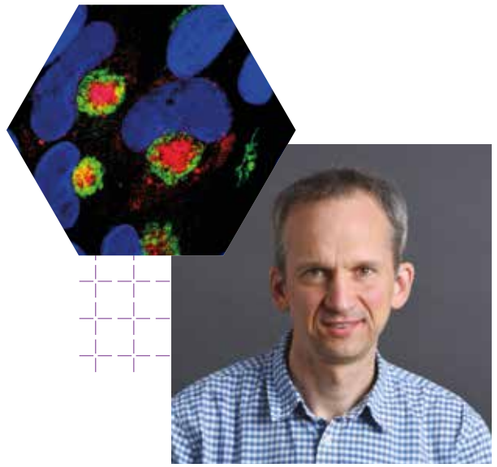
Organelle Biology, Rare Genetic Diseases

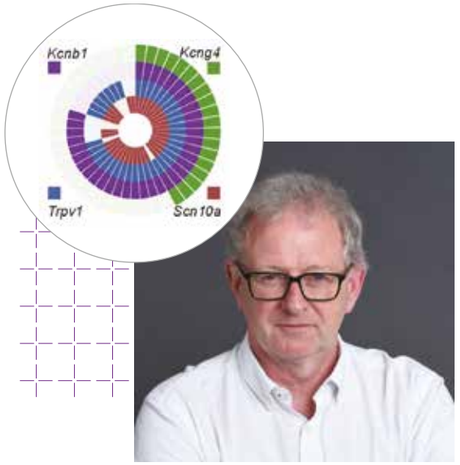
The origins of inherited and acquired forms of blood cancer have recently been linked to defects in so-called 'housekeeping' processes in our cells, specifically in the assembly of the machines (called ribosomes) that make proteins. A major focus of our work is to understand in detail how ribosomes are put together from their component parts. To do this, we are learning about the three-dimensional shape of some of the key proteins involved and how these proteins work together in large complexes. As well as experiments in the test tube, we also use a range of cellular and animal models to test the effects of manipulating ribosome assembly in living organisms. The fundamental insights that we hope to obtain will potentially provide a deeper understanding of disease mechanisms and inform new approaches to the treatment of blood cancer.

Professor Michael Weekes - Innate immune evasion by intracellular pathogens

Intracellular Infections

Human cytomegalovirus (HCMV) affects ~1/100 pregnancies and is the leading infectious cause of deafness and intellectual disability in children, and the most significant infectious cause of birth defects in the global North. There are only three anti-HCMV drugs; two of them have treatment-limiting side effects and all exhibit problematic drug resistance. To be able to persist in an infected individual lifelong, HCMV has evolved multiple 'evasins' – proteins that subvert different parts of our immune system. We hope to discover how each 'evasin' works, and which are the most important. We use a technique called proteomics, which allows precise measurement of changes in thousands of viral and cellular proteins during infection. By understanding how HCMV subverts immunity, we may be able to inhibit the most important evasins, providing new treatments for viral infection.

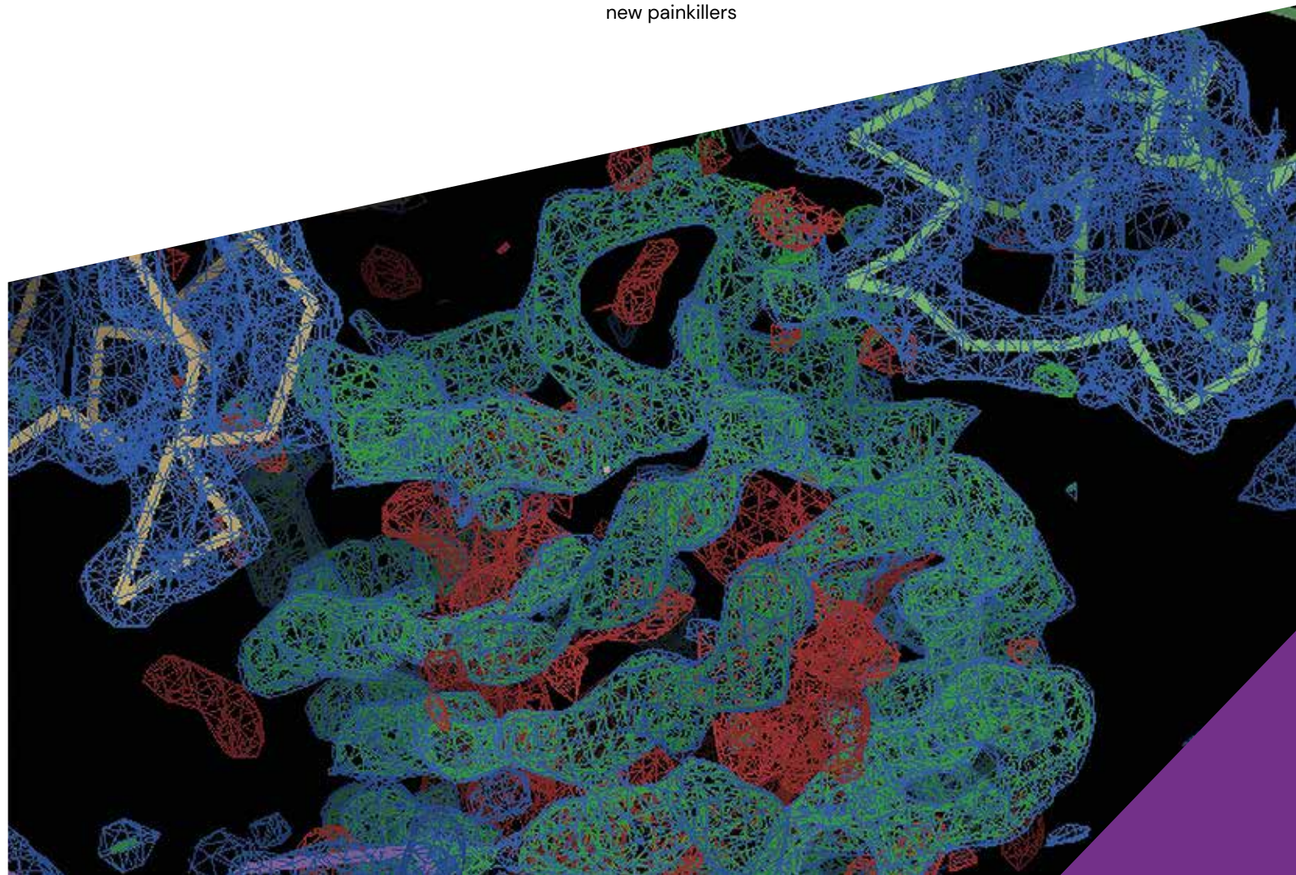




Professor Geoff Woods - Understanding Mendelian disorders of neurodevelopment

Rare Genetic Diseases, Neurological Diseases

Mendelian disorders are inherited in families in a particular pattern that reflects the inheritance of a single mutated gene on one or both copies of the chromosome. There are more than 5000 such disorders in humans, and detailed understanding of the underlying gene changes is needed. By determining the DNA codes of family groups with new disorders, it can be possible to find the gene mutation that is responsible for that disease. We are currently focusing on the inherited disorders that result in the inability to feel pain or conversely excess pain. Our work has found the genes that are responsible for some of these disorders, and our hope is that these findings may contribute to the development of new painkillers

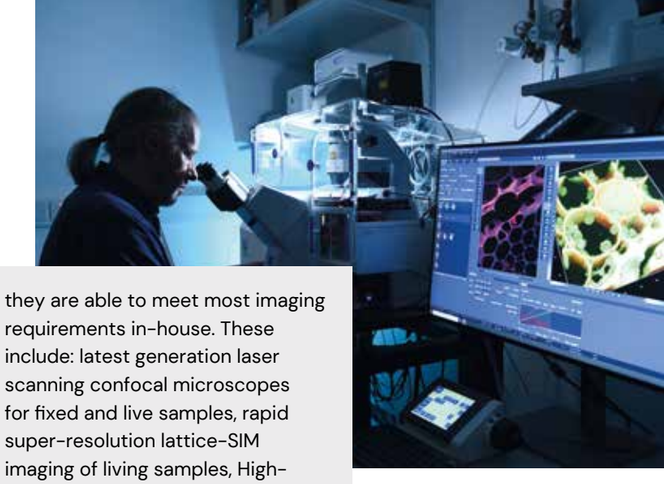


Core facilities

The provision of world-class research facilities has always been a top priority at CIMR, providing our researchers access to state-of-the-art methods. We currently have four facilities: proteomics, microscopy, flow cytometry and structural biology. Each of these is managed by in-house experts in these technologies, who provide training and technical support for our researchers.

Flow Cytometry

The Flow Cytometry Core Facility is headed by Dr Reiner Schulte and provides state-of-the-art flow cytometry services, consisting of expert advice for experimental design, individual instrument training, and data analysis. The facility is capable of performing cell sorting for researchers to isolate cell populations for further phenotyping, including single cell RNA sequencing. This year the purchase of a Big Foot spectral cell sorter has increased capacity and allowed for the sorting of clinical samples.



Microscopy

The Microscopy Facility is managed by two experienced microscopists, Matthew Gratian and Mark Bowen, who provide all training and support on the instruments. The primary aim of the facility is to enable high-quality research by providing the very latest and best instrumentation and imaging software to researchers at the Institute. The variety of instruments and image analysis options in the facility ensure that they are able to meet most imaging requirements in-house. These include: latest generation laser scanning confocal microscopes for fixed and live samples, rapid super-resolution lattice-SIM imaging of living samples, High-Content Screening and Analysis, histology (with processing, cutting and staining equipment). There is also an EM Facility with two Electron Microscopes and sample preparation equipment which is managed by Dr Nick Bright.

Structural and Computational Biology

Our facility supports a range of structural and computational research laboratories using X-ray crystallography, cryo-electron microscopy, molecular modelling and new methods development. Our structural biology research is providing new insights into the molecular mechanisms underlying a range of human diseases. Our users combine structural work with complementary methods in cell biology, biochemistry and biophysics to develop a comprehensive understanding of fundamental biological processes.

Proteomics

Led by Dr Robin Antrobus, the Facility allows researchers access to cutting-edge proteomics technologies. With users from CIMR and beyond Cambridge, the Facility focuses on peptide analysis by liquid chromatography with tandem mass spectrometry (LC-MS-MS) and has a number of instruments capable of supporting a variety of different experiments, including quantitative surface proteomics, organellar mapping and post-translational modifications of proteins.

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Deputy Director: David Rubinsztein

Business & Operations Manager: Sarah Smith

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Mark Wills	Acting Head Dept Medicine
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Building Services Apprentice: Lawrence Fitch

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Laboratory Coordinator: Daniel Morrison
Assistant Laboratory Coordinator: Kevin Bussey
Research Laboratory Technician: Ewelina Bolton
Media Technician & Assistant to Analytical Facilities: Claire Carter
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Goods-in Clerk: Andrew MacIntosh
Custodian: Joe Poeira
Custodian: Neil Taylor

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PA to the Director: Sara Asbury

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RESEARCH IMAGES:
Front cover: Primary neurons expressing a marker of the Golgi apparatus (Green) with Amyloid Precursor Protein in a kinetic trafficking system (Magenta). Image taken by Dr Jessica Eden, Gershlick Lab.

Inside front cover:
Top left: HeLa cells co-expressing AP-1 (red), LAMP1 (green), and gadkin (blue). Robinson lab.

Top right: Three-dimensional rendering of Z-stacked confocal images of CHO-K1 cells following a hypotonic shock demonstrate solidified Z-α1-antitrypsin (tagged with mEmerald, green) within distended cisternae of endoplasmic reticulum containing the soluble marker HaloTag-KDEL (labelled with TMR HaloTag, magenta). Marciniak lab.

Bottom left: Phase separated droplets of alpha-synuclein. Lautenschläger lab.

Bottom right: A fibroblast cell (COS-7) expressing a fluorescent endoplasmic reticulum marker (mEm-Sec61b) imaged with superresolution Structured Illumination Microscopy (SIM). Nixon-Abell lab.

P14/15: Visual abstract from Üstok FI, Huntington JA. Mapping the prothrombin-binding site of pseutarin C by site-directed PEGylation. Blood. 2022 May 12;139(19):2972-2982, showing prothrombinase bound to prothrombin on a phospholipid membrane surface. Huntington lab.

P16: iPSC-derived glutamatergic neurons with labelled axons (Orange; TUJ1) and somatodendritic compartments (Blue; MAP2). Nixon-Abell lab.

P17: Ultrastructure expansion microscopy of *Plasmodium falciparum* parasites within a human erythrocyte. Parasite nuclei are stained blue, rhoptries in red and the parasitophorous vacuolar membrane in green. Rayner lab.

P21: Human cortical neurons labelled to show mitochondria (green), acetylated tubulin (magenta), and the nucleus (blue). Image by Isabelle Hall, Reid Lab.

P37: Electron density maps, calculated from X-ray diffraction data by Holly Monkhouse, showing how the lipid-binding protein GM2ap (green) interacts with the lipid-processing enzyme HEXA (blue). Deane lab.

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