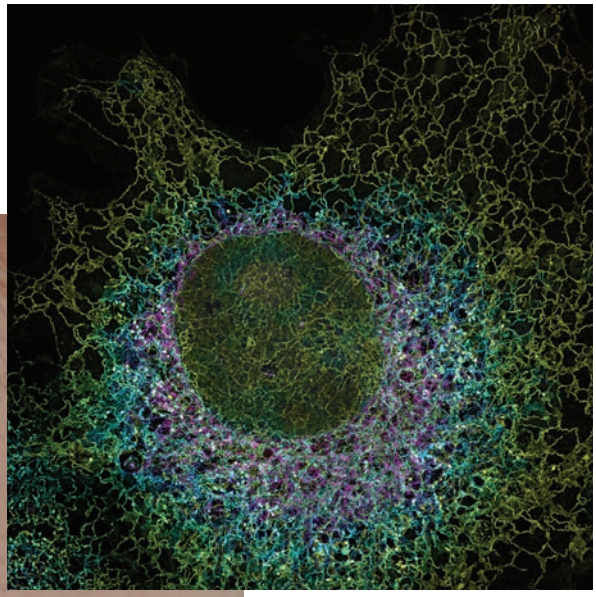
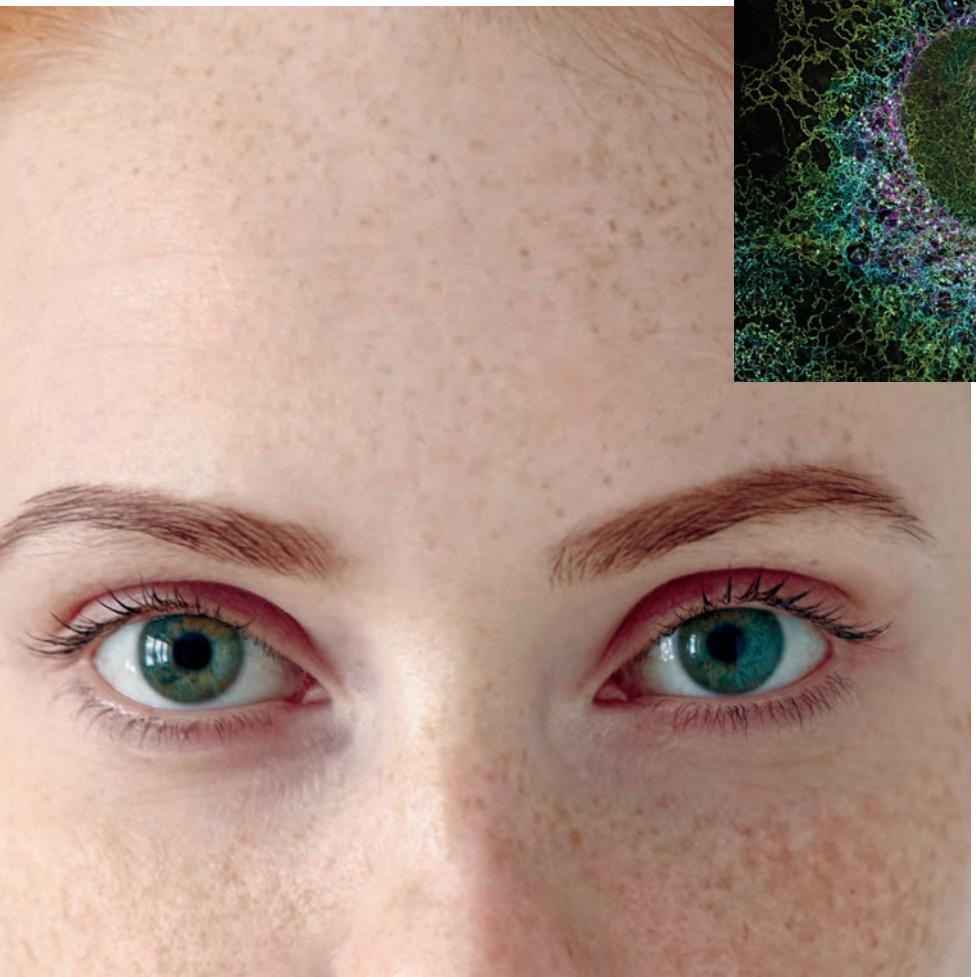
CIMR
Cambridge Institute for Medical Research

UNIVERSITY OF CAMBRIDGE
School of Clinical Medicine

CIMR Report 2022

Transforming our understanding of human disease





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THE KEITH PETERS BUILDING

CIMR Report 2022

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

Contents

"It is a huge honour and privilege to be Director of the Cambridge Institute for Medical Research. CIMR is an extraordinary place – not just because of its storied track record of scientific excellence and innovation, but also because of its engaged, interdisciplinary and collaborative environment."

Introduction

from Professor Julian Rayner, the Director of CIMR

The past three years since my appointment in mid 2019 have of course been dominated by the COVID19 pandemic. While this has been a time of enormous personal and professional challenge for us all, it has also been extraordinary proof of the value of biomedical research in tackling major, complex problems facing humanity. The rate of progress in battling SARS-CoV2 has been astounding – from the identification of a novel respiratory pathogen in late 2019 to the delivery of multiple licensed and effective diagnostics, drugs and vaccines in less than two years.

That progress has of course been completely dependent on decades of previous work understanding the biology of how viruses and host cells interact, and developing the vaccine and diagnostic technologies so that they were available to apply to SARS-CoV2 as soon as it was identified. It has also emphasised how knowledge of fundamental biological processes is essential to understand disease, and how different, complementary types of scientific approach and expertise are required to work together to produce new interventions. This is CIMR in a nutshell – at the interface between biology and patients, with the mission to determine the molecular mechanisms of disease to improve human health.

I am proud of the way that my colleagues at CIMR have persevered to keep delivering outstanding research over the past three years, in some cases while also on the clinical frontline or volunteering in testing laboratories. These uncertain times have also demonstrated just how important the communication of science is, and the value of open, two-way engagement between researchers and public audiences. This is a particular passion of mine, and an area in which CIMR will continue to innovate.

The story of the COVID19 pandemic has been both tragedy and triumph, and gives us all renewed impetus for our work on other devastating diseases. We still face many other significant health challenges, from malaria to rare paediatric genetic disease to dementia, which of course haven't gone away – and for which research remains the best hope. In 2021 we revised our research strategy in order to articulate more clearly than ever our focus on fundamental processes of cellular homeostasis and how they are disrupted in genetic and infectious diseases. We are actively recruiting new research groups within these themes, who will continue the track-record of innovation and discovery at CIMR. It is an extraordinarily exciting time to work in medical research, and a joy to work alongside my outstanding colleagues. Thank you all for your support and encouragement.

News highlights

CIMR INVOLVEMENT IN A NEW WIDENING PARTICIPATION INITIATIVE FOR UNDERGRADUATE STUDENTS

Experience Postgrad Life Sciences is a residential summer internship programme at Cambridge for undergraduate students of biological / biomedical science subjects who may not otherwise be able to gain experience of postgraduate research. This is part of a wider move at the University encourage more students from underrepresented backgrounds to apply for postgraduate study and increase diversity.

CIMR's Dr Janet Deane is a co-lead for this programme, and the Institute is very pleased to host students as part of it.

NEW TREATMENTS FOR RARE DISEASES DEVELOPED FROM RESEARCH IN THE CIMR

Breakthroughs in the lab of Prof. Jim Huntington have lead to two drugs currently in clinical development for haemophilia and alpha-1-antitrypsin deficiency (AATD). SerpinPC is a new modality in the prevention of bleeding caused by haemophilia, developed by the spin-out company ApcinteX Ltd through to clinical proof of concept. Prof. Huntington served as the company's CEO. Insights into the folding defect behind the disorder AATD led to the formation of the spin-out Z Factor, for which Prof. Huntington also served as CEO, taking the development candidate ZF874 to a proof-of-concept phase 1 clinical trial. Both companies have been acquired by Centessa Pharmaceuticals for continued clinical development.

INSPIRING SCIENTISTS AT THE CAMBRIDGE INSTITUTE FOR MEDICAL RESEARCH (ISAC)

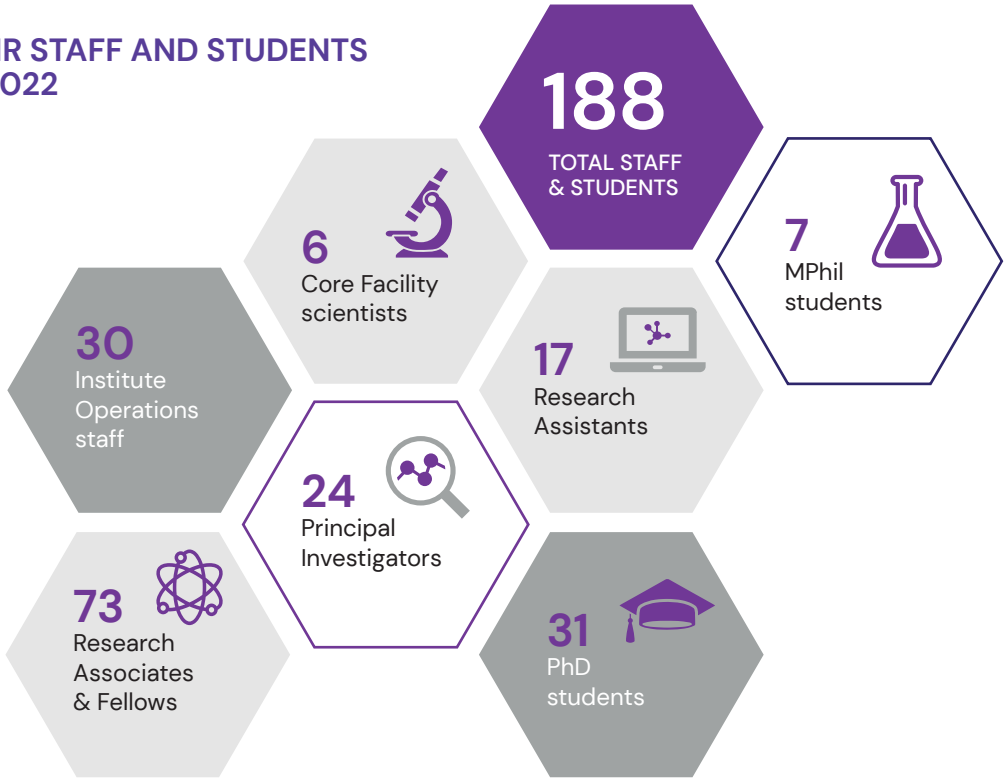
In February 2022 we were pleased to host our first ever ISAC programme in partnership with St Catharine's College. Twelve students from Cambridgeshire 6th Form state schools took part in interactive seminars and research projects over three days at CIMR. The final day was spent at St Catharine's College, where the ISAC students presented findings from their lab projects, found out more about student life at Cambridge and how to apply. The programme was supported by a grant from the University of Cambridge Widening Participation Project Fund.

CIMR RESEARCHER RECOGNISED IN 2021 NEW YEAR HONOURS

Professor Mike Weekes was awarded a British Empire Medal for services to the NHS during the COVID-19 pandemic. Prof. Weekes developed a comprehensive COVID-19 screening programme for all Cambridge University Hospitals healthcare workers, and Cambridge University staff and students with symptoms of COVID-19. He simultaneously continued to lead his laboratory research at CIMR on how viruses evade intracellular defences.

CIMR in summary

CIMR STAFF AND STUDENTS IN 2022



46%

of CIMR people from outside the UK

34 Nationalities

6 Continents

CIMR Principal Investigators

33%	Female
42%	Clinically trained
7%	Fellows of the Royal Society
11%	Fellowship of the Academy of Medical Sciences
5%	Members of European Molecular Biology Organisation

THE LAST 5 YEARS OF CIMR RESEARCH OUTPUTS AND IMPACT

466
RESEARCH
articles published and cited 13,492 times by subsequent research papers

OVER 20
collaborations with industry

1 NEW
CIMR spin out company:

Kalium Health™

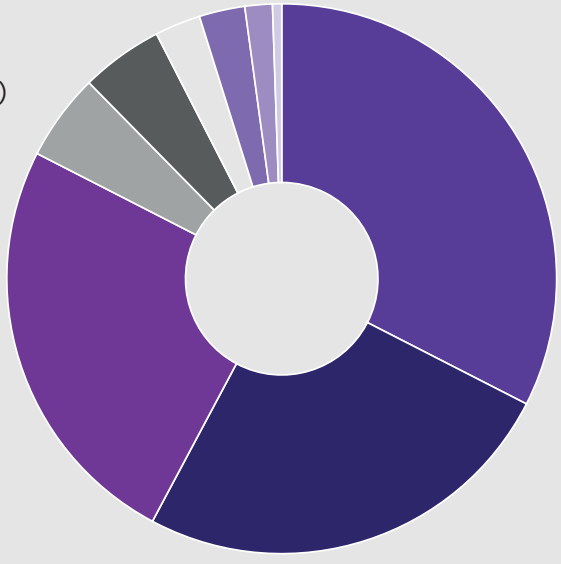
2 EXPERIMENTAL
medicines which originated from CIMR research in clinical development

THE LAST FIVE YEARS OF FUNDED RESEARCH AT CIMR

373 active grants worth a total of around £160 million from 68 funding sources

5 years of CIMR Grant Funding

- Wellcome
- UK Government Funders (incl. MRC, NIHR, BBSRC)
- UK Charities (excluding Wellcome)
- Industry
- Non-UK Charities
- EU
- Non-UK Government Funders
- UK Professional Bodies
- Individual philanthropy



(Numbers of active grants from April 2017 – March 2022 and categories of funding sources shown)

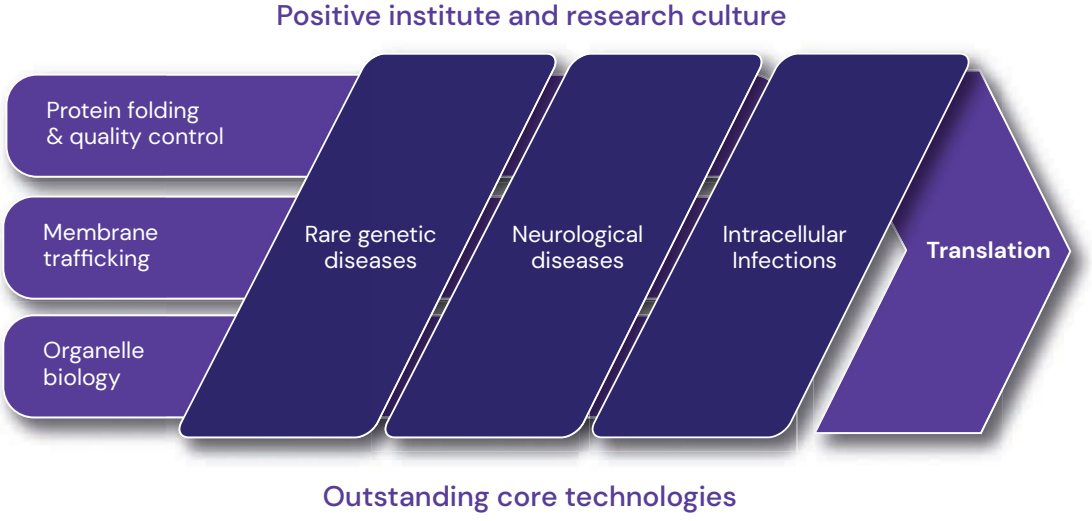
CIMR's strategy and approach

We believe that connecting the fine 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** by using insights from fundamental biology to inform understanding of human disease and vice versa.

Our strategy is to:

- Encourage extensive collaboration between expert research scientists (leaders in fundamental molecular discovery) and experienced clinicians (with real-life expertise and understanding of disease) on areas of shared interest.
- Invest in and deploy a range of outstanding, high-quality platforms and technologies that allow us to understand mechanism at molecular resolution.
- Focus on specific areas of disease and biology in order to maximise connections and synergy

CIMR research is centred on fundamental mechanisms of cellular homeostasis and the diseases that occur when they 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**. These pathways are fundamental to normal cellular function, and when impeded lead to diseases that are 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 are united by the fact that they are caused by disruptions of cellular homeostasis and are frequently neglected and overlooked, meaning there is significant unmet patient need.

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

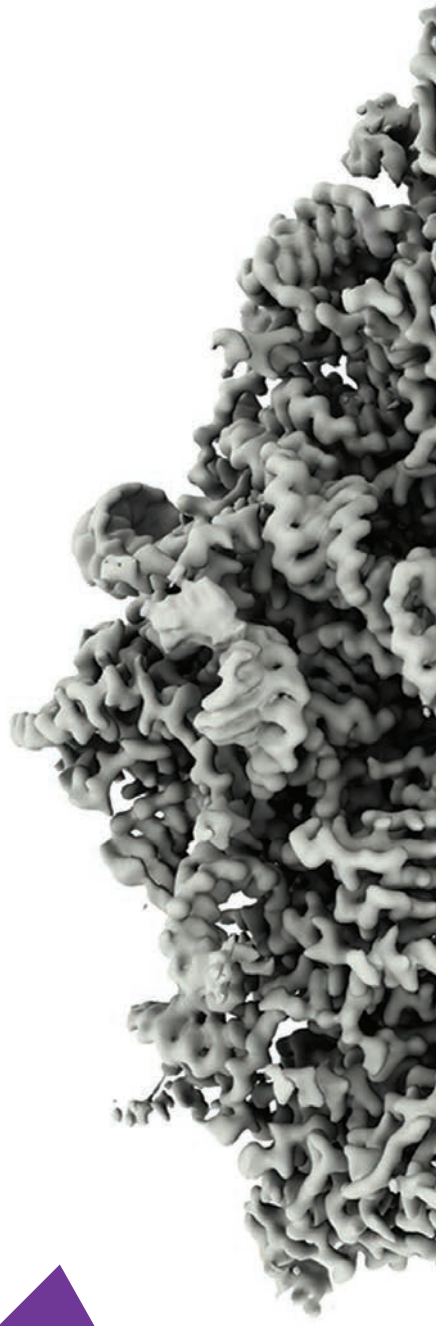
We actively encourage the **translation** of fundamental discovery into new treatments and diagnostics by leveraging the outstanding clinical and commercial environments of the Cambridge Biomedical Campus and University of Cambridge. We also believe that for science and research to have the greatest 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.

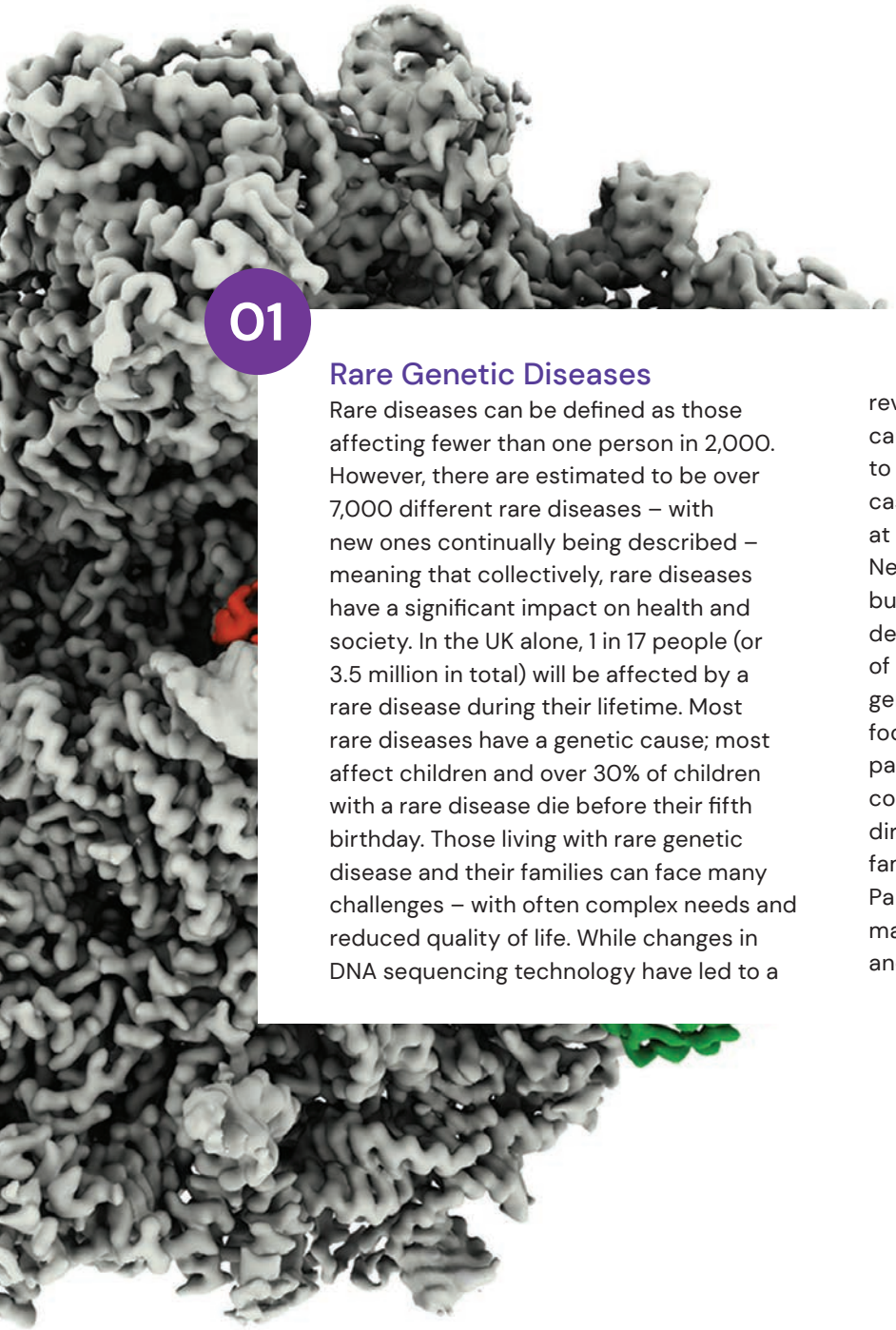
Research themes

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 whether they are single-celled organisms such as bacteria and parasites that infect us.

Maintaining cellular function, known as homeostasis, depends on many thousands of different proteins, all of which much be produced, folded into three-dimensional structures, and transported to the location, or organelle, within the cell where they function. At CIMR, many researchers are world-leaders in these fundamental processes - how protein structure is created through correct folding, how and when proteins interact with each other and with other molecules to form and regulate cellular organelles, how they are transported to their correct destination within the cell, and how they are destroyed when their function is no longer required.

Understanding such fundamental but highly complex biological processes in turns helps us understand how they can be altered by genetic changes, or subverted by infectious pathogens, leading to disease. Conversely, understanding disease frequently adds to our fundamental understanding of biological processes. CIMR's strength is its ability to combine both disciplines synergistically and so it can translate towards patient benefit, with a 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 collectively, rare diseases have a significant impact on health and society. 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; most affect children and over 30% of children with a rare disease die before their fifth birthday. Those living with rare genetic disease and their families can face many challenges – with often complex needs and reduced quality of life. While changes in DNA sequencing technology have led to a revolution in the diagnosis of the genetic causes of rare disease, this has not yet led to revolution in treatment, which in most cases remains limited and primarily aimed at alleviating or managing symptoms. New therapeutic approaches are needed, but developing these approaches often depends on understanding the mechanism of the disease, rather than simply its genetic cause – it is this area that CIMR focuses on. CIMR expertise in fundamental pathways of cellular homeostasis combined with clinical knowledge and direct interaction with patients and families at Addenbrooke's and Royal Papworth hospitals means that we can make real progress towards understanding, and ultimately treating these conditions.

02

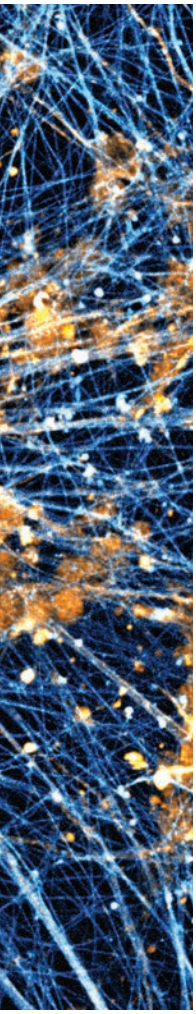
Neurological Diseases

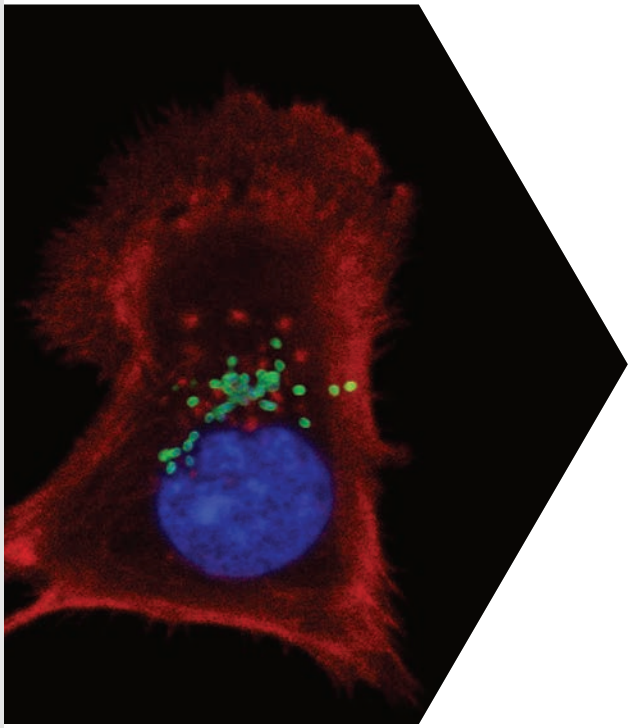
The human brain has been described as the most complex object in the known universe. Its vast and intricate complexity gives us our personalities, our memories and our creativity – but can also leave us vulnerable to the many types of neurological disease. Some of these conditions are very rare, while others such as Alzheimer's and Parkinson's diseases affect hundreds of thousands of people in the UK alone. Because of their association with older age, the prevalence of both these neurodegenerative diseases is set to increase as populations age. The current lack of transformative treatments for such conditions is largely a product of our incomplete understanding of their disease-causing mechanisms. Some of these mechanisms will be unique to specific neurodegenerative diseases, while there may also be some mechanisms in common. CIMR research covers both approaches, and from which new therapeutic angles could be developed.

03

Intracellular Infections

The COVID19 pandemic has brought into sharp focus the impact of intracellular infections on human health, whether caused by viruses such as SARS-CoV2, bacteria such as those that cause tuberculosis, or parasites such as those that cause malaria. In low and middle income countries, infectious diseases continue to be the major cause of childhood mortality, with malaria alone killing nearly half a million children under the age of five every year. Intracellular pathogens have evolved to target and hijack particular cellular processes of their hosts in order to replicate, whilst avoiding host intracellular defences. Understanding how these pathogens subvert host cells therefore often requires understanding biological pathways of particular focus at CIMR such as membrane trafficking. A greater understanding the different components of the pathogen-host interface can lead to new strategies for anti-infective therapies, or preventions such as vaccines. CIMR is expanding its work on intracellular infections, and in the last two years has established a large and active CL3* laboratory where human malaria parasites are routinely cultured.





Institute culture

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

We believe that diversity is at the heart of science – the best science and research take place when great ideas can be heard, and the brightest and best work together in a positive and vibrant research environment. Therefore, we are committed to recruiting people from diverse backgrounds, with varied experiences and perspectives and champion an inclusive and positive culture, in which different ideas and opinions are actively welcomed and everyone is valued and respected. There is an active Equality, Diversity and Inclusion Champions Group at CIMR.

As part of the University of Cambridge we aim to support our people and their careers through excellent mentoring, a wide range of training opportunities and clear career pathways to enable all to thrive. We have a vibrant and active postdoctoral researcher community, which plays a leading role in many of the discoveries that our PI teams deliver.

"We all work better when we feel valued, encouraged and supported. At CIMR we put that culture at the heart of what we do."

Training

Scientific progress fundamentally depends upon ideas, and ideas come from people.

Training future generations of researchers is therefore a particular focus at CIMR. In the last five years over forty PhD students and eighteen MPhil students have had world-class research training at CIMR in our friendly and supportive environment, with the added benefits and opportunities offered by our position as part of the University of Cambridge School of Clinical Medicine. CIMR students have gone on to use their CIMR research training across a range of careers including medicine, biotech / pharma, education, policy, academic research, and some also lead their own research programmes. Some recent examples are shown below:

Dr Iain Hay
(former PhD student in the Deane lab), now a postdoctoral researcher at the MRC Laboratory of Molecular Biology

Dr Alice Fletcher Etherington
(former PhD student in the Weekes lab), working in health policy

Dr Nivedita Sarveswaran
(former PhD student in the Woods lab), now a postdoctoral researcher at Yale University

Public engagement

We believe for science and research to have the greatest benefit and impact it must be integrated with, and informed by society.

Therefore, across the Institute we continually champion and seek out new and innovative ways to engage the public and patients in and with our research, so both are positively impacted and to connect our science with wider society. We are particularly interested in connecting with new and underrepresented audiences, where there may be greatest impact. For example, in 2022 we ran the first 'Inspiring Scientists at CIMR' programme. With funding from the University's Widening Participation Project Fund, and in partnership with St Catharine's College we hosted 12 students from Cambridgeshire 6th Form Schools to experience biomedical research and learn more about studying at the University - all with the aim of inspiring students and breaking down barriers.

Principal investigators

Professor Folma Buss - Myosin motor proteins in health and disease

Membrane trafficking, Organelle Biology, Intracellular Infections

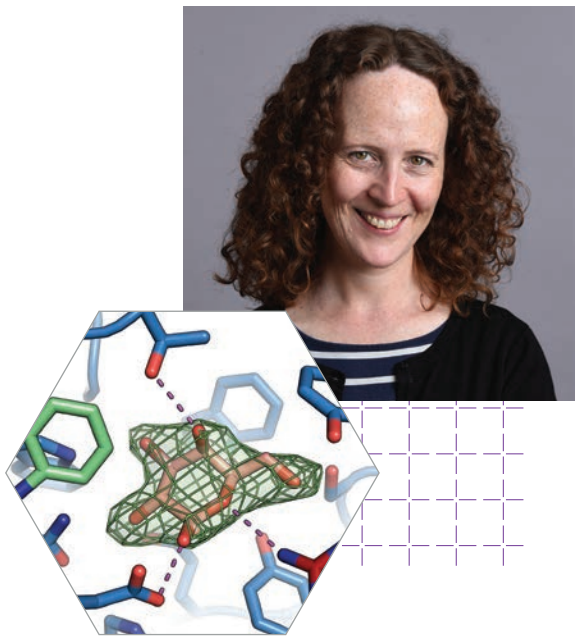
In living cells dynamic processes such as muscle contraction and intracellular transport are powered by myosin motor proteins, which are nanomolecular machines that move cargo along actin tracks rather like a train running along a railway network to specific destinations. In our lab we follow the activity 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.

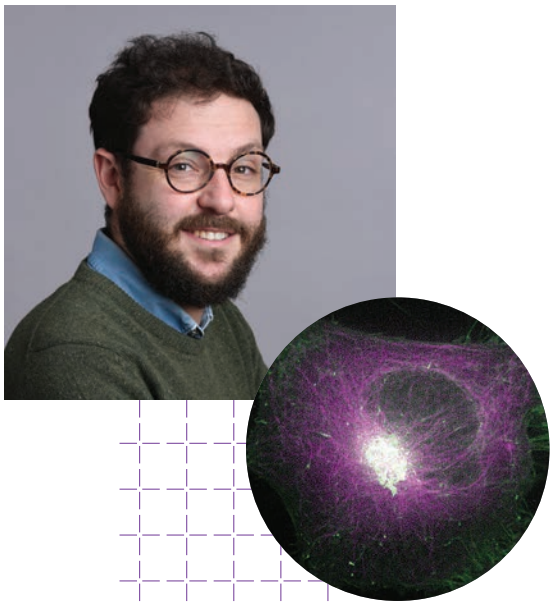
Dysfunction of motor activity is linked to many human diseases including deafness, cancer and neurodegeneration. Therefore, a deeper understanding how motors are switched on/off, fine-tuned and which cargo is transported, will guide our efforts to modulate myosin activity as a therapeutic strategy.

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

Membrane Trafficking, Rare Genetic Disease, Neurological Disease

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.





Dr David Gershlick – Characterising the secretory pathway machinery

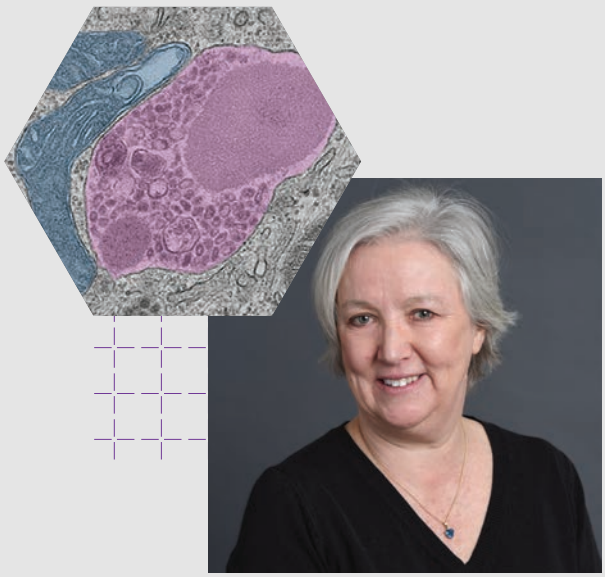
Membrane Trafficking, Organelle Biology, Rare Genetic Diseases

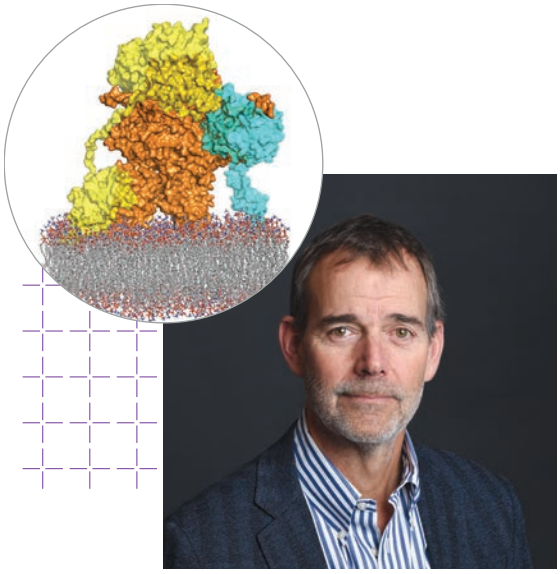
Cells are internally compartmentalised. This allow proteins and lipids that participate in the same biochemical pathways to have higher local concentrations, and proteins that could potentially damage other cellular components (e.g. protein degrading enzymes called proteases) to be segregated from other cellular components. Establishing and maintaining this sub-cellular organisation is a complex task that requires sophisticated machinery to allow proteins to be delivered to the correct place in the cell, without mis-delivering other proteins. Defects in these sorting pathways result in protein accumulation or mislocalisation, and is one of the major causal factors for neurodegenerative disorders such as Parkinson's or Alzheimer's diseases. Our group is focussed on trying to understand the fundamental cell biology that allows the cell to sort proteins to the correct subcellular compartments.

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 recognizing 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 pin-point 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.





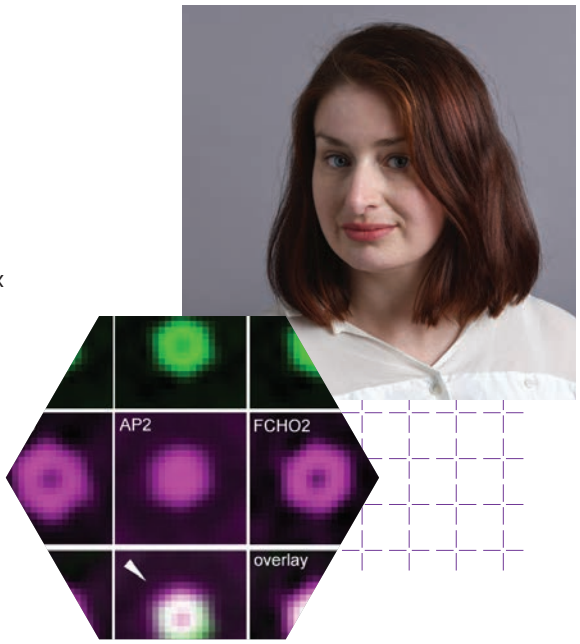
Professor Jim Huntington, FMedSci - Basic and translational research into thrombosis, haemophilia and antitrypsin deficiency

Rare Genetic Diseases, Protein Folding and Quality Control

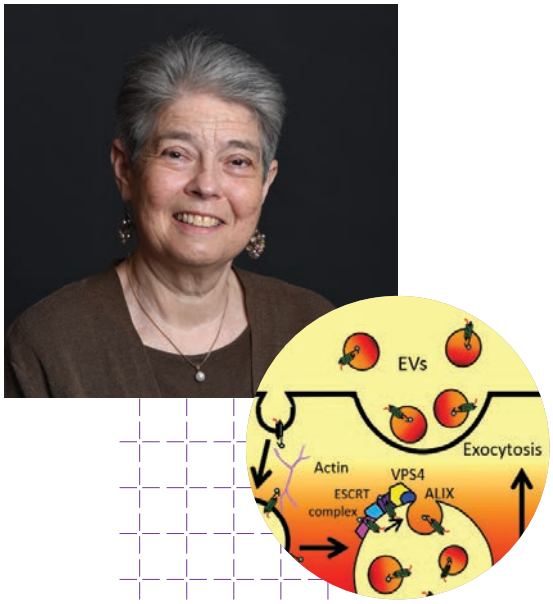
Blood must be able to flow to deliver nutrients and signals to cells throughout the body. When blood vessels rupture, clots must form quickly to limit bleeding, but overgrowth of clots can cause thrombosis. We study the structure of proteins that regulate blood clotting, and use these insights to devise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

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 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

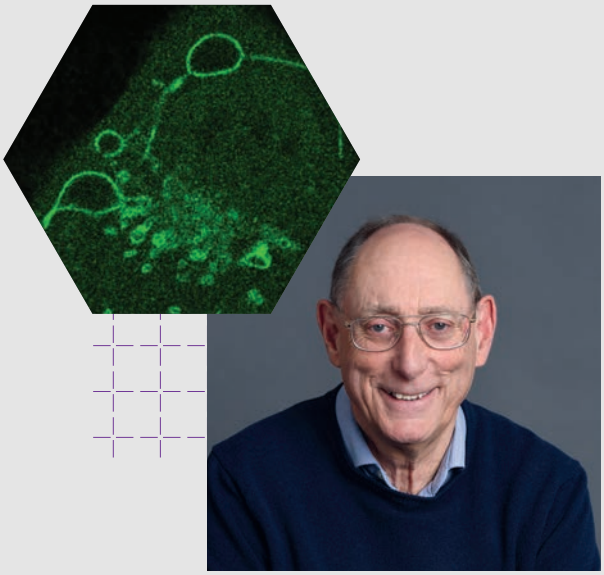
Rare Genetic Diseases

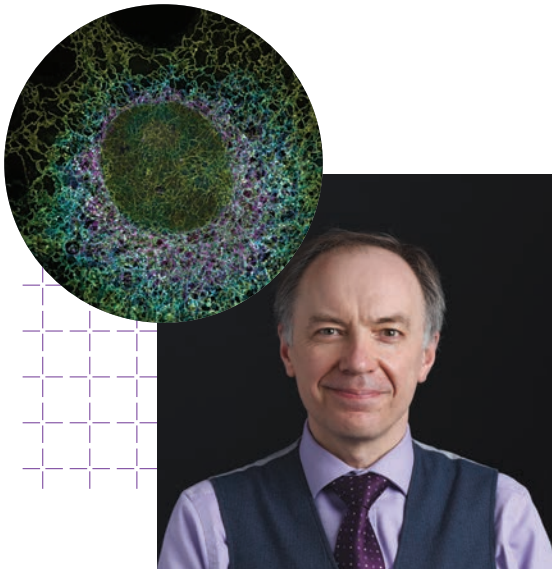
Our kidneys are responsible for keeping many substances in the body in balance (such as salt, potassium, calcium and acid) and, when any of these goes wrong, disorders including Gitelman syndrome, hypertension or recurrent kidney stones can result. We have previously characterized the genes that are 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.

Professor Paul Luzio - Membrane traffic in the late endocytic pathway

Membrane Trafficking, Organelle Biology

Cells are compartmentalized by specialized 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 organelle. 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.





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

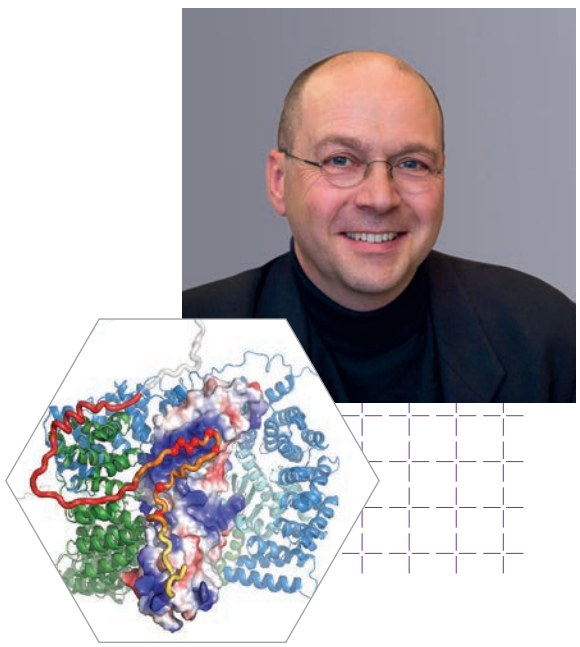
Protein Folding and Quality Control, Organelle Biology, Rare Genetic Diseases

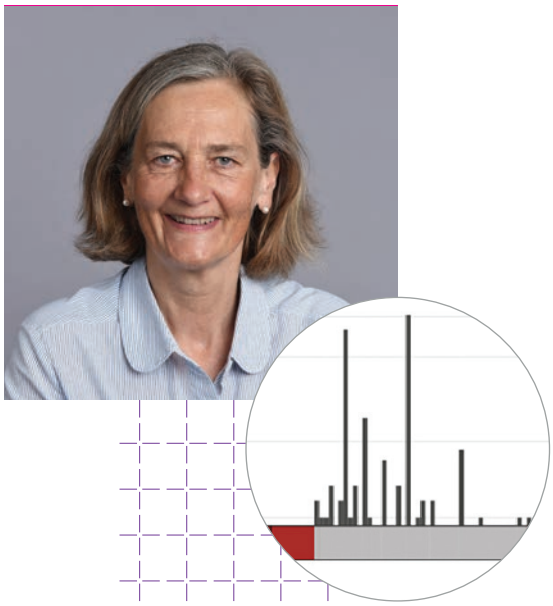
Proteins must be folded properly to function. If this becomes defective, cells experience stress and respond by clearing away these misfolded proteins for destruction. We are investigating how the response to this form a cellular stress is important in lung health and disease. Current projects in our 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.

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

Membrane Trafficking, Organelle Biology

Many proteins move within cells using carefully-orchestrated transport vesicles and tubules, and we research how different transmembrane protein cargoes are transported. We determine atomic resolution structures of protein complexes by X-ray crystallography and EM, which then guide the generation and functional testing of mutant proteins in cellular and in vitro models. Around one third of human genes encode either transmembrane protein cargo or the machinery that controls their intracellular transport; hence understanding their mechanisms is key to understanding cell function – and with important, wider implications. These processes goes awry in many disease states, while pathogens, including viruses, enter host cells using this system.





Professor Lucy Raymond – The genetic basis of intellectual disability

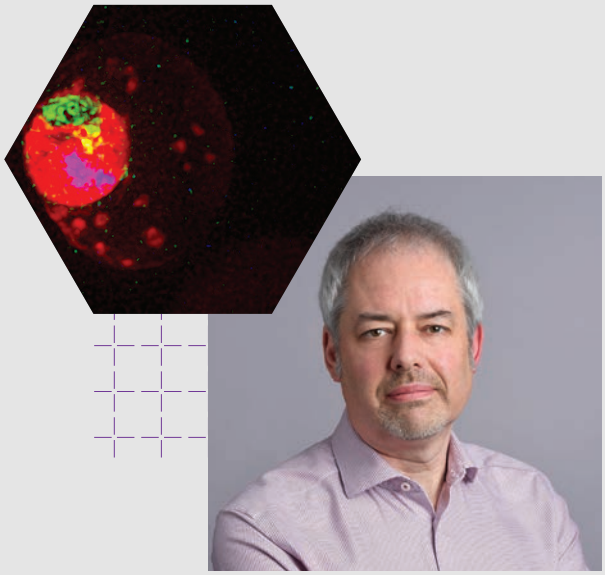
Rare Genetic Diseases

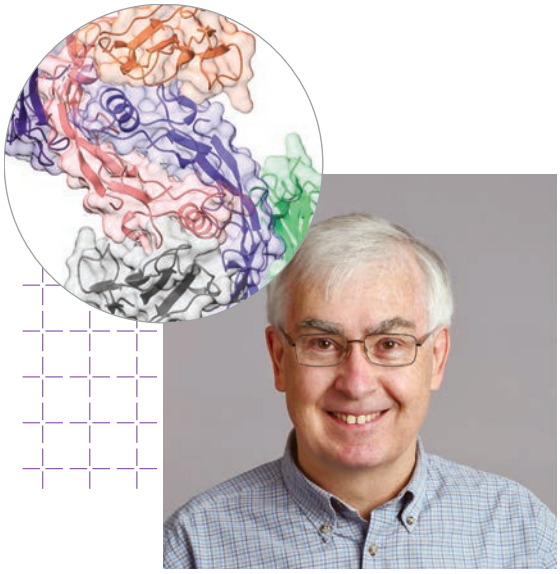
Intellectual disability is present in 0.5% of the population. The effects are wide ranging, and affected individuals may have difficulty learning and developing skills for everyday life. Our research goal is to understand the genetic changes that are present in the DNA of these patients, in the hope of characterizing the causes of this disorder. We conduct detailed analysis of the whole DNA genome in affected families, and this has allowed us to identify novel genes that contribute to this disease. A vital new part of this is our participation in a collaborative UK initiative to analyse the genomes of 10,000 patients in unprecedented detail.

Professor Julian Rayner – 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

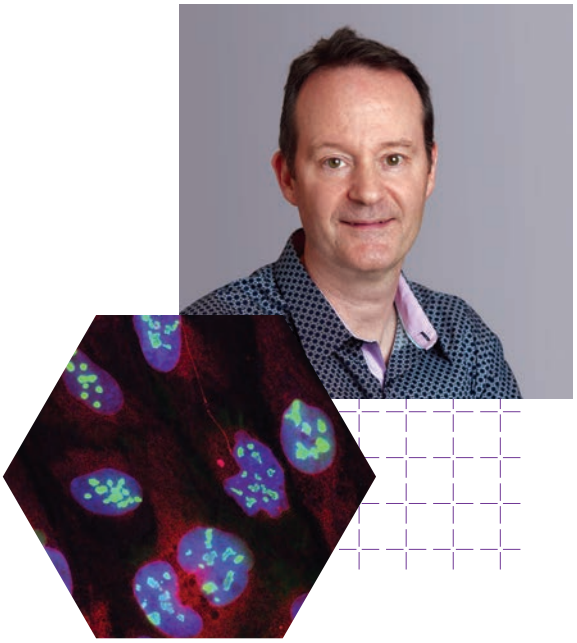
Protein folding and quality control

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 pathology 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 spastin 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 FRS – Coated vesicle adaptors

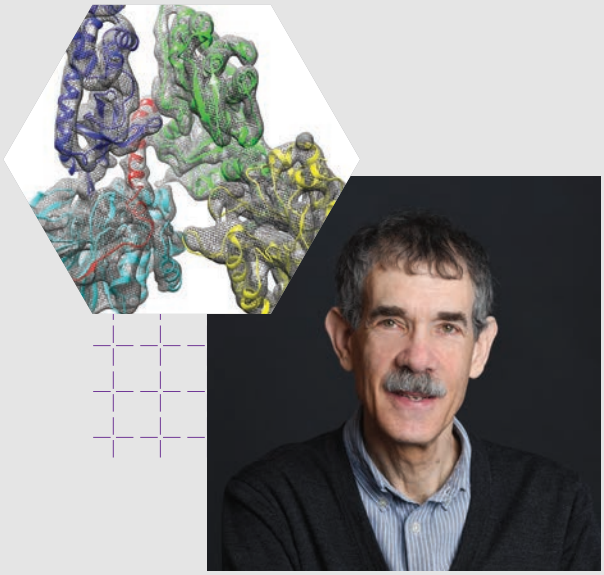
Membrane Trafficking, Rare Genetic Diseases

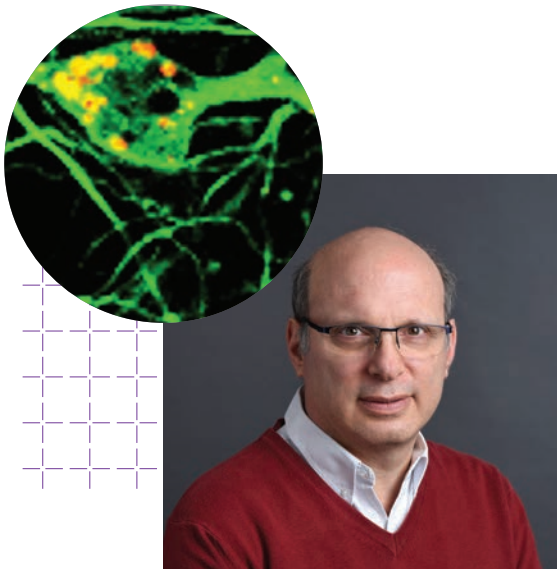
Cells are divided into special compartments called organelles. But normal cell function requires the constant movement of factors between these compartments, and this is mediated by the cellular transport machinery. Protein and other cargo are packaged into small membrane-bound packages called vesicles 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.





Professor David Rubinsztein FMedSci, FRS – Autophagy and neurodegeneration

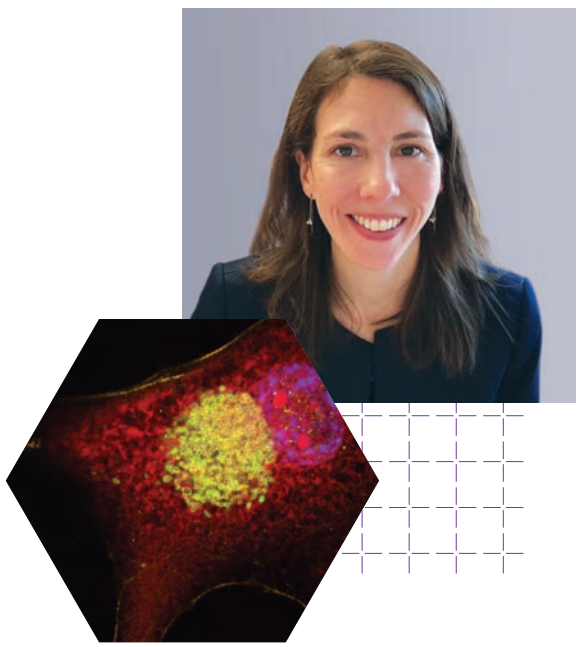
Protein Folding and Quality Control, Membrane Trafficking and Organelle Biology, Neurological Diseases, Rare Genetic Diseases

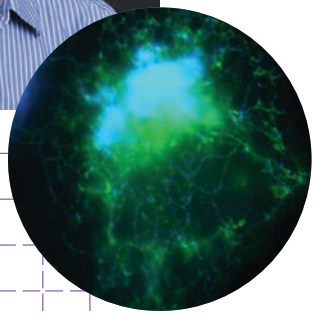
Neurodegenerative diseases, such as Alzheimer's, Parkinson's and Huntington's Disease, are associated with the accumulation of particular proteins that form clumps because they are not folded properly. Our research goal is to understand the links between these diseases and autophagy – the bulk recycling 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 of 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

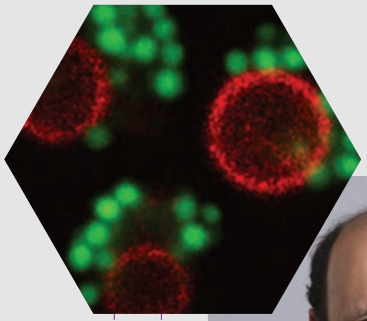
Membrane Trafficking, Organelle Biology

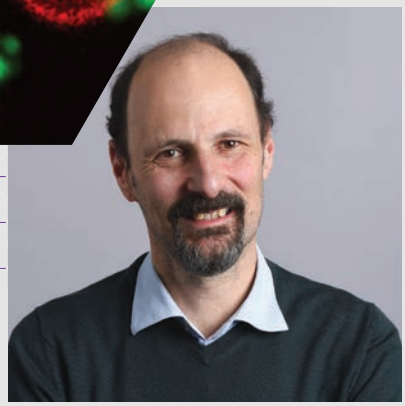
Cells are divided up into specialized compartments called organelles, each surrounded by membrane. This provides control by segregating different biological processes. Communication between these compartments is also a vital part of cell function, and this is achieved by the transport of small parcels 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 characterizing 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.

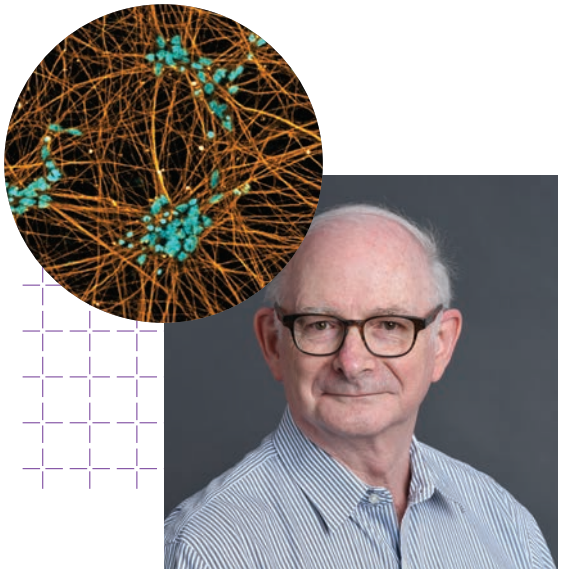
Dr Symeon Siniossoglou - Linking phospholipid metabolism to membrane and organelle function

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.







Professor Peter St George Hyslop FRS - Genetics of human neurodegenerative disease

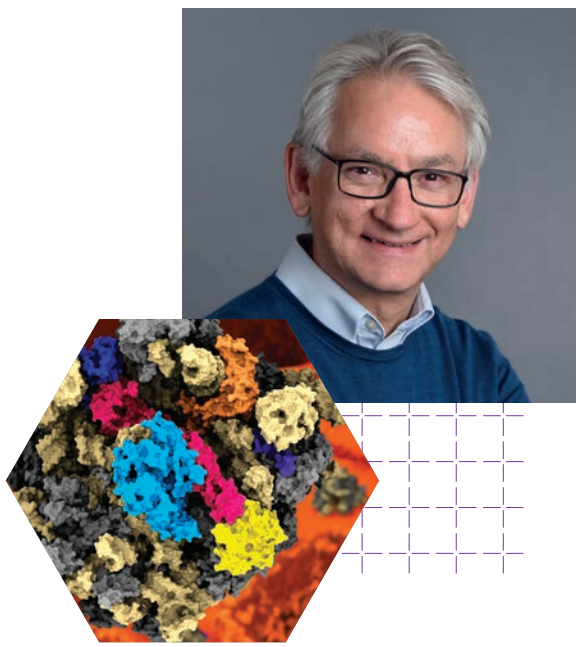
Neurological Diseases, Rare Genetic Diseases

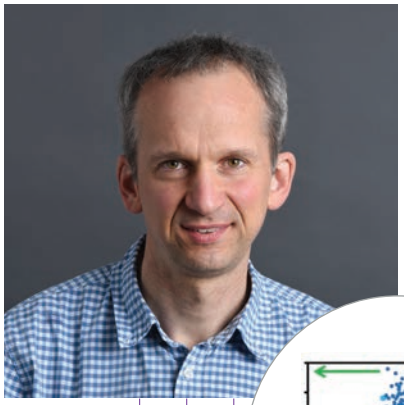
Neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's disease share the common feature of neuronal cell death, or neurons that have lost their structure and function in the central nervous system. This group of diseases often show abnormal folding of particular neuronal proteins, resulting in toxic aggregate formation. Through detailed DNA analysis of large groups of patients, we have determined the DNA changes that increase susceptibility to development of specific disease types. We are also interested in the mechanisms by which protein aggregates form, and how changes in protein function might increase the development of neurodegenerative disease.

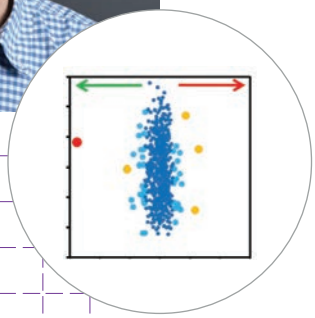
Professor Alan J Warren FMedSci - Mechanisms of ribosome assembly

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 model organisms such as yeast and flies 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.







Professor Michael Weekes - Innate immune evasion by intracellular pathogens

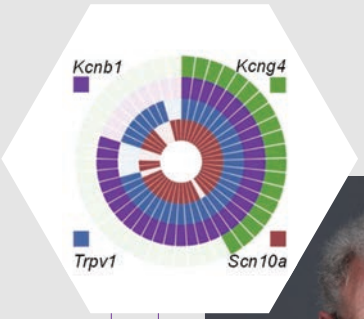
Intracellular Infections

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. When a virus infects a cell, the cell fights back by producing antiviral proteins, which inhibit viral reproduction. The virus tries to destroy these proteins in order to survive. We hope to discover which are the most important antiviral proteins that inhibit HCMV and other viruses using a technique called proteomics, which allows precise measurement of changes in thousands of viral and cellular proteins. By understanding how HCMV interacts with antiviral proteins, we may be able to inhibit these interactions, 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.



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Core facilities

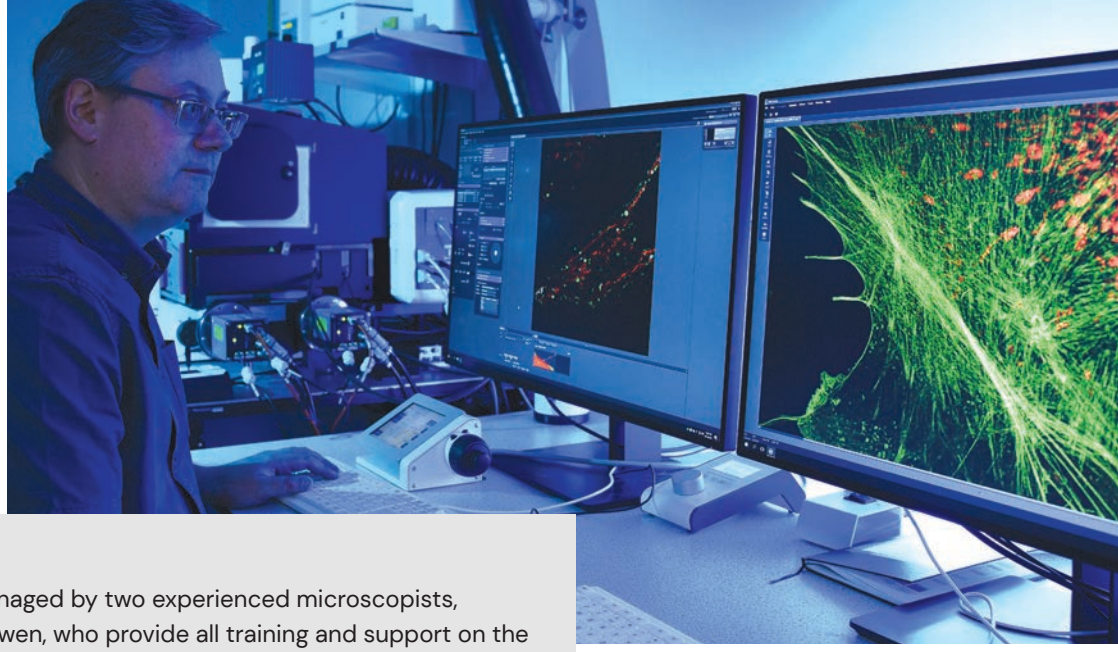
The provision of world-class research facilities has always been a top priority at CIMR, providing our researchers access to state-of-the-art methods. We currently have four facilities: proteomics, microscopy, flow cytometry and structural biology. Each of these is managed by in-house experts in these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

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.



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 in-house imaging requirements. These include: laser scanning confocal microscopy for fixed and live samples, rapid super-resolution imaging of living samples, High Content Screening and Analysis, histology (with processing, cutting and staining equipment). The Facility also owns an Electron Microscope 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.

Governance and operations

Institute Director: Julian Rayner

Deputy Director: David Rubinsztein

Business & Operations Manager: Sarah Smith

Institute Governance Committee:
Patrick Maxwell (Chair), Julian Rayner, David Rubinsztein, Eamonn Maher, Ken Smith, Geoffrey Smith, Fiona Gribble, Tony Green, Patrick Chinnery, David Rowitch and Anna Philpott.

Institute Management Committee:
Julian Rayner (Chair), Folma Buss, Janet Deane, Sarah Smith, David Rubinsztein, David Ron, Evan Reid, Mike Weekes, Mike Murphy (MRC Mitochondrial Biology Unit) and Mariann Bienz (MRC LMB).

General Purposes Committee:
David Rubinsztein (Chair), Neil Kent, Dave Cheesman, Jonathan Wilson, Symeon Siniossoglou, Mike Weekes, David Ron, Evan Reid, and representative PhD students and post-doc researchers.

Science is a collective endeavour, built on the talents and support of a wide range of people. CIMR has a team of dedicated and skilled professionals who play an essential role in keeping our research running smoothly and at the cutting edge. From the financial and administrative teams who support grant applications, people and financial management, to the building teams who keep the facilities running, the cell culture media flowing and the lights on, none of the outstanding work in these pages would be possible without them.

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Flow Cytometry Senior Assistant: Gabriela Grondys-Kotarba
Microscopy Facility Manager: Matthew Gratian
Deputy Microscopy Facility Manager: Mark Bowen
Proteomics Facility Manager: Robin Antrobus
Proteomics Facility Assistant: John Suberu
Proteomics Bioinformatician: Harriet Parsons
Crystallography Facility Assistant & Media Technician: Claire Carter

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Research Images:
Front cover from Dr Joseph Chambers (Marciniak Lab): a structured illumination microscopy image of the endoplasmic reticulum (ER) of a COS-7 cell after chemical fixation. It is imaged using HaloTag-KDEL localised to the ER lumen and labelled with BODIPY-HaloLigand, a reagent they developed for measuring microviscosity within intracellular organelles. The image is a maximum intensity projection of a Z-stack, colour coded by Z.

Other research images:
P5: Dr Jonathon Nixon-Abel (St George-Hyslop Lab); confocal image iPSC-Glutamatergic neurons (TUJ1+DAPI)

P14/15: Dr Alexandre Faille (Warren Lab); high resolution cryo-EM map of the large subunit of the human ribosome

P16: Dr Jonathon Nixon-Abel (St George-Hyslop Lab); confocal image of an iPSC-GABAergic interneuron (TUJ1+MAP2)

P17: Dr Jeanne Salje: *Orientia tsutsugamushi* bacteria (green) inside a mouse fibroblast cell

From molecular details to medical breakthroughs.

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