Welcome to the School of Clinical Medicine’s Research Overview which highlights the excellent, diverse and innovative research that goes on at the University of Cambridge’s School of Clinical Medicine.

The School of Clinical Medicine is a little over 40 years old. Before 1976, Cambridge students studied at London teaching hospitals for their clinical training. Over the last 40 years, the School has grown into a remarkable organisation providing excellent education and making major contributions to patient care, with an impressively broad range of world-class research programmes.

This compendium is an overview of the School’s research that takes place in our Departments, Units and Institutes. It also provides an overview of our medical education and postgraduate study courses, the NIHR Cambridge Biomedical Research Centre and our strategic partnerships.

The strength of the School’s research, outlined here, is based on great people who benefit from, and contribute to, the extraordinary environment on the Cambridge Biomedical Campus. I believe that the keys to our success are our integration in an outstanding University and the power of our partnerships with NHS organisations, Public Health England, national research institutes, industry, patients and the public across the East of England, the UK and beyond.

Patrick Maxwell
The National Institute of Health Research (NIHR) Cambridge Biomedical Research Centre (BRC) is a partnership between Cambridge University Hospitals and the University of Cambridge. Based on the Cambridge Biomedical Campus which combines, on a single site, world-class scientific research, patient care in NHS hospitals and drug discovery in pharmaceutical companies including AstraZeneca and GlaxoSmithKline (GSK).

The NIHR Cambridge BRC reaches out to scientists on the campus and beyond to ensure that their discoveries are pulled into the NHS, where clinical researchers can use them, in partnership with the life sciences industry, to improve health.

By creating an environment that engages patients and the public, it trains and nurtures the next generation of researchers, promotes equality and diversity, and encourages all staff working in the NHS to engage in research.

The NIHR Cambridge BRC works on cancer, cardiovascular and respiratory disease, dementia, disorders of the nervous system and mental health, infections and their resistance to antibiotics, obesity and diabetes, bone disease, digestive disorders and the effect of nutrition, diet and lifestyle on health, transplantation and the use of stem cells to repair tissues, and women’s and children’s health.

Additionally, funding from the Government to establish the NIHR BioResource for Translational Research in Common and Rare Diseases is building on the success of the NIHR BioResource and NIHR Rare Diseases Translational Research Collaboration.

The School of Clinical Medicine at the University of Cambridge is one of the UK’s leading medical schools. There are approximately 2250 staff and 1700 medical and postgraduate students in the School. Its strength is built on close relationships with pre-clinical science and translational partnerships with NHS organisations.

**Artificial pancreas an international success**

Poor management of blood sugar levels for people with diabetes can lead to serious health complications such as kidney disease, heart disease or eyesight problems.

Cambridge researchers from the Metabolic, Endocrinology and Bone research theme collaborated with our Women’s Health and Paediatrics theme to develop a world-leading artificial pancreas system (a continuous glucose monitoring device) for people with type 1 diabetes. The system uses smartphone technology to communicate with an insulin pump and a continuous glucose monitor.

The system calculates and delivers the correct amount of insulin needed at any particular time, therefore cutting out the need for injections, improving glucose control and reducing the risk of hypoglycaemia (low blood sugar). The continuous glucose monitor is worn 24/7 meaning that blood sugar levels are continuously measured including through the night leading to less disturbed sleep patterns.

More than 150 children and adults have trialled the device and compared it with the best available therapy in diabetes clinics internationally, including the UK, Germany and Austria. Longer-term trials are ongoing, testing the artificial pancreas in newly diagnosed children and adolescents and young children aged 1 to 7 years old.

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The discovery of a revolutionary new drug that has the potential to reduce the likelihood of thrombosis but, unlike previous treatment methods, will not heighten the risk of bleeding, saving millions of lives.

Thrombosis, the underlying cause of both coronary heart disease and strokes, is responsible for a third of all deaths worldwide, and new anticoagulants are needed which can prevent these lethal blood clots. In a healthy body, blood coagulation is typically under tight regulatory control, so that neither bleeding nor thrombosis occur. The molecular control of this process has been the long-term research focus of Professor Jim Huntington, whose research aims to uncover the structural basis of these regulatory mechanisms, with the expectation that such information will help improve therapies for the prevention and treatment of thrombosis.

Through a long-term collaboration with clinician Trevor Baglin at Cambridge University Hospitals, structural biologist Professor Huntington has developed a new potential anticoagulant, chorcumab. Unlike existing treatments, this has the ground-breaking potential to target blood clots without risk of bleeding.

Ichorcumab’s story began with a chance clinical observation. In 2008, Professor Huntington and Dr Baglin encountered a patient who was suffering with an intercranial bleed and displayed a degree of anti-coagulation consistent with severe haemophilia. “We thought it might be fatal, but to our surprise the bleeding stopped quite normally,” explained Dr Baglin. Further analysis revealed that the patient was generating an unusual antibody against the blood clotting enzyme thrombin.

By applying their extensive knowledge of the molecular and structural mechanisms that regulate haemostasis, Professor Huntington’s research group was able to translate the insights gained from this chance discovery into development of a novel synthetic antibody, chorcumab, as a potential new anticoagulant.

Indeed, Professor Huntington emphasizes that in preclinical studies “this antibody can deliver a high degree of anticoagulation without increased bleeding, something we’ve never seen before.” This key feature sets it apart from all existing anticoagulants, including warfarin, and may remove the need to control dosage so tightly. It could thereby dramatically change the way that patients are treated and have the potential to save millions of lives.

The development of chorcumab formed the basis of a spin-out company X01 Ltd in 2013, established through Cambridge Enterprise with $11 million Series A funding from Index Ventures. It was then sold to Janssen Pharmaceutical in 2015, where it will enter phase II clinical trials. The sale represents a key step in the progress toward this drug being used in patients, as Dr Andrew Walsh, former technology manager at Cambridge Enterprise, notes that Janssen has “the capability not only to take this pre-clinical opportunity to the clinic but also to market it across the globe so that it is available to patients worldwide.”

CASE STUDY
Tackling thrombosis
Development of an anticoagulant that reduces bleeding risk
Professor Jim Huntington
Cambridge Institute for Medical Research / Department of Haematology

Our research strategy is to use cell biology to understand the basis of disease and conversely to exploit human disease to reveal crucial mechanisms of cell biology.”

Previously eluded researchers. Our institute is well placed for structural studies, providing significant insights into mechanisms of cell biology. These technical advances are being applied by our researchers in innovative ways and have uncovered diverse aspects of fundamental cell biology. Selected recent discoveries include: a unifying model of lysosomal dysfunction for hereditary spastic paraplegias; a mechanism by which polyQ proteins alter cell recycling in neurodegenerative, mutagenic, silencing in Charcot-Marie-Tooth disease, chaperone control of the unfolded protein response, the structural basis of Hunter syndrome, and the role of the myosin VI motor in actin dynamics during mitophagy.

www.enterprise.cam.ac.uk/case-studies/x01-and-a-ground-breaking-drug-candidate

This work was supported by the Medical Research Council.
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RESEARCH SYNOPSIS
We unite more than 700 laboratory researchers and healthcare professionals from University Departments, world-leading research institutions, NHS Foundation Trusts (Cambridge University Hospitals and Royal Papworth Hospital) and major pharmaceutical companies sited across Cambridge and the wider area.

Our mission is to end death and disease caused by cancer. Through research, treatment and education. As one of three CRUK major centres in the UK, we serve as a national and international resource for patients with cancer and their families, researchers and health care providers, and cancer professionals in training.

Our laboratory-based research leaders work across a broad range of disciplines including biology, physics, chemistry, genetics, engineering, astronomy, mathematics and data science. Our clinical consultants specialise in oncology, haematology, surgery, radiology, pathology, medical genetics, general practice and public health.

As an Interdisciplinary Research Centre (IRC), we facilitate new collaborations and drive the translation of new scientific discoveries into clinical applications to improve patient care. This enables our members to break down the barriers between the laboratory and the clinic, so that patients can benefit from the latest innovations in cancer science.

MAIN RESEARCH THEMES
Working together across multiple academic, hospital and private sector settings our programmes design and drive mission-centric cancer research.

Detection and diagnoses of cancer

Our aim is to improve the detection and diagnoses of cancers that will ultimately limit the spread of the disease improving the outcome for patients. We invented endosonography\(^1\), a simple to implement relatively non-invasive diagnostic device that can rapidly and accurately detect Barrett’s oesophagus – the only known precursor of oesophageal cancer – in primary care. We demonstrated that endosonography is the most accurate, safe and inexpensive way to stage lung cancer. Consequently, endosonography has replaced surgery as the first line investigation for mediastinal staging. Over 100 UK centres now provide this service and the rate of surgical staging in the UK has fallen dramatically.

Cancer Imaging

We developed clinical hyperpolarised \(1^2\)C magnetic resonance imaging (MRI) in close collaboration with GE Healthcare, which resulted in the production of SPINlab, a clinical device that enables visualisation of tumour metabolic activity using MRI. SPINlab is now being used at multiple centres internationally. We performed the first clinical proof-of-concept studies of this approach in Europe and founded the first and currently the only GMP-grade pharmacy in Europe for generating hyperpolarised probes for clinical imaging.

New and innovative treatments of cancer

We are translating Cambridge laboratory discoveries into multiple new treatments of cancer. Our aim is to discover new ways to diagnose, monitor and treat the most common and hard to treat cancers through the *Aerodigestive Cancer*, *Neuro-Oncology*, *Breast Cancer, Haematological Malignancies*, *Ovarian Cancer, *Paediatric Cancer*, *Pancreatic Cancer and Urological Malignancies* Programmes. (Cancer Research UK has designated these as cancers of unmet need).

Our fundamental research discoveries in cancer biology and new diagnostic and treatment approaches are achieved through our Advanced Cancer Imaging, Cell and Molecular Biology, Early Detection and Oncology-Innovation Programmes. The Oncology-Innovation Programme includes professionals from the CRUK MedImmune Alliance and AstraZeneca, and brings together pharmaceutical partners and academics to develop new cancer treatments.

We are adopting a proactive approach to the way we treat cancer. Instead of a reactive system that waits for cancer to present, we are developing a personalised strategy for all patients that detects cancer in its earliest form, integrates different types of patient data to inform clinical decisions on the best treatment, and uses non-invasive technologies to monitor how the disease is responding to treatment.

“**Our mission is to end death and disease caused by cancer, through research, treatment and education.**”

CASE STUDY

Bespoke treatment

Bringing breast cancer genomics to the bedside

Professor Carlos Caldas

Professor of Cancer Medicine, Director of the Cambridge Breast Cancer Research Unit Department of Oncology, Cancer Research UK Cambridge Centre

With 1 in 7 women in the UK developing breast cancer in their lifetime, identifying new targeted treatments will improve the prognosis of these patients. Professor Caldas has developed and optimised the ability to test treatments in cultured tumour cells derived from patients (PDTXs), identifying treatments depending on tumour type. Subsequent collaborative studies have determined the genomic make up of several breast cancers, leading to bespoke treatments for patients according to their genome sequencing results.

The Cambridge Personalised Breast Cancer Programme (PCP) uses the latest genome sequencing technology to look at, and classify, breast tumours with the aim of improving diagnosis and personalising treatment for each patient. The trial is underpinned by outstanding research from Professor Carlos Caldas and his lab, who have described the distinct molecular types of breast cancer and created the world’s largest collection of patient-derived tumour xenografts (PDTXs). These PDTXs were used to produce short-term cultures where the morphological and molecular characteristics of the originating tumour were preserved, providing a powerful high-throughput platform for pre-clinical breast cancer pharmacogenomic studies.

Over 400 breast cancer patients at Addenbrooke’s have been recruited so far for whole genome sequencing of their tumour and genomics sequencing from a blood sample. This has enabled them to be given the best treatment based on the precise genetic signature of their tumour.

Catherine Scott, 51, from Cambridge was diagnosed with breast cancer in September 2016. She was one of the first patients to be enrolled on the PCP by co-lead Dr. Joan Abraham. The genome sequencing results identified the PPAR (peroxisome proliferator activated receptor gamma) inhibitor for breast cancer as the best treatment option for Catherine.

“I had always thought breast cancer was breast cancer. I hadn’t realised there were different types. That’s why the research into personalised medicine works because they can treat you more effectively.” The consultant told me there was a new research programme coming up: My tumour was triple negative and so I was eligible for the trial. When I went to see Jean, she explained that because of the type of cancer that I had, they could give me this new tablet as the best treatment option for my condition.

“This programme will continue to gather essential data on breast cancer genetics to enhance the range of bespoke treatments offered to patients.”

Brunet J, Cell 2016

Pereira et al, Nature Comm 2016


This work is supported by Cancer Research UK, Addenbrooke’s Charitable Trust, Cambridge University Hospitals NHS Foundation Trust, NIHR Cambridge Biomedical Research Centre and AstraZeneca
Our focus on tackling questions relating to cancer screening, diagnosis, treatment and prevention to drive the development of new approaches.

Clinical studies and clinical trials
We have organised over 20 clinical trials since 2007. The ProtecT trial compared radiotherapy, surgery and active monitoring to identify the best treatment for men with localised prostate cancer. We found that while the numbers of men who died from prostate cancer was low in all three-treatment groups, men who had surgery and radiotherapy had lower rates of tumours growing or spreading. We also found differences in side effects - surgery was linked to problems with sexual function and incontinence and radiotherapy with problems with sexual function and the bowel.

Molecular imaging, genomics, bioinformatics, cancer evolution and biomolecular modelling
We focus on the application of computational biology, bioinformatics, and statistics to cancer biology, using computational techniques to better understand gene expression and improve image analysis techniques, developing novel pipelines for analysis of single-cell sequencing data, and stochastic modeling to understand tumour heterogeneity.

With a Cancer Research UK Grant we aim to build a 3D virtual reality tumour. Using a combination of established techniques, including DNA sequencing and imaging, and new technologies, we will invent and develop breast cancer samples derived from the METABRIC study. The information we collect about the cells in a tumour will be used to construct a 3D model that can be displayed and studied using virtual reality technology. This will allow our scientists to immerse themselves in a tumour, meaning we can study patterns and other characteristics within it in entirely new ways that are not possible in 2D. Using this technique, we aim to change and improve how the disease is diagnosed, treated and managed.

"Importantly, this advance means that we will be able to screen a much larger number of genes in the blood to test if specific genetic changes in the cancer explain resistance to treatment. The low cost and high acceptability of a blood sample means that this can be done across hundreds or thousands of patients. This is vital to discover reliable clinical biomarkers."

Dr James Brenton.

In 2014, these liquid biopsy methods led to the spin out company Inivata, that has raised over £35M of investment. By 2018 Inivata was employing about 65 staff members, and in parallel to generating data for research, was generating molecular pathology data from patient plasma samples through a validated assay that was approved for clinical use. Inivata’s platform brought together Next-Generation Sequencing (NGS) technology, with proprietary algorithms and databases. The company is making significant steps in improving personalised healthcare in oncology. Using its best-in-class liquid biopsy platform, they can detect and characterise ctDNA via a simple non-invasive blood test, with proprietary algorithms and databases.

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RESEARCH SYNOPSIS

Our mission is to reduce the morbidity and mortality of patients with cancer through research, treatment and education. We have close collaboration links with the Cancer Research UK (CRUK) Cambridge Centre, participating in a broad range of research enterprises, as well as patient care.

Our researchers are based within multiple sites within the Cambridge Biomedical Research Campus. The Campus encompasses The School of Clinical Medicine, Addenbrookes Hospital, internationally renowned research institutes and biopharmaceutical companies. The co-location of researchers provides access to state-of-the-art clinical and research facilities and enables interdisciplinary collaboration among world-class laboratory scientists and doctors.

We are at the forefront of oncology research and education with a strong focus on translating basic scientific findings into clinical applications for treatment, diagnosis and prevention of cancer. Our major funders include Cancer Research UK, the NHS, Wellcome Trust and the Medical Research Council.

MAIN RESEARCH THEMES

We support the activities of clinical and academic oncologists as well as basic and translational cancer researchers. In addition, we co-lead Centre Programmes, sit on the Cancer Centre Executive Committee, play prominent teaching roles in the Clinical School and lead the Cambridge Experimental Cancer Medicines Centre.

Our aim is to conduct impactful interdisciplinary cancer research by deploying Cambridge innovation to better understand the biology and treatment of cancer, including cancers of unmet need.

By adopting a proactive approach to cancer, we are changing the way we treat cancer. Moving from a reactive system that waits for cancer to present, to a proactive personalised strategy for all patients that detects cancer in its earliest form, intervenes precisely, and closely monitors the disease course with non-invasive technologies. A new training scheme will develop and produce a new generation of cancer leaders, trained in early detection and integrative cancer medicine, producing a step-change in the way we practice oncology. We partner with the public and deliver our mission to create a step-change in the way we practice oncology.

“Identify the ineffective

Anti-VEGF monoclonal antibody, bevacizumab, found to be an ineffective therapy for breast cancer

Professor Holena Earl

Department of Oncology—UK

Work by Professor Holena Earl has identified that although the expensive anti-VEGF monoclonal antibody initially showed promising results, the follow-up studies demonstrated bevacizumab as an ineffective addition to breast cancer therapy resulting in revised licensing for this product.

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INTERIM UNIT DIRECTOR AND PROFESSOR OF CANCER PREVENTION
Professor Rebecca Fitzgerald

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RESEARCH SYNOPSIS
Our mission is to advance our understanding of the earliest steps in the emergence of cancer, and to use this knowledge for early diagnosis, risk stratification and clinical intervention, through the development of innovative enabling technologies.

Our work spans fundamental research to clinical translation, and draws together researchers from the Departments of Biology, Physics, Chemistry and Engineering, as well as clinicians. Based in the Cambridge Biomedical Campus, we are at the hub of biomedical research in the University, where students and staff benefit from extensive collaborations with both academic and industrial partners. We are supported by a core award from the MRC, supplemented by research grants from many other sources including Cancer Research UK and the Wellcome Trust.

Our researchers have made many key discoveries including: identification of DNA replication proteins as markers for early cancer diagnosis; discovery of the functions of the breast cancer susceptibility gene BRCA2 and its role in promoting cancer development; development of the CytoSponge test for the early detection of oesophageal cancer and characterisation of its genomic evolution; elucidation of how inappropriate stem cell division spurs carcinogenesis; identification of mechanisms underlying how cellular metabolites promote carcinogenesis.

MAIN RESEARCH THEMES
Understanding epithelial cancer progression

We seek to identify the molecular and cellular events which drive epithelial cancer progression from pre-cancerous to invasive disease. We aim to understand these processes in order to develop new approaches for early intervention in the clinic.

Our broad-ranging research programme studies key biological processes that promote early carcinogenesis. Our work has helped define how the breakdown of tumour suppressive mechanisms that control genome integrity, inhibits and drives the evolution of inherited and sporadic cancers. It has traced the multi-step progression of oesophageal adenocarcinoma from pre-invasive Barrett's oesophagus through to invasive cancer, and helped identify key steps in the evolution of mutant Kras-driven lung cancers. We study early stages of squamous epithelial carcinogenesis, focusing on the evolution of mutant clones in non-metastatic skin cancer and carcinogen-induced squamous carcinoma of the oesophagus. We investigate how early metabolic reprogramming and mitochondrial dysfunction in cancer cells enables environmental adaptation, and drives further progression. Our research considers the role of the non-cancer cells (stroma), specifically, how stromal populations communicate with tumour cells to drive the acquisition of invasive properties, and the mechanisms used by stromal cells to mask a tumour from immune destruction. We study transcriptional regulatory networks involved in tissue and organ development that interact with tumour-initiating genetic pathways to enable tumour progression, early invasion and metastasis. We also use complementary computational approaches to model cellular behaviours and multi-dimensional tumour datasets to develop fundamental new insights into tumour evolution.

Developing tools for early diagnosis and risk stratification of patients

Our research has underpinned the creation of the CytoSponge device, an important development enabling simple early diagnosis without endoscopy for patients at risk of Oesophageal cancer. We are also developing and clinically standardising new biomarkers with wider significance for other cancer types alongside exploring new methods for molecular imaging in endoscopy.

Furthermore, we use functional and genomic analyses to identify new markers for risk stratification in patients who carry inherited mutations in genes like BRCA2, and we have developed a new microarray suite that can enable high contrast digital imaging of unprocessed tissue sections using wide light, with wide applications in cancer diagnosis.

Developing new approaches for early intervention in cancer

We are engaged in a multi-disciplinary international collaborative effort to establish new methods and platforms for the efficient identification and validation of therapeutic target events during early steps in cancer progression. This area is widely recognized as the emerging critical interface between the pharmaceutical industry and academia. A Cambridge University spinout company, PharmaMode, formed to commercialise these new approaches is already nucleating collaborations between the Unit and industry.

“Developing tools for early diagnosis and risk stratification of patients”

Professor Rebecca Fitzgerald

CASE STUDY

Pill on a String

Developing a new method for the early detection of oesophageal cancer

Professor Rebecca Fitzgerald FMedSci

MRC Cancer Unit

The CytoSponge TFF3 test, created in the lab of Professor Rebecca Fitzgerald, is a revolutionary development in the detection of Barrett’s Oesophagus. It is a highly cost-effective, non-invasive testing method, which has the potential to improve the prognosis for many patients who are at risk of developing oesophageal cancer.

A new testing method, developed by Professor Rebecca Fitzgerald and her colleagues, is intended to replace the traditional endoscopy. The Cytopsponge TFF3 test, known as the ‘Pill on a String’ involves swallowing a small encapsulated sponge which emerges when the capsule dissolves in the stomach. The sponge can then be pulled back out of the throat using the string attached and it collects cells as it is withdrawn. Adherent cells thus collected are then analysed using very sensitive and specific tests developed in Professor Fitzgerald’s lab to detect the presence of genetic and cellular abnormalities.

By capturing cells from across a wider area than a focussed biopsy would, the test is more likely to detect the prevalence of pre-cancerous conditions and thereby improve chances of stratifying those patients for therapy who might most benefit from such early detection. Equally, the Cytopsponge test can be taken at GP surgeries at a fraction (c 1/24th) of the cost of a standard endoscopy. The biomarkers that have been developed are also an improvement over the current Histopathology examination of Barrett’s samples which is highly subjective and time consuming.

The assay developed to detect Barrett’s relies on a single antibody test to detect a protein expressed in Barrett’s cells called TFF3, this is scored positive or negative and is thus the suitable for automation. If this test is positive then a second tier of testing is done on the same sample to see how likely the patient is to progress to cancer. This means that only patients at highest risk will need to have an endoscopy and treatment.

Those who are completely negative for Barrett’s can be reassured and discharged and those at low risk for cancer can repeat the Cytopsponge test again in three years’ time. These assays are still being refined to maximise the accuracy and the clinical utility to ensure that they are applicable to a routine NHS laboratory at low cost.

The Cytopsponge is now being tested across GP surgeries in the UK as part of a Phase III clinical trial. Professor Fitzgerald and her colleagues look forward to the widespread use of the ‘Pill on a String’ in order to improve the cost-effectiveness, ease of operation and specificity in picking up in-situ oesophageal cancers at the stage of Barret’s Oesophagus.


The research was funded by the Medical Research Council and Cancer Research UK.

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The Cambridge Institute for Medical Research (CIMR) is a cross-departmental institute. Our goal is to uncover scientific discoveries that will transform our understanding of the cell and to use this knowledge to reveal how fundamental cell biological mechanisms become disrupted in disease.

All Principal Investigators affiliated with the Department of Clinical Biochemistry are members of either the Cambridge Institute for Medical Research (CIMR) or the Metabolic Research Laboratories with the embedded MRC Metabolic Diseases Unit (MRL + MRC MDU) the latter being part of the Wellcome Trust-MRC Institute of Metabolic Science (IMS). Please see the sections of the document dedicated to these entities for further details.

HEAD OF DEPARTMENT AND PROFESSOR OF CLINICAL BIOCHEMISTRY AND MEDICINE
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RESEARCH SYNOPSIS FOR THE MEDICAL RESEARCH LABORATORIES (MRL)
The MRL, with the embedded MRC Metabolic Diseases Unit, is part of the WT-MRC Institute for Metabolic Science (IMS) and focuses on how the body controls its metabolism and energy balance in health and disease. As hormones play such a crucial regulatory role in these processes we have a major interest in endocrinology, the science of hormones. We use the results of our research to aid the development of better approaches to classifying, treating and preventing obesity, type 2 diabetes and other related endocrine and metabolic disorders. We apply a broad range of technologies including studies in cells, animal models, and humans to better understand how metabolic and endocrine systems function.

RESEARCH SYNOPSIS FOR THE CAMBRIDGE INSTITUTE FOR MEDICAL RESEARCH (CIMR)
The CIMR is a cross-departmental institute. Our goal is to uncover scientific discoveries that will transform our understanding of the cell and to use this knowledge to reveal how fundamental cell biological mechanisms become disrupted in disease. This will in turn identify new therapeutic strategies and translational opportunities.

We have a particular biological focus on protein trafficking and homeostasis, and organelle dynamics and homeostasis, including how these become adapted in particular cell types and in response to a changing environment. By combining the complementary perspectives of structural biologists, cell biologists, geneticists and clinicians in one institute, we facilitate interdisciplinary collaborations. This makes it possible to understand these processes at different levels, from structural interactions to function in specialized cells, and in both health and disease.

“The University of Cambridge Metabolic Research Laboratories and its embedded MRC Metabolic Diseases Unit investigate the mechanisms through which metabolic health is maintained and how this is disturbed in disease. We seek to use this knowledge to aid better treatment and prevention of obesity, type 2 diabetes and related endocrine and metabolic diseases.”

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Our research falls into three main areas with major relevance for human disease: haematopoiesis and leukaemia, structural medicine and thrombosis, and transfusion medicine.

RESEARCH SYNOPSIS

Our research falls into three main areas with major relevance for human disease: haematopoiesis and leukaemia, structural medicine and thrombosis, and transfusion medicine.

We conduct our research from laboratories on the Cambridge Biomedical Campus, including the Cambridge Institute for Medical Research, the Clifford Allbutt Building, the NHS Blood and Transplant Cambridge Centre and at the Wellcome Sanger Institute on the Wellcome Genome Campus. From 2019 the majority of our researchers will be located in the Jeffrey Cheah Biomedical Centre, a brand new purpose built research facility on the Cambridge Biomedical Campus.

MAIN RESEARCH THEMES

Haematopoiesis and leukaemia

Haematopoiesis represents the best characterised adult stem cell system and continues to provide important paradigms for understanding other stem cells as well as cancer biology. We focus on the transcriptional regulation of blood stem cells, and the mechanisms whereby such stem cells are subverted to form leukaemias. Our current research programmes include: myeloproliferative neoplasms, JAK/STAT signalling and stem cell subversion, transcriptional networks regulating blood stem cells, the pathogenesis of bone marrow failure syndromes and leukaemia, the biology of leukaemia stem cells, immunotherapy and pathogenesis of multiple myeloma, the interplay between haematopoietic stem cells and tumour microenvironment, pathogenesis of B cell lymphoma, the niche as a therapeutic target in chronic lymphocytic leukaemia.

Structural medicine and thrombosis

Structural biology gives us an unparalleled insight into the molecular details of biological mechanisms, an insight that has the potential to lead to rationally-designed therapies. This is illustrated by some of our recent studies. We are studying the molecular mechanisms behind the delicate control of blood coagulation. As a result, we have determined crystal structures of the major inhibitory complexes that down-regulate clotting, and we are now focusing on the large protein complexes that promote clotting, the Xase and prothrombinase complexes. We also conduct research in the field of protein crystallography, focusing on the serpin family and development of the Phaser programme.

Transfusion medicine

Our research focuses on the biology and genomics of megakaryocytes and platelets. Particular highlights include a Genome-Wide Association Study meta-analysis which identified 15 genetic loci which regulate the volume and count of platelets and discovered novel genetic loci which regulate platelet function, alongside work towards blood cell production from human pluripotent stem cells.
HEAD OF DEPARTMENT AND PROFESSOR OF MEDICAL GENETICS AND GENOMIC MEDICINE
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RESEARCH SYNOPSIS
Our research is wide-ranging and includes the identification of genetic causes of human diseases using state-of-the-art genome-wide DNA sequencing techniques, and studies to elucidate the mechanisms whereby genetic variations cause major human diseases. Our aim is to develop novel diagnostic and therapeutic strategies for inherited disorders. Our main areas of interest include cancer genetics and genomics; genetics of developmental disorders; genetic components of neurological disease, including cellular mechanisms of neurodegeneration and developmental biology of neural cell development and repair; genes contributing to X-linked disease, particularly intellectual disability; renal genetics; autoimmune liver disease; rare diseases; and disorders of genomic imprinting.

In addition to making fundamental scientific discoveries, we are at the forefront of advancing genomic analyses into medical practice. We have close links with the East Anglian Medical Genetics Service, the East of England Genomic Medicine Centre as part of the 100,000 Genomes Project, and many other departments within both the University and Cambridge University Hospital NHS Trust.

MAIN RESEARCH THEMES
Whole genome and exome sequencing
Advances in genome technologies, such as whole genome and exome sequencing, have transformed medical genetics research and are impacting on the practice of genomic medicine. We are utilising whole genome (WGS) and exome sequencing to understand the genetic and other causes of inherited and sporadic cancers and neurodevelopmental disorders.

For example, Lucy Raymond, Eamonn Maher and Geoff Woods led projects within the NIH Rare Disease BRIDGE project that undertook WGS on cohorts of patients with rare diseases. (https://bridgestudy.medschl.cam.ac.uk/whats.html) and Serena Nik-Zamal decodes mutational signatures from WGS analysis of human cancers.

Transcriptomics and epigenomics
We are home to the Stratified Medicine Genomics Core Laboratory (SMCL), which provides access to clinical grade genomics, transcriptomic and transcriptomic analysis to aid our research, experimental medicine investigations and clinical trials. We use this facility to apply transcriptomics and epigenomics when investigating the pathogenesis of both primary biliary cirrhosis and disorders of genomic imprinting.

We are also studying the genetic causes of primary sclerosing cholangitis as part of the PSC Genetics Study with the aim that researchers may have a better chance of developing more effective treatments for this disease and understanding what causes PSC.

Translational research
Our translational research is facilitated by a variety of multidisciplinary clinical activities. For instance, in order to define the molecular mechanisms of neurogenetic disorders we use state-of-the-art cellular biology models to identify pathways of disease and potential therapeutic strategies.

We are presently investigating the links between autophagy and neurodegenerative disorders such as Alzheimer’s and Huntington’s Disease. We have found that autophagy might be inhibited in these diseases and have been trying to elucidate the pathological consequences of autophagy compromise. We have identified 15 genetic loci which regulate the volume and count of platelets and discovered novel genetic loci which regulate platelet function, alongside work towards blood cell production from human pluripotent stem cells.

Diagnostics Development Unit
For instance, in order to define the molecular mechanisms of neurodegeneration and developmental biology of neural cell development and repair, genes contributing to X-linked disease, particularly intellectual disability; renal genetics; autoimmune liver disease; rare diseases; and disorders of genomic imprinting.

We aim to develop innovative tests that are rapid, simple, cost-effective and more sensitive than currently available rapid tests. We have developed a rapid low cost diagnostic test for Chlamydia trachomatis which is now widely available. We are also submitting a test for HBsAg for licensing.

CASE STUDY
Find the mutation
Delivering improved access to genetic testing in epithelial ovarian cancer

Dr Marc Tishkowitz
Department of Medical Genetics

Research led by Dr Marc Tishkowitz has ensured that women with epithelial ovarian cancer (the most common form of ovarian cancer, around 90 per cent of diagnoses) receive the appropriate genetic counselling both before and after genetic testing for the BRCA1 and BRCA2 gene mutations. The research team wanted to see if a more streamlined model of genetic counselling alongside testing for BRCA1 and BRCA2 mutations was cost effective, feasible and acceptable to women and could be implemented in the NHS.

Testing women who are diagnosed with ovarian cancer for gene mutations allows other family members to seek vital help and information if they find out they have a familial risk, resulting in either prevention (if family members opt for preventative surgery) or earlier diagnosis (through increased awareness). However it is essential that women are supported with qualified genetic counselling throughout the process, especially as testing becomes more widespread and routine.

Over 200 women in the East Anglia region with newly diagnosed epithelial ovarian cancer took part in the study. It showed that streamlined genetic counselling alongside genetic testing was indeed cost-effective, feasible and acceptable.

This model has already been rolled out to benefit women and their families across East Anglia, and has been published in the Journal of Medical Genetics. Based on their findings, the research team worked with the Public Health Genomics Foundation to develop and publish a new protocol, ‘Delivering improved access to genetic testing in epithelial ovarian cancer’. This will allow other NHS providers to help set up similar models and services in their regions, benefiting even more women with ovarian cancer and their families.

This research has directly impacted healthcare by providing improved access to genetic testing for women with ovarian cancer and by facilitating better outcomes for women in the use of targeted treatments for those with BRCA1/2 mutations.


www.phgfoundation.org/Improving-access-to-genetic-testing-in-epithelial-ovarian-cancer
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RESEARCH SYNOPSIS
The Department of Medicine contains 12 divisions with broad interests that are of relevance to human disease. Our work extends from fundamental biomedical research through to the clinic, and is intimately linked to other scientists throughout the Cambridge Biomedical Campus, the UK and the wider international community.

We are the largest department in the School of Clinical Medicine, located at Addenbrooke’s Hospital, the MRC Laboratory of Molecular Biology, the Cambridge Biomedical Centre for Clinical Investigation and the Jeffrey Cheah Biomedical Centre. We also have research groups in the Cambridge Institute of Medical Research, CRIU Cambridge Institute, and the Institute of Metabolic Sciences.

Research is our major focus, spanning fundamental aspects of biology through to work on disease mechanisms and its clinical translation.

“Research is our major focus, spanning fundamental aspects of biology through to work on disease mechanisms and its clinical translation.”

From genetics to new treatments in pulmonary arterial hypertension

Professor Nick Morrell
BHs Professor of Cardiovascular Medicine, Department of Medicine  
Research Director, National Pulmonary Hypertension Service, Royal Papworth Hospital  
Dr Wei Li and Dr Paul Upton

Department of Medicine

Pulmonary arterial hypertension (PAH) is a rare but devastating disease. Professor Morrell’s group have defined a receptor pathway (BMPR2) as a therapeutic target for treating PAH. This work has led to a spin-off biotech company, Morphogen-IX that will commercialise the BMP9 approach providing a potential, lifesaving therapy for patients.

Pulmonary arterial hypertension (PAH), or severe high blood pressure in the lungs, is a rare but devastating disease caused by a narrowing of the blood vessels that lead from the heart to the lungs. Affecting some 6000 people in the UK, death due to heart failure often results within 3-5 years from diagnosis as the heart works harder and harder to pump blood through the lungs. Current treatments can help symptoms but prognosis remains poor; the only long-term treatment is a lung or a heart-lung transplant, subject to a very limited donor supply and survival rate.

Research by Professor Nick Morrell identifies the major genetic drivers of PAH and helps to develop new therapies based on that knowledge. His research has found that mutations in the bone morphogenetic protein type 2 receptor (BMPR2) underlie approximately 75% of familial cases of PAH and, up to 30% of sporadic cases. In 2015-2016, Professor Morrell led an international collaborative study that brought together experts from across the world to determine that PAH patients carrying BMPR2 mutations are younger at diagnosis, have more severe disease and have worse survival than patients without mutations.

Until this point, genetic testing in PAH patients was not commonly implemented. Now, the knowledge that patients with mutations, in BMPR2 have a particularly poor prognosis justifies more intensive therapy and early referral for lung transplantation. Incorporation of these into the 2018 international guidelines on the clinical management of PAH should improve outcomes for these patients.

The research has also led to important advances in the search for a cure for PAH. Building on the genetic studies, Morrell’s research group confirmed that a protein, bone morphogenetic protein 9 (BMP9), circulates in the blood and specifically and powerfully activates the BMPR2 receptor on the cells that line lung blood vessels. Crucially, Professor Morrell was able to demonstrate that therapeutic administration of BMP9 to rodents with genetic and non-genetic forms of PAH led to reversal of the disease. “We have discovered that patients suffering from pulmonary arterial hypertension don’t make enough of this protein,” says Morrell. “Our next steps indicate that BMP9 (which is relatively easy to manufacture) could restore blood vessels in patients’ lungs to a healthy condition.”

Having defined the BMPR2 pathway as a therapeutic target for treating PAH, Morrell established a spin-out biotech company, Morphogen-IX, to commercialise the BMP9 approach together with colleagues Wei Li and Paul Upton. The company develops BMP ligands as a PAH therapy and intends to start clinical studies in patients within the next two years at the Royal Papworth Hospital. “We think this therapy has the potential to reverse PAH in patients since it targets the single most important pathway in this disease,” concludes Morrell.

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Kerr: WC0016: 1207516 A1

www.med.cam.ac.uk/morrell

This work has been supported by the NHR Cambridge Biomedical Research Centre, the British Heart Foundation and the ARC, and was awarded the University of Cambridge Vice-Chancellor’s Impact Award 2017.
interested in leukocyte biology in acute lung injury and critical illness, with the purpose of explaining the role of host responses in injury and repair, and utilising novel interventions to improve patient outcomes. We have a growing programme in translational pain research, which includes early phase clinical trials, quantitative sensory testing, functional brain imaging and genotyping. These research areas are underpinned by a cross-cutting research theme addressing data science and the use of novel analytic methods such as machine learning and artificial intelligence.

**Cardiovascular Medicine**

We have an international reputation in the areas of atherosclerosis (arterial thickening), cardiovascular stem cells and vascular imaging. We use human and mouse cell models to study the role of specific gene products, cellular pathways and cell types in the progression of vascular disease. Our clinical research examines the utility of artificial intelligence.

**Diabetes, Endocrinology & Metabolic Disease**

We conduct research that helps people with diabetes achieve better control of blood glucose and reduce the risk of long-term complications. We are studying safe ways to administer insulin by structured education, and the use of medical technology such as insulin pumps and glucose sensors. Our research looks at how the brain detects falling blood glucose and how this may become altered in diabetes. This supports our collaboration with the Metabolic Research Laboratories in which an artificial pancreas is being developed and clinically tested.

We are recognised for our translational research in both rare (TSH-secreting pituitary tumours, acromegaly) and common (primary aldosteronism) endocrine conditions. Our development and introduction of routine molecular PET imaging to guide personalised treatment in pituitary and adrenal neoplasia has attracted referrals from the UK and international centres. We also study the behavioural consequences of endocrine and neural function. In particular, we are looking for an explanation as to how fluctuating levels of natural steroids contribute to risk behaviour in financial decision-making.

**Computational Medicine**

With the emergence of increasing computing power, new computer algorithms and rising levels of clinical data we are able to predict increasingly complex outcomes for patients. We develop statistical tools to identify genetic associations of different diseases and robustly link them with specific genes, cell types, stimulatory conditions and ultimately to biological pathways. Our research probes the correlations relating to autoimmune diseases with the aim of understanding its causes. This identifies common links between different diseases and provides opportunities to identify pharmaceutical targets, pushing forward new drug development programmes and re-purposing existing therapies.

Incorporating health informatics, bench science, mathematics, statistics, and social sciences into classical and molecular epidemiology, we are able to understand disease transmission at all levels. This provides opportunities to profile health-related settings, predict healthcare risks, and establish innovative and effective health solutions. We work closely with members of the MRC Biostatistics Unit, Public Health England, the Cambridge University Hospitals?

**Thyroid hormones** are vital for fundamental processes including brain development, growth and controlling metabolic rate. We focus on nuclear hormone synthesis, by studying patients who have disorders that effect thyroid hormone metabolism and action. This includes resistance to thyroid hormone and lipoatrophy: insulin resistance associated with a specific gene defect that mediates lipid metabolism (PPARG). We use candidate genes and whole exome approaches to identify novel genetic aetiologies, which are accompanied by complementary studies that define their clinical phenotypes. Our research can be used to develop genetic tests and identifies biomarkers for use in a national diagnostic service for rare and unusual thyroid disorders.

We also study the molecular targeting and the delivery of lysosomal proteins to their sites of action, the pathogenesis of lysosomal diseases, and the development of new therapeutic solutions to improve patient health. This work will refine the interventions that are used to control associated disorders and several clinical trials of substrate-reducing drugs and enzyme therapies are underway.

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**CASE STUDY**

**Predictimmune**

Predicting patient outcome in inflammatory bowel disease

Professor Ken Smith, Dr Paul Lyons, Dr James Lee, & Dr Eoin McKinney

Department of Medicine

Inflammatory bowel disease (IBD) affects over 620,000 people in the UK, half of whom have an aggressive relapsing form of the disease. Research in the Department of Medicine found a transcriptional signature that is detectable within peripheral blood that correlates with the long-term clinical outcome in IBD. This work has led to a spinout company, Predictimmune Ltd that was created to translate this work into the clinic.

One in every three hundred people in the developed world has inflammatory bowel disease (IBD; comprising Crohn’s disease & ulcerative colitis) and its incidence is rising fast in developing countries. In the UK alone there are around 620,000 sufferers with an annual cost to the NHS of £1bn. Around half of patients have an aggressive, relapsing disease course, while in others the disease is more quiescent.

Unfortunately, prognostic markers that can reliably identify these patient groups are not available in clinical practice. This hinders disease management because patients with aggressive disease will be undertreated by conventional escalating dose therapy, while those with quiescent disease can be exposed to the risks and side-effects of unnecessary immunosuppression.

Research in the Department of Medicine found a transcriptional signature that is detectable within peripheral blood CD17+ T-cells (a type of white blood cell) at diagnosis, and which correlates with long-term clinical outcome in IBD. The signature reflects a process called exhaustion, in which T-cells progressively lose the ability to sustain an effective immune response. Patients following an aggressive disease course have less exhaustion than those with a quiescent course. However, translating these findings to the clinic originally presented a technical challenge as blood cell populations needed separating to see a signal, something that is not practical in a routine clinical setting. To meet this challenge our researchers utilised novel approaches to find a whole blood biomarker that could provide the same results without the need for cell separation.

The answer was to measure gene expression using microarrays and then use machine learning to identify the suitable whole blood biomarker. Ultimately, this led to the identification of a 15 gene assay that could identify different disease courses by stratifying patients into aggressive and quiescent types of IBD, and an independent, prospective multicentre study validated these findings.

Having established these principles, a spinout company, Predictimmune Ltd was created through Cambridge Enterprise to translate this work into the clinic. The prognostic tests it provides for immune-mediated conditions can aid disease management and improve patient outcomes. As differing IBD patients may require different treatment regimens, the test can ensure that they receive the most appropriate course of treatment and avoid excessive side effects resulting from over-treating the quiescent group, or excessive morbidity from under-treating the aggressive group. With funding from the Wellcome Trust, Predictimmune is also running a biomarker-stratified trial that is a first of its kind for inflammatory disease and will determine whether the biomarker can deliver personalized care.

The test uses a small blood sample to accurately predict each patient’s outcome at the point of diagnosis, and is available as a laboratory testing service and soon also as a kit. The group is also developing predictive tests for other immune-mediated diseases that pose long-term burdens on patients as well as imposing a financial burden on society. They include tests for lupus, multiple sclerosis, diabetes mellitus and rheumatoid arthritis.

www.biorxiv.org/content/10.1101/335135v1
www.med.cam.ac.uk/predict
www.predictimmune.com
Gastroenterology and Hepatology

Many digestive system neoplasms (e.g. gastrointestinal (GI) and liver diseases. This includes a wide range of GI diseases, with a specific focus on inflammatory bowel disease (IBD).

Cohn's disease and ulcerative colitis are both IBDs. The prevalence of these conditions has profoundly increased over the last decades, with the UK featuring one of the highest prevalence rates in the world. Our research has made substantial contributions to the discovery of the genetic risk landscape, and hence the hereditary component of Cohn's disease and ulcerative colitis. The basis for this has been the assembly of large patient cohorts, the latest initiative being the UK IBD BioResource. Our research has provided important leaps forward regarding cellular pathways affected by genetics. For example, we have found how autophagy and endoplasmic reticulum stress drive the disease process, and discovered entirely novel immunometabolic circuits that are important in Cohn's disease. We explore how these pathways interact with each other and how environmental factors may trigger the disease process in genetically-susceptible individuals. We have identified biomarkers that can predict the severity of disease at an early stage and reveal biological circuits that determine the severity of the disease. Our research translates into new therapies, which have the potential to contribute to phase I/II and phase IIIa/b studies, and the design and execution of large global phase III trials. We also monitor how alcohol damage DNA and what implications this has for alcohol-related liver disease, and for bone marrow failure in patients with primary biliary cirrhosis.

Infectious Diseases

Many infectious diseases epidemiologically and molecular studies on viruses and bacteria as well as their interactions with the cell and host immune responses. We study new treatments for the deadly liver disease alcoholic hepatitis, discovering key mediators that drive liver damage in this acute condition. We have made important contributions to the genomic risk landscape of primary sclerosing cholangitis and primary biliary cirrhosis, for which a national BioResource has been assembled. Affiliated researchers have developed innovative strategies to survey Barrett's oesophagus, a pre-malignant condition that can lead to oesophageal adenocarcinoma, and have made key contributions to the Cancer Genome Atlas.

Immunology

The major impact of immunological pathways in the pathogenesis of human disease makes immunology a key discipline in the Department of Medicine. Our vision is to understand the molecular mechanisms underlying immune-mediated disease and use these insights to inform new diagnostic and therapeutic strategies. In the last 25 years, these have defined the current standard of care and informed systematic reviews and international consensus management guidelines. This has led to the first study of B-cell depletion therapy in vasculitis which has resulted in subsequent Phase II studies and drug registration.

One third of all current medicines target G-protein coupled receptors (GPCRs). We explore the role of novel GPCRs identified from the human genome project, but until recently were not paired with the molecules that activate them. Our work helps to understand the role of these in cardiovascular disease, and we have developed novel compounds that are ideal as a laboratory tools and form the basis for new drugs for the treatment of cardiovascular conditions such as pulmonary arterial hypertension (PAH).

A major success of our division is our ability to bridge the gap between research and the clinic, by having an essential role in the translation of laboratory science into novel diagnostics and disease treatments.

During a heart attack, blockage of a coronary artery prevents blood flow to part of the heart (ischaemia). As a result, the mitochondria are deprived of oxygen and energy production stops. We have demonstrated that one of the mitochondrial fuels (succinate) builds up during ischaemia and is consumed by mitochondria via a route that produces oxygen radicals that destroy heart muscle. Lost heart muscle cannot be regenerated, leaving the patient with a weakened heart that is prone to recurrent heart failure. We identify therapeutic strategies that protect heart muscle in ischaemic hearts, reducing this potential for failure.

We also focus on the biological pathways, responsible for systemic hypertension and atherosclerosis, with a strong emphasis on basic physiology, experimental medicine and early phase interventional clinical trials. By assessing the effect of the disease, we develop and validate novel biomarkers. For example, a portfolio of studies on ANCA vasculitis has been co-ordinated from Cambridge over the last 25 years. These have defined the current standard of care and informed systematic reviews and international consensus management guidelines. This has led to the first study of B-cell depletion therapy in vasculitis which has resulted in subsequent Phase II studies and drug registration.

Molecular Immunity Unit (MIU)

Our overarching goal is to understand the molecular and cellular mechanisms of host immunity and viral and bacterial pathogenesis. We use diverse approaches that span structural, molecular, optical, chemical, and cellular biology, and utilise forward and reverse genetics to explore host susceptibility and microbial virulence. We employ cell culture based assays, primary cells and clinical samples, model organisms, and where appropriate human clinical studies, to understand key processes. Highlights of our research include how immune cells are capable of discriminating between healthy cells that we must retain and infected cells that must be eliminated, how antibody generation and function is regulated with a particular focus on improving kidney transplantation, and how specific tissue environments shape immune function and activation. We are interested in how the immune system responds to, and is sometimes subverted by, viral and bacterial pathogens. Finally, we are tackling the problems of antimicrobial resistance through the development of novel small molecule hypoxia signalling targeting agents with therapeutic potential.

Renal Medicine

The division of renal medicine includes groups working across five major areas, using a variety of computational, laboratory and clinical methods to pursue our research goals.

Regulatory mechanisms of hypoxia signalling: Oxygen is central to life and we are interested in the sensing machinery, in particular hypoxia-inducible factor (HIF). HIF regulates DNA transcription in response to changes in oxygen availability and shapes many aspects of behaviour at both the cellular and whole-organism level. It contributes to a range of cardiovascular and renal diseases, as well as the most common form of kidney cancer, clear cell renal cell carcinoma. We use multidisciplinary collaborative approaches to develop novel small molecule hypoxia signalling targeting agents with therapeutic potential.

Tumour necrosis factor (TNF) signalling. TNF mediates immunity and contributes to vascular disease. We are scrutinising its role in kidney inflammation and transplantation, using cell culture systems and histological analysis of primary human tissues.

Genomic and transcriptomic studies in autoimmune diseases: We have prospectively recruited and monitored cohorts of patients with autoimmune diseases (with a focus on small vessel vasculitis, systemic lupus erythematosus, inflammatory bowel disease) for more than ten years. Transcriptomics studies of peripheral blood immune cell subsets have allowed us to identify biomarkers/signatures that are predictive of long-term outcomes. Predictimmunize Ltd is a university spin-out company based on this research, and provides tools to guide physicians in the treatment of patients with immune-mediated disease. We have also investigated international consortia to perform genome-wide association study (GWAS) in vasculitis.

Regulation of antibody generation and effector function: IgG antibodies play a pathogenic role in a number of autoimmune diseases, and in transplant rejection. We have used an experimental medicine study to investigate the use of novel B-cell targeted immunosuppressants in transplantation, and use primary human cells and tissues, as well as murine models to investigate the cellular effector functions of antibody mediated by Fc gamma receptors.

Tissue-specific immunity in the kidney: The kidney is a unique tissue environment with regulatory programs and mechanisms that are specific to the kidney. We are investigating the immune landscape in human kidneys using single cell approaches.
Respiratory Medicine
Our research probes the cell biology, genetic and molecular foundations that underpin respiratory diseases such as chronic obstructive airways disease, cystic fibrosis, pulmonary arterial hypertension and tuberculosis.

We examine the development of pulmonary hypoxia, and determine how protein turnover is regulated in cells, with a focus on oxygen and nutrient sensing pathways. We observe how dysfunction of the endoplasmic reticulum leads to pulmonary pathology and identify key early molecular drivers of lung cancer to develop novel strategies for early detection and chemoprevention. We study the genetic and molecular mechanisms of pulmonary arterial hypertension (PAH) and translate these findings into experimental medicine studies of new treatments for PAH patients. We also lead national and international studies to elucidate the genetic architecture of PAH.

Our researchers strive to understand how bacteria interact with the immune system by using population-level genomics, forward and reverse genetic screens, and comparative biology to create novel antibiotics and host-directed therapies. Our research reveals the causes of dysfunctional cell signaling, gene transcription and vascular cell biology. It also suggests new approaches to rescue these deficiencies by gene therapy and by inhibiting the turnover of cellular components using existing drugs. This research has led to a university spin-out company, MORPHOGEN-IX to take these innovations to the clinic.

Rheumatology
We have a strong focus on understanding and treating human bone and joint diseases. We study osteoporotic fragility fractures and osteoarthritis by examining bone structure, shape and biology in health and disease. With the Engineering Department, this allows us to create state-of-the-art methods to diagnose osteoporosis and osteoarthritis with 3D imaging. This has been used to identify focal bone defects that lead to hip fracture, and to determine the beneficial effects of drugs and exercise regimens on bone health. With researchers from Bristol, we study the genetics of excessively high bone density, and have discovered a family from Cambridge with mutations that disrupt the binding of an important bone protein called sclerostin. Clinical blockade of sclerostin increases vertebral bone density by almost a quarter within one year. At this time, more than 20 clinical trials are being conducted by the Rheumatology Research Unit ranging from phase Ia to IV.

We have also identified the role of these stress signals in pathogen responses by experiments with Chlamydia trachomatis. This is a pathogen that has a large burden on society, by significantly contributing to the prevalence of sexually transmitted diseases, infertility and preventable blindness. By identifying a role for endoplasmic reticulum stress, this has allowed us to understand some of the fundamental mechanisms of how Chlamydia activates this pathway. Using multiplexed proteomic techniques that allow the relative abundance of Chlamydia and host proteins to be determined accurately, we now have the first opportunity to interrogate the Chlamydia-host protein response and closely inspect their interaction. This enables us to further address how this pathogen activates the cellular stress pathways and potentially develop new strategies to overcome the disease.

Cambridge Institute for Therapeutic Immunology and Infectious Disease
The Cambridge Institute for Therapeutic Immunology and Infectious Disease (CITIID) was established by the Department of Medicine to support both fundamental and translational research on human disease. It houses up to 250 scientists working within diverse research groups. Our work focuses on understanding the pathogenesis and improving the management of immune-related disorders such as Crohn’s disease, vasculitis, systemic lupus erythematosus and ulcerative colitis, and by transforming our understanding of how the infectious agents such as tuberculosis, enteric pathogens, HIV/AIDS, human cytomegalovirus and Zika virus interact with humans. There is also a strong focus on health issues of global importance, and on antimicrobial resistance. In particular, we work closely with key overseas partners including universities, agencies and industry to increase our global impact in a coordinated programme.

CITIID brings together geographically dispersed groups working on immunity and infection across the Cambridge Biomedical Campus. This stimulates new research alliances, enables recruitment, and promotes the development of early career scientists. By encouraging research at the clinical interface, for example in the Addenbrooke’s Centre for Clinical Investigation and with industry, CITIID also facilitates the translation of scientific discoveries into clinical benefits.

CITIID is primarily located in the Jeffrey Cheah Biomedical Centre, with its state of the art research laboratories alongside those of the Cambridge Stem Cell Institute and the Minkin Therapeutics Institute. CITIID also has a footprint in Addenbrooke’s Hospital to facilitate clinical translation, and incorporates the Molecular Immunology Unit that is embedded within the MRC Laboratory of Molecular Biology. Its location on the Cambridge Biomedical Campus places it at the centre of the Cambridge Cluster where it benefits from the proximity of several other major health-related organisations such as Royal Papworth Hospital, the MRC-LMB, CRUK Cambridge Institute and AstraZeneca’s global research and development headquarters. CITIID also has strong links with The Wellcome Trust Sanger Institute.

CITIID transforms immunity and infection research in Cambridge by providing researchers with advanced facilities that are in close proximity, and enables them to optimise work on human immune, inflammatory and infectious diseases. By bringing together its clinical capabilities and key industry partners, CITIID is also well-placed to drive therapeutic breakthroughs, improve patient outcomes and advance population health both in the UK and abroad.
We have programmes of basic, translational and clinical research addressing the determinants of pregnancy complications. Amongst our major research themes is the discovery of new biomarkers that will be clinically effective in predicting the outcome of pregnancy. With that goal, we have assembled a very large collection of data and samples from over 4,500 women. As well as the ultrasound data has already shown that third trimester screening dramatically improves the detection rate of small for gestational age (SGA) babies. Our ultrasound data and samples of placenta obtained at birth. This is being used to understand better the role of the placenta in determining adverse pregnancy outcome and, it is hoped, to identify novel biomarkers which may be clinically useful. A major component of this research involves tissue and single-cell RNA and DNA analysis. We make extensive use of mouse models to study key genes involved in murine placentation to better understand normal reproductive function. This includes study of placental and blood-vessel cells and detailed investigation of the function of the immune system in pregnancy. We are also interested in how genes are controlled, in particular how DNA methylation affects placental growth and function. We have collaborative links with the School of Biological Sciences, the Babraham Institute and the Wellcome Trust Sanger Institute.

**RESEARCH SYNOPSIS**
We have programmes of basic, translational and clinical research addressing the determinants of pregnancy complications. The major focus of our translational research is the analysis of a prospective cohort study of women in their first pregnancy in which we recruited 4,512 women and is funded by the NIHR Cambridge Biomedical Research Centre. We have created a central resource of data, blood samples collected throughout pregnancy, and samples of placenta obtained at birth. This is being used to understand better the role of the placenta in determining adverse pregnancy outcome and, it is hoped, to identify novel biomarkers which may be clinically useful. A major component of this research involves tissue and single-cell RNA and DNA analysis. We make extensive use of mouse models to study key genes involved in murine placentation to better understand normal reproductive function. This includes study of placental and blood-vessel cells and detailed investigation of the function of the immune system in pregnancy. We are also interested in how genes are controlled, in particular how DNA methylation affects placental growth and function.

**MAIN RESEARCH THEMES**
**Predicting pregnancy outcomes**
Amongst our major research themes is the discovery of new biomarkers that will be clinically effective in predicting the outcome of pregnancy. With that goal, we have assembled a very large collection of data and samples from over 4,500 women. Analysis of the ultrasound data has already shown that third trimester screening dramatically improves the detection rate of small babies. Our biological samples including maternal blood sampled four times during pregnancy, together with parental DNA and placental samples collected at the time of delivery, provide a unique resource.

We are currently analysing the active genes in healthy and abnormal placentas using high throughput RNA sequencing. These data will lead to the definitive description of genes that are active in the human placenta in health and disease. These analyses in combination with ultrasound have already led to the identification of new predictive biomarkers.

**Determining immune cell functions**
During pregnancy, two immunologically distinct individuals, the mother and fetus, are in intimate contact with the placenta at the interface. There are numerous immune cells at this site and we seek to determine their function. Using genetically modified mice and multispectral single-cell analysis we have shown that these immune cells play an important role in modulating the maternal blood vessels necessary to ensure a suitable blood supply to the placenta and required for optimal fetal growth.

**Identifying factors which determine the transfer of nutrients in the placenta**
A critical function of the placenta is the transfer of nutrients between mother and fetus. The appropriate matching of maternal supply to fetal demand is an important aspect of this. We seek to identify signals – metabolic or hormonal for example – that pass between the mother and fetus to achieve this balance.

We have identified one such factor which regulates the growth and function of the blood vessels within the placenta. Some of the genes that regulate these processes function differently depending on whether they are inherited from the mother or the father – so-called imprinting; therefore we also study how perturbations of this affect fetal growth.

These analyses exploit unique biological sample sets, genetically modified animals, and complex cellular and molecular analyses – all with the aim of deepening our mechanistic understanding of placental growth and function and with the expectation of translation to clinical utility.

**CASE STUDY**
A child born to a woman who had received third trimester screening was at an increased risk of neonatal morbidity. We showed that a subset of SGA fetuses who had normal birth weight were at an increased risk of neonatal morbidity. Our ultrasound data and samples of placenta obtained at birth. This is being used to understand better the role of the placenta in determining adverse pregnancy outcome and, it is hoped, to identify novel biomarkers which may be clinically useful.

The first main paper arising from the Pregnancy Outcome Prediction study, led by Dr Ulla Sovio and Professor Gordon Smith, involved analysis of screening pregnant women who had never given birth before. The results demonstrated that such screening among women with universal third trimester foetal biometry (measurements taken using ultrasound) tripled detection of SGA infants. The study also showed that a subset of SGA fetuses whose abdominal growth rate was slow were at an increased risk of neonatal morbidity.

“Paediatrics in Cambridge is at the heart of a global revolution that is re-imaging the way we think about health, and how disease prevention could start from birth.”

As part of a study to investigate pathophysiology of gut barrier dysfunction in critical illness, we are undertaking research into the role of gut-derived bacterial endotoxin in the pathophysiology of inflammation and organ dysfunction in critically ill children.

Oncology

The NHS paediatric haematology and oncology team is truly multidisciplinary and requires vital inputs from many individuals to allow the delivery of high quality patient care as part of clinical research trials. Our translational programme involves the study of genetic changes in solid tumours of childhood. We have identified that the same genetic changes seen in germ cell tumours may also be found in the patient’s bloodstream at the time of diagnosis, offering the potential to improve the accuracy of diagnosis, disease monitoring and follow-up.

Epidemiology and Population Science

Using genetic epidemiology and cohort studies, we examine early growth and puberty timing as predictors of disease risk. Our studies on mammalian sex development are applied to the management of infants with disorders of sex development (DSD). We examine the effects of environmental variants in genes controlling androgen production and action that appears to affect normal development, including growth at puberty. Much of this research is undersigned by the Cambridge Baby Growth Study (CBGS). The recent study explores the role of putative endocrine disruptors in the development of common (CSD) such as hypopituitarism.

Children’s Hospital and Cambridge Children’s Health Research Institute

Children’s Hospital and Cambridge Children’s Health Research Institute In 2019, we begin planning in earnest for a new Children’s Hospital that will serve the East of England region. Embedded within this hospital, Cambridge Children’s Health-Research Institute (CHR) will develop core genomic technologies for rapid turnaround diagnosis and stratified medicine. Our industry-facing approach will encourage clinical trials for children with rare diseases and will develop new paradigms for management of chronic diseases such as diabetes, inflammatory bowel disease, cancer and other conditions.

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RESEARCH SYNOPIS

We are a centre for teaching, research and clinical excellence in a range of topics. One focus is developmental neuroscience and genetics. We have set up an award-winning regional service for neonatal neuroprotection, with whole genome sequencing available in the neonatal intensive care unit (NICU), and paediatric intensive treatment unit (ITU) for diagnosis of children at risk of brain injury. We also incorporate basic science investigations of diversity of glial cells, leukodystrophy and origins of mental health conditions in children.

MAIN RESEARCH THEMES

Neuroscience

Our study of neonatal neurological care addresses the challenges of applying best research to improve clinical care for infants with brain injury, which has led to developing the neonICU, an award-winning regional service for neonatal neuroprotection in the East of England. The Evelyn Perrin Imaging Centre provides a dedicated facility to scan mothers, infants and children. We are also involved in neoLAB, a joint venture with University College London, developing novel optical and electrophysiological technologies to identify infants at risk of brain injury and developmental problems at an early stage. We investigate precision medicine focusing on applications of genomic technologies to diagnose and better understand the biological basis and rational treatment of rare neurological disorders. One area is the genetic factors that determine development and diversity of glial cells of the brain and their response to injury. We have initiated health records research to determine how genotype and long-term outcomes are linked over the life course with HDR-UK. We have active collaborations with the Departments of Psychology, Psychiatry and The Autism Research Centre.

Diabetes and Obesity

Our research examines the genetics and pathophysiology of diabetes and extreme obesity in children, aiming to identify primary prevention and improved treatments. We have launched the first international study of the use of ACE inhibitors and statins in adolescents with type 1 Diabetes (TED). Other studies of TED include the role of the growth hormone, IGF1. We have research that focuses on clinical testing of closed-loop insulin delivery in T1D. Under supervised conditions, overnight closed-loop insulin delivery reduced the risk of nocturnal hypoglycaemia and improved glucose control. We are exploring genetic, environmental determinants of size at birth, future growth and risk for adult disease.

Gastroenterology

We look at the epigenetics of the intestinal immune system in health and disease particularly inflammatory bowel diseases (IBD). Specifically, the impact of epigenetic mechanisms such as DNA methylation and histone modifications on regulating gene expression in purified cell subsets.

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Emeritus Professor of Paediatrics, Paul Ehrlich Laboratory, Sydney Medical School, University of Sydney. Professor Rowitch is a leading international researcher in investigative nephrology and renal histopathology. His research has involved the application of molecular techniques to elucidate the pathophysiology of renal disease and has allowed the identification of new therapeutic targets for vascular remodelling in primary hypertension and diabetic nephropathy. He is currently investigating the role of gut-derived endotoxin in the development of organ dysfunction following critical illness, with the aim of developing new therapies to ameliorate this process.

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RESEARCH SYNOPSIS
We strive towards international excellence through undertaking innovative research in medical imaging. Our team of academic radiologists work with imaging scientists to conduct oncological, cardiovascular, neurological and musculoskeletal imaging in different programmes of research. We develop novel imaging techniques and undertake phase I and II imaging studies in new technologies.

Situated within the Cambridge Biomedical Campus, we use both University and NHS machines to conduct imaging studies in Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), Computed Tomography (CT) and breast imaging. As part of our research activities, we make use of the new scanners at Addenbrooke’s Hospital, including our 3T MRI, five 1.5T MRI machines, PET CT and four CT machines together with a large ultrasound department and a nuclear medicine facility. In the University we have 3T MR machines, a 7T MRI machine and a PET MRI machine. The University cyclotron and Radiochemistry facility produce the widest range of radiotracers in the UK. We have hyperpolarised MRI-collocated with our PET MRI machine as well as one in the hospital facility. This provides us with extensive opportunities for innovative research in clinical imaging translating new tracers into clinical practice. We have preclinical facilities with MRI, PET and IVUS.

Our major strengths include novel imaging in MRI in order to develop and implement new sequences, multicentre trials, a strong preclinical programme, an exciting clinical hyperpolariser programme and optoacoustic imaging. We are home to a large biomedical engineering team, which mainly conducts cardiovascular imaging, and works on Artificial intelligence in imaging in conjunction with Oncology and the Centre for Maths in Healthcare Imaging.

MAIN RESEARCH THEMES
Cancer Imaging
We work closely with the CRUK Cambridge Centre delivering novel functional imaging in cancer trials as part of an Integrative Cancer Medicine programme in the major cancer types. We are studying radiogenomics and circulating tumour biomarkers to correlate with imaging findings. We use high quality multiparametric MRI imaging in breast, prostate, ovarian and renal cancer with novel functional imaging sequences, such as magnetization-transfer, diffusion kurtosis, sodium-MR imaging and tracers such as 11C-acetate and 11C-Gallium-PSMA-PET, combined with whole-body MRI. In breast imaging we are gathering evidence for a personalised approach for breast screening with trials of Abbreviated MRI, Automated Breast Ultrasound, Contrast Enhanced Mammmography and Digital Breast Tomosynthesis to overcome limitations of mammography in dense breast tissue.

"C-hyperpolariser imaging
We are pioneering Clinical hyperpolarized 13C MRI for the first European study of the method commenced in Cambridge in 2016. Tissue metabolism is imaged in real time by increasing the sensitivity of MRI by more than 10,000-fold. By focussing on the spatial distribution of the breakdown product of glucose, termed pyruvate, which is converted in lactate, we aim to image tumour metabolism. Our research covers breast, glioma, ovarian, prostate cancers and liver.

Neuroimaging
We use advanced MRI and PET techniques in high grade brain tumours, such as glioblastoma multiforme (GBM) and brain metastases, to better delineate the local extent of the tumour and to predict the pattern of its recurrence. As a result, we aim to improve the intra-operative diagnosis of high-grade glioma using a fluorescence biomarker (GALA-BECDO) and predicting sites of tumour progression in the invasive margin of glioblastomas (Pram-GBM).

Our neurovascular work focuses on morphological and functional MRI characterisation of atheromatous plaques, in particular on detecting vulnerable plaques that are prone to rupture, and are therefore principally responsible for thromboembolic events such as ischaemic stroke. We are also interested in using MRI to characterise biomechanics of the vessel, for example for detecting high levels of shear stress in the vessel wall that contributes to plaque instability. Our work on plaques in carotid arteries supplying the brain has important implications in other vascular beds, including the coronary vessels in the heart.

"Our team of academic radiologists work with imaging scientists to conduct oncological, cardiovascular, neurological and musculoskeletal imaging in different programmes of research."
RESEARCH SYNOPSIS

Central to our research strategy is a strong clinical emphasis and a shared mission to improve the surgical management of disease through basic and translational research, together with clinical trials. Our bench to bedside focus links laboratory work to applied clinical research and a key feature of the Department is the close integration of University and NHS surgeons. University surgeons, in parallel with directing programmes of research, play an important role in the development and delivery of specialist surgical services.

Our experimental medicine approach features advanced imaging and tissue analysis (including at a molecular level) and aims to improve stratification of patient groups so as to better match the timing and type of treatment. Our clinical themes are transplantation, trauma and orthopaedic surgery, urology and vascular surgery which are aligned to world class underpinning research strengths in stem cell medicine, immunology, organ perfusion, cell biology and surgical oncology. Across the Cambridge Biomedical Campus, world class surgical research also takes place within other Institutes and Departments, for example Gastrointestinal Surgery, Neurosurgery, Otolaryngology, Ophthalmology, and Plastic Surgery.

We are committed to high-quality education, including clinical and non-clinical students, at undergraduate and postgraduate levels. We look to train the next generation of academic surgeons and enjoy a large and vibrant academic surgical training programme including Academic Foundation Doctors, Academic Clinical Fellows and Clinical Lecturers.

We collaborate widely within the School of Clinical Medicine, more widely across the University, and externally, both nationally and internationally.

MAIN RESEARCH THEMES

Transplantation

We have been at the international forefront of clinical developments in organ transplantation for many years. Our world-renowned clinical programmes in abdominal organ transplantation, at the Cambridge University Hospitals NHS Foundation Trust, and thoracic organ transplantation, at the Royal Papworth NHS Foundation Trust, are each underpinned by well-established multidisciplinary research programmes. Our research is also part of the National Institute of Health Research (NIHR) Blood and Transplant Research Unit in Organ Donation and Transplantation, which is a joint unit in collaboration with Newcastle University. The strategic aim of the NIHR unit is to develop and evaluate novel technologies that increase the number of suitable organ donors in the UK and to improve long-term transplant survival. Our translational approach has consistently produced basic and translational clinical research that has received many national and international prizes and awards. There are strong programmes of basic research into the molecular basis of allograft rejection and analysis of physiochemical properties determining the immunoporosity of HLA (tissue matching) molecules, leading to development of a novel means of improving the accuracy of organ matching and therefore to reduce transplant rejection episodes.
We have an interest in the field of repair and regenerative therapies in orthopaedic surgery, particularly for a disease called osteoarthritis (OA), which affects around 8 million people in the UK alone. Our research encompasses basic sciences, translational and clinical research and relates to mechanisms of disease and the action of therapy. Our experimental medicine approach includes advances in the imaging of bones and joints and more detailed understanding of disease by tissue analysis. We facilitate Cambridge Musculoskeletal Sciences, which is an interdisciplinary approach to musculoskeletal research across Schools and Departments. We have a programme: the Arthritis Research UK Tissue Engineering Centre. This brings together leading UK clinicians, engineers and biologists to develop stem and stromal cell therapy for the generation of artificial tissues and organs.

We are closely aligned with the Cambridge Regional Vascular service and have a major focus on the clinical evaluation of innovative techniques and novel devices in vascular surgery. In association with NHS vascular surgeons, we are undertaking research to evaluate endovascular repair of aortic aneurysms, and performing studies in peripheral vascular disease, leg ulceration, remote ischaemic pre-conditioning and aspects of the diabetic foot. The introduction of NMP in Cambridge has led to the successful transplantation of a series of kidneys and livers that were declined by other transplant units that deemed them untransplantable. On-going research is developing new biomarkers and personalised prognostic stratification tools. A series of studies in new biomarkers are being investigated for early detection as well as for potential screening in partnership with academic, biotech and industry partners.

The results of the multi-organ transplant programme are some of the best in the world. Similarly, kidney transplants release patients from dialysis and pancreatic transplants remove the need for daily insulin injections in patients with diabetes. In the long term kidney transplantation, and combined kidney and pancreas, are much cheaper than life on dialysis thus ultimately reducing the cost to the NHS.

Funding: Kidney Research UK and National Institute for Heath Blood and Transplant Research Unit (BTRU)

Professor Chris Watson, Professor Michael Nicholson, Dr Sarah Hosgood, Mr Andrew Butler

The Department of Surgery, at the University of Cambridge, has been leaders in introducing transplant organ perfusion systems into clinical practice in the UK. Normothermic machine perfusion is a novel method for the preservation of kidneys and livers before transplantation. Traditionally transplant organs are stored on ice at 4°C and although this is simple and relatively effective it does have limitations and organs deteriorate during storage. Normothermic machine perfusion (NMP) involves circulating an oxygenated red cell-based solution through the donor organ in order to mimic the conditions in the human body. This NMP technique has a number of advantages over cold storage; it can condition organs that have sustained some injury prior to their removal from the donor and it can be used as an ex-vivo pre-transplant assessment platform to determine whether a kidney from, for example, an elderly donor with hypertension has sufficient functional capacity to yield a successful transplant. In a similar way, NMP can be used to assess the suitability of donor livers for transplantation.

The introduction of NMP in Cambridge has led to the successful transplantation of a series of kidneys and livers that were declined by other transplant units that deemed them untransplantable. On-going research is developing organ perfusion machines as a new method of delivering treatments to kidneys before they are transplanted. This technique allows accurate targeting of therapies to the kidney without causing any harmful effects in the transplant patient. This will allow the testing of treatments designed to reduce transplant rejection.
We are committed to making an impact on dementia, ageing and Alzheimer’s disease, cardiovascular and metabolic diseases, rheumatology, auto immune diseases, rare blood disorders, oncology, blood-borne viruses, respiratory infections and antibiotic resistance.

We work with leading trial centres, clinical departments, epidemiology groups and public health bodies such as Public Health England. We are developing links with major programmes in stratified medicine and in big data analytics such as Health Data Research UK and the Alan Turing Institute.

The work of Dr Daniela De Angelis and her team has changed the nature of HIV research. Indeed, thanks to their novel evidence synthesis approach, it is now possible to accurately estimate HIV prevalence within populations. This has contributed to the improvement of health care and overall public health.

Human immunodeficiency virus (HIV) damages the immune system and weakens the body’s ability to fight infections. Shortly after infection with HIV, most people suffer with a flu-like illness. This is typically followed by no further symptoms for a long period whilst the virus continues to damage the immune system. As a result, many people with HIV are unaware that they are infected. Early diagnosis and treatment would provide the best prognosis for infected individuals.

Dr Daniela De Angelis and her team have developed a new methodology to estimate the HIV burden. They use the Multi-Parameter Evidence Synthesis (MPES) to generate such estimates; this approach applies statistical methods to characterise HIV prevalence through fully and correctly exploiting the complex body of available information on different aspects of the infection.

MPES has been, and continues to be, the chosen method to obtain UK official annual estimates of the number of individuals living with HIV, particularly the number of those unaware of their infection. Estimates of undiagnosed HIV infections have underpinned public initiatives to encourage HIV testing in order to ensure the earliest possible treatment. For example, the “Halve It” campaign, which aims to halve the proportion of undiagnosed infections by 2030, the Terrence Higgins’ Trust “It Starts with Me” campaign, and the National HIV Programme for England, all rely on information provided by Dr De Angelis and her colleagues.

The MPES framework has also been adopted by European organisations to estimate HIV burden elsewhere. Indeed, the BSU has collaborated with organisations in the Netherlands and Poland to generate such estimates. The framework has also been used to characterise other epidemics across the globe. For instance, MPES has been used to quantify flu severity in both the UK and the USA, and to produce estimates of Hepatitis C prevalence in the UK.

www.iph.cam.ac.uk/public-health-policy/case-studies/hivstatistics

**CASE STUDY**

**Novel approach**

**Statistical methods to influence HIV policy**

**Daniela De Angelis**
MRC Biostatistics Unit

**“Statistics is applicable in all aspects of medicine, epidemiology and public health. It is fundamental for designing clinical trials, modelling disease programmes, asserting the influence of the genetic make-up of our health, as well as evaluating the effectiveness of public health policies.”**
in, so it can be recycled by the molecular machine mitochondria and brings the spent fuel (ADP) back which transports the cellular fuel (ATP) out of

Molecular basis for inherited mitochondrial disease
We are interested to identify and characterize new disease genes responsible for primary mitochondrial disorders, define the factors and mechanisms involved in the formation, activity and quality control of the mitochondrial respiratory chain and develop and test new therapeutic approaches to mitochondrial disorders.

Mitochondrial genomics and human diseases
We aim to understand the molecular mechanisms regulating mitochondrial genome maintenance and expression, and to provide technologies for the genetic modification of mammalian mitochondrial DNA.

Mitochondrial complex I: from molecular mechanism to human disease
Complex I is a crucial enzyme in oxidative phosphorylation and a major contributor to cellular reactive oxygen species production. We combine structural, biochemical and functional methods to understand how human complex I functions on the molecular level, and to elucidate the role of complex I dysfunctions in genetically, environmentally and pharmacologically-linked mitochondrial diseases.

Understanding transport processes in mitochondria
We study mitochondrial cell biology and focus on the mechanisms regulating mitochondrial dynamics and organelle contact sites. We use microscopy, cell biology and biochemical approaches to understand how mitochondrial morphology and inter-organelle contact sites are affected by the metabolic state of the cell or by different genetic mutations, and how these events contribute to cell physiology and diseases progression.

Mitochondrial redox biology in health and disease
We investigate how oxidative damage to mitochondria contributes to human pathologies and how mitochondrial ROS alters the activities of proteins in putative signalling and protective pathways by reversibly modifying the redox state of critical protein thiols in mitochondria. We use a range of free radical and proteomic approaches to identify the proteins and residues involved, and their modifications.

“Ours aims are to understand the fundamental processes taking place in mitochondria and their involvement in human diseases.”

Our focus for therapy is the ischaemia/reperfusion injury that arises from stroke and heart attack.

Mitochondrial gene maintenance and expression in human health and disease
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Researchers and academic staff of the Department of Clinical Neurosciences, University of Cambridge, have demonstrated that people taking anti-inflammatory drugs are less prone to cognitive impairment.

Evidence that inflammation is present in the brains of people with Parkinson’s disease, spastic paraplegia, movement disorders and neurodegenerative diseases. Whole genome sequencing is revolutionising our capacity to diagnose rare neurological disorders, with the prospect of a comprehensive diagnostic test for all diseases in the future. Working with the NHR Translational BioResource, we are harnessing these advances to develop personalized treatments based on a precise genomic diagnosis, including small molecule and gene therapy approaches. Using cell and animal models we are defining disease mechanisms, and working with the pharmaceutical industry to develop new therapies.

Treating inflammation in the nervous system

We are ambitious about conducting innovative therapy trials across all diseases of the nervous system involving inflammation. Our research partnerships have shown that – 7% of people with early Parkinson’s have serum antibodies directed against neuronal membrane targets, and that they seem to respond to immunotherapy in open-label studies. This underpins a randomised placebo-controlled national multicentre trial to test this innovative treatment approach for the first time.

Evidence that inflammation is present in the brains of people with neurodegenerative disease is increasing, but its causal role remains unclear. We have demonstrated that people taking anti-inflammatory drugs are less prone to dementia associated with Parkinson’s disease, and that Parkinson’s disease is associated with an inflammatory serum cytokine profile and abnormal peripheral blood lymphocyte phenotype. We will conduct the first placebo-controlled trial of an immunosuppressant in people with Parkinson’s disease to prevent cognitive impairment.

**MAIN RESEARCH THEMES**

Rare neurological disorders

We play a key role in the 100,000 Genomes Project, studying rare neurological disorders, based on our track record of gene discovery in mitochondrial diseases, inherited ataxia, spastic paraplegia, movement disorders and neurodegenerative diseases. Whole genome sequencing is revolutionising our capacity to diagnose rare neurological diseases, with the prospect of a comprehensive diagnostic test for all diseases in the future. Working with the NHR Translational BioResource, we are harnessing these advances to develop personalized treatments based on a precise genomic diagnosis, including small molecule and gene therapy approaches. Using cell and animal models we are defining disease mechanisms, and working with the pharmaceutical industry to develop new therapies.

**RESEARCH SYNOPSIS**

Our aim is to understand the nervous system in both health and disease in order to develop new treatments for intractable neurological disorders. Embedded within the Cambridge University Hospitals, our research aims to solve problems we have encountered in the clinic, and directly address the needs of patients and families. Working in close partnership with the Departments of Psychiatry, Genetics and Ricketsiology, we use innovative cross-cutting technologies which link the laboratory and the clinic to unravel the mechanisms of brain disease that impact from childhood to old age. We use genetics and genomics, to study rare and common neurological diseases, cell biology and human stem cells, model organisms, and state-of-the-art human brain imaging through the Wolfson Brain Imaging Centre, which we host, along with a UK Dementia Research Institute centre.

New treatments, tested in the clinic, are now in use worldwide. These include; immunological treatments against brain inflammation including multiple sclerosis, surgical and metabolic interventions to reduce the impact of head injury; understanding the causes and consequences of stroke, preventing the loss of vision and hearing, and developing new treatments to stop neurodegeneration and dementia including Parkinson’s disease and Alzheimer’s disease.

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Having established Alemotuzumab as an effective anti-inflammatory therapy for multiple sclerosis, we now tackle the post-inflammatory phase of the disease by testing a novel remyelinating therapy, a licensed retinoid X receptor agonist against.

**Traumatic brain injury and disorders of consciousness**

Our neurotrauma research, between Neurosurgery and Anaesthesia, aims to enhance the understanding of mechanisms of brain injury to develop novel treatment strategies to improve clinical outcomes. We have developed model brain monitoring of intracranial pressure (ICP), brain oxygen and microdialysis, all undeployed by ICM+ software, which is now licensed to 100 centres worldwide. We have also developed PET/MRI imaging paradigms for critically ill patients, and computationally cerebral fluid infusion tests for hydrocephalus and shunt malfunction. This is linked to a national shunt registry, which we lead, and aims to refine the indications for shunt use and avoid unnecessary surgery.

We have developed novel treatments through randomised controlled trials in several indications, including central venous stenting, decompressive craniectomy (RESCUE studies), chronic subdural drains and desmopressin, and silver external ventricular drains. Building on our successes, our future strategy involves networked brain monitoring studies, state-of-the-art brain imaging and clinical trials. Our work will deliver personalized targeted therapies for neurotrauma in real-time by modulating brain metabolism and neuroinflammation, with both surgical and technological interventions underpinned by ICM+ software. We are strongly committed to improving outcomes in low and middle income countries embedded within the NIHR Global Neurotrauma Research Group, hosted within the Department.

**Hearing and vision**

We study the mechanisms of neurodegeneration in optic nerve diseases, particularly glaucoma, and we are developing new treatments to protect and regenerate the optic nerve using gene therapy and stem cells. A major focus is to develop an effective gene therapy for glaucoma progressing towards blindness despite current medication treatment. Our team was runner-up in the UK Government’s Biostart Synthetic Biology Competition and has secured funding to progress this work towards the clinic. National cohorts of patients with genetic eye diseases provide us with a key resource, as they enable new disease gene discovery, deep phenotyping, and biomarker profiling, which will lead to personalised therapies. These particularly involve gene therapy for inherited optic neuropathies caused by mitochondrial dysfunction.

The Cambridge Eye Institute integrates translational research into the very large clinical cohort in the Ophthalmology, Neurology, Skull Base and Auditory Implants programme at Addenbrooke’s Hospital. We focus on measures of neurophysiological mechanisms underlying patient symptoms and disease manifestations, and have a very strong collaboration with the Department of Engineering. Projects include the development of novel sensors to measure electrical stimulation spread in cochlear implant models and patients; novel psychoacoustic and electrophysiology tests to determine auditory lesion site; wearable technologies to interrogate relevant physiology and its dysfunction within the patient environment; and new multimodal sensory tools for balance rehabilitation.

**Neurodegeneration and dementia**

Our research ranges from genetic, molecular and cellular models of neurodegeneration through the characterisation of human neuropathology of dementia, to early phase clinical trials. Our success is built on the effective integration of clinical and preclinical research programmes with major specialist NHS services. We have strategic partnerships with the UK Dementia Research Institute (hosted within the Department), the MRC Laboratory of Molecular Biology, the Alzheimer’s Research Drug Discovery Unit, the NIHR Biomedical Research Centre, Departments of Psychiatry and Public Health and Primary Care, and the Wolfson Brain Imaging Centre.

Our clinical research programmes build on our longstanding natural-history studies of Parkinson’s disease, Alzheimer’s disease and Mild Cognitive Impairment, Frontotemporal Dementia, Progressive Supranuclear Palsy, Huntington’s disease, Normal Pressure Hydrocephalus and Vascular Dementia. Our clinical cohorts support biomarker development and validation, genetics and cognitive neurosciences, and are the foundations for multiple intervention studies. We are particularly specialised in early-phase clinical trials, which vary from experimental psychopharmacological agent trials to novel cell-based therapies and gene therapies, in precision cohorts with deep phenotyping for stratification and endpoint analysis including novel cognitive and imaging biomarkers.

With our preclinical programmes we have discovered the genetic associations of Alzheimer’s disease and Frontotemporal Lobar Degeneration, and the specificity of molecular multifactorial and connectively biased spread in the brain. The molecular biology and -syndromes and tau, their aggregation and autophagy, and the mechanisms of cellular injury and tolerance through unfolded protein responses (UPR) has led to the development of novel therapeutics and clinical trials. Together our preclinical and clinical research programmes are actively engaged with academic and pharmaceutical industries, delivering novel therapeutics to treat and prevent dementia.

**Wolfson Brain Imaging Centre (WBIC)**

We host Europe’s most comprehensive brain imaging facility for human research, which has the capacity to conduct research from fundamental cognitive and metabolic science to translational research in mental health and dementia, to biomarker-based mechanistic trials. Our facilities include both PET-MRI, MRI hyperpolariser and 7T Terra MRI for ultra high field MRI, MagSTIM transcranial magnetic stimulation and both shielded and mobile EEG units. In partnership with the Department of Radiology, and the MRC Cognition and Brain Sciences Unit, PET CT and Magnetoencephalography are also part of the brain imaging portfolio. Our PET imaging is supported by a coalition for IC and FE ligands, with state-of-the-art radiopharmacy for novel ligand development and early clinical pull-through. The imaging facility is placed directly between the Neuro-Intensive Care Unit and the Herschel Smith Building Clinical Research Facility, providing ease of access for patient studies, from the most severely ill to healthy out-patient cohorts.

The value of brain imaging is magnified by our commitment to advanced informatics, and to the integration of imaging innovations within precision cohorts. Imaging data are analysed at the University’s High Performance Hub for Informatics, with internal leadership in connectomics and lifespan cohorts. We also work upstream in linking imaging research within electronic healthcare records. These augment the long term cohort studies in development, aging, genetic and degenerative disorders. Together, the imaging and analysis of brain structure, function, and pathology provide unparalleled resources for translational medicine that differ significantly from normal human ones, and they are controlled by different mechanisms. We want to understand these differences in structure, function and regulation so as to devise drugs to kill pathogenic bacteria by stopping their turbines without influencing the human ones.

**CASE STUDY**

**Head first**

**Reshaping the treatment of traumatic brain injury**

**Professor Peter Hutchinson**

Department of Clinical Neurosciences

**Professor David Menon**

Department of Medicine

Collaborative research led by Professor Peter Hutchinson and Professor David Menon has the potential to revolutionise the treatment of traumatic brain injury by identifying the best methods of treatment.

Aiming from multiple causes such as transport accidents, assaults, falls or sporting injuries, traumatic brain injury (TBI) affects 10 million people a year worldwide and is the leading cause of death and disability in children and young adults. However, both the pattern of brain damage between patients and the eventual outcome are highly variable – making it extremely difficult to link particular characteristics of a TBI to an optimum treatment and improved outcomes.

As an incredibly complex disease in our most complex organs, research in TBI needs to bridge traditional disciplines to understand brain injury – and crucially, needs to collect a robust evidence base at scale in order to identify the most effective treatments. This is the approach taken by neurotrauma research at Cambridge, which spans the Divisions of Neurosurgery, led by Professor Peter Hutchinson, and Anaesthesia, led by Professor David Menon.

To link diagnosis, treatment and outcome following brain injury, Professor Hutchinson and his group have developed a combined monitoring technology to measure brain pressure, oxygenation and chemistry, explaining that, “A better understanding of brain injury puts us in the best possible position to improve patient outcomes and to shed light on effective treatments”.

The team also led international studies to assess novel treatments, including the RESCUE trials to evaluate decompressive craniectomy in TBI. This work is supported by the Academy of Medical Sciences, the European Commission, the Evelyn Trust, Health Foundation, NHS and the NIHR Cambridge Biomedical Research Centre, MRC, and the Royal College of Surgeons of England.

“International collaboration is vital to characterise TBI as a disease and to identify the most effective clinical interventions,” explains Menon. With this in mind, the neurotrauma team alongside Andrew Maas from Antwerp, are leading the Collaborative European Neurol Trauma Effectiveness Research in TBI (CENTER-TBI) project, which aims to provide large-scale evidence on which to base best practice treatment. In total, data will be collected for 20,000—30,000 patients, including extremely detailed data for over 5,000 patients, allowing both detailed and statistically powerful analyses.

Further afield, the team have also set up the Global Health Research Group on Neurotrauma in collaboration with colleagues and partners in low and middle income countries (LMCs). This initiative will translate these major gains in the management of TBI to improve the prevention, investigation, treatment and outcome of head-injured patients in LMCs.

This collaborative research provides an unparalleled opportunity to refine both the clinical characterisation of TBI and to develop individually on-going disability after a serious TBI. In order to establish a robust evidence base for the procedure, the RESCUE trial carefully evaluated patient outcome, enrolling 487 patients from 52 centres in 20 countries around the world. The trial demonstrated lower rates of mortality and severe disability associated with decompressive craniectomy when compared against standard medical treatment.

“International collaboration is vital to characterise TBI as a disease and to identify the most effective clinical interventions,” explains Menon. With this in mind, the neurotrauma team alongside Andrew Maas from Antwerp, are leading the Collaborative European Neurol Trauma Effectiveness Research in TBI (CENTER-TBI) project, which aims to provide large-scale evidence on which to base best practice treatment. In total, data will be collected for 20,000—30,000 patients, including extremely detailed data for over 5,000 patients, allowing both detailed and statistically powerful analyses.

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This collaborative research provides an unparalleled opportunity to refine both the clinical characterisation of TBI and to develop individually targeted care. Professor Hutchinson concludes, “There are many treatments that show promise, we can move to a more personalised approach for TBI based on knowledge of which treatment works best for whom and under what circumstances, these studies could benefit millions of people.”

Hutchinson PJ et al. NEJM 2016; 375(12):1119-1130

Maas AM et al. Neurosurgery 2015; 76(3):47-50

This work is supported by the Academy of Medical Sciences, the European Commission, the Evelyn Trust, Health Foundation, NHS and the NIHR Cambridge Biomedical Research Centre, MRC, and the Royal College of Surgeons of England.
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RESOURCESYNOPSIS

Our research promotes the mission of the University of Cambridge to contribute to society through the pursuit of education, learning, and research at the highest international levels of excellence. We particularly focus on the determinants of mental health conditions, their treatments and the promotion of mental health through innovative translational research.

We maintain close working relationships with the Cambridgeshire and Peterborough Foundation NHS Trust and the Cambridge University Hospitals NHS Trust. We also enjoy extensive interactions and on-going collaborative projects with other university departments and have many national, international and industrial collaborations.

Our areas of research include cognitive neuroscience, neuroimaging and neuropsychiatry; developmental psychiatry, old age psychiatry, epidemiology and health services research and molecular neuropathology. We are active in teaching psychiatry and related sciences at several different levels and maintain significant clinical activities.

MAIN RESEARCH THEMES

Autism

The Autism Research Centre (ARC) has major research programmes that examine perception and cognition, screening and diagnosis, intervention, genetics and proteomics as well as neuroscience and synaesthesia.

Brain mapping

Our core interest, within the Brain Mapping Unit, is to use advanced brain scanning techniques, primarily magnetic resonance imaging (MRI), to map the structure and function of the human brain. We are particularly interested in mapping normal memory and learning, ageing, drug effects on brain function, and neuropsychiatric disorders such as schizophrenia, autism and depression.

Drug addiction

We investigate the effects of chronic drug use on brain function, question how occasional drug use turns into addiction in some people, what renders some people vulnerable for developing dependence whilst others remain resilient to the addictive effects of drugs. Research aims to elucidate the neurobiological substrates of vulnerability and resilience for drug dependence.

Intellectual & developmental disabilities

The Cambridge Intellectual & Developmental Disabilities Research Group examines the health experiences of adults with learning disabilities. We also look at epilepsy in adults with intellectual disabilities and dementia in people with Down’s syndrome.

Developmental psychopathology

NSPN (Neuroscience in Psychiatry Network) is a venture from the University of Cambridge and University College London where we are researching how the adolescent mind and brain develops into early adulthood. The NSPN includes the ROOTS study, which has the primary aim of determining the contributions of genetic, physiological, psychological and social variables to well-being and the emergence of mental health problems during adolescence.

We are involved in the Improving Mood with Psychoanalytic and Cognitive Therapies (IMPACT) trial, which is the largest clinical trial of psychological therapies for adolescent depression. We are also part of the Systemic Therapy for At Risk Teens (START) trial, which is a multicentre UK-wide randomised controlled trial of multisystemic therapy (MST) developed for young people and their families who are having trouble with life challenges.

Cambridge EpiCentre group

Our Cambridge EpiCentre group works at the interface between population-based research, neuroscience and clinical psychiatry in order to understand the causes, mechanisms and treatments for psychosis (particularly schizophrenia) dementia, depression and bipolar disorder.

Health neurosciences

Our health neurosciences projects focus on two areas of human clinical research, the neurobiology of mental illness and the cognitive neuroscience of appetite and over-eating.

Old age psychiatry

Our work aims to improve the diagnosis and management of neurodegenerative dementia of Lewy body type in the NHS. We use multimodal imaging in Lewy Body disorders to determine the predictors and outcomes of people with dementia.

Overall, our aims are to enhance our understanding of the neural basis of cognitive, emotional and behavioural dysfunction in order to develop effective pharmacological and psychological treatments.

CASE STUDY

‘Heilbladé’ psychosis

A computer game that explores real-life mental health issues

Professor Paul Fletcher
Department of Psychiatry

Ninja Theory

Game development

Hallucinations and delusions are psychotic symptoms that occur in mental health. Professor Paul Fletcher and colleagues studied the emergence of this loss of contact with reality based on current models of normal brain function. The research showed that early psychosis and psychosis proneness both entail a basic shift in visual information processing, favouring prior knowledge over incoming sensory evidence. The research led to a collaboration with the games company, Ninja Theory, who developed a computer game based on the experiences of people living with psychosis.

The team of researchers based at the University of Cambridge and Cardiff University explored the idea that hallucinations arise due to an enhancement of our normal tendency to interpret the world around us by making use of prior knowledge and predictions.

The team worked with clinical individuals experiencing early psychosis and nonclinical individuals with high levels of psychosis proneness, who showed that their visual perception was characterised by a shift that favours prior knowledge over incoming sensory evidence. Given that these alterations in information processing are evident early on in psychosis and even in association with subtle perceptual changes indicating psychosis proneness, they may be important factors contributing to the emergence of severe mental illnesses.

Ninja Theory worked with Professor Fletcher to develop a game based on mental health. By speaking to people about their hallucinations the data could be translated to the small screen. The game ‘Heilbladé’ (Latin: scintilla) was part of a more realistically immersive approach to sharing the hallucinatory world of psychosis.

“We particularly focus on the determinants of mental health conditions, their treatments and the promotion of mental health through innovative translational research.”

“Something like a video game offers really unique opportunities to represent these experiences because the player is so immersed in it. I've had some fairly in-depth conversations with the team about ways in which this sort of technology, whether games or virtual reality, could usefully be applied in my work. For example, either in medical education or beyond that even in therapeutic approaches to patients with mental illness.” – Professor Paul Fletcher, University of Cambridge.

Critically, the game’s impact in representing a neglected and misunderstood form of mental illness has been unique. Opening up a widespread, mature and reflective conversation across social media with feedback from those who have suffered directly or indirectly from mental illness has been frequent and gratifying.

Tsvel, C et al. PNA, 12 Oct 2015

The Welcome Trust and the Bernard Wolfe Health Neuroscience Fund supported this work, with additional support from the MRC.
Our research investigates fundamental human cognitive processes such as attention, language, memory, and emotion.

MAIN RESEARCH THEMES

Our mission is to advance mechanistic understanding of human cognition, and to use these advances to benefit human health and wellbeing across the lifespan. Our research spans five overlapping themes: sensory and neurological disorders, ageing and dementia, fundamental cognitive neuroscience, childhood development and mental health. Cross-cutting these topics are particular methodologies, cohorts and clinical activities. Methodologies include behavioural experiments, individual differences, computational modelling, neuroimaging and neuromodulation. Cohorts include: (i) a large healthy volunteer panel, (ii) a cohort of 800 children with typical and atypical cognitive development (CALM), (iii) the Cambridge Centre for Affective Disorders (C2:AD) for individuals with disorders of anxiety and depression, (iv) a cohort of 3000 adults from 18 to 88 years of age (CamCAN), (v) a neuropsychological cohort of 330 individuals with brain damage (CCNRP), (vi) Centre for Frontotemporal Dementia, and (vii) Centre for Parkinson Plus. Our on-site research facilities include a T1 and T2-weighted magnetic resonance imaging (MR) scanner, several electroencephalography (EEG) devices, and a 306-channel magnetoencephalography (MEG) scanner. We are co-stakeholders in the ITN MRI facility at the WBC.

The CBU's clinical research activities are considerable and span paediatric, adolescent and adult neurology, neuropsychology, psychiatry and neurosurgery. These activities include: Numerous neuropsychological studies of memory, affective control, attention, executive function, language, perception, Atypical development in neurodevelopmental disorders including cognitive, social and neurodevelopmental conditions; Multivariate, objective, longitudinal and high-resolution brain imaging data (MR, PET, EEG, MEG, fMRI, ECoG) in children and adults; and Multivariate, high-resolution neuroimaging datasets for autism, ADHD, Tourette’s, bipolar disorder, schizophrenia, and other neuropsychiatric and neurodevelopmental conditions.

Some recent major achievements include the systematic examination of cognitive training (‘brain games’), revealing limitations in the extent to which the training generalises to educational achievement, but also for future improvements. We have identified how ageing affects brain structure and function, and how these changes, in turn affect memory and reasoning. We have advanced early detection and differentiation of the different forms of dementia and neurodegenerative disease. We have developed new tests and interventions to help recovery of cognitive and language functions after stroke and inform the design of cochlear implants to improve hearing, particularly for speech in noisy environments. We have also investigated and evaluated mindfulness interventions in adolescents with mental health problems. In addition, we contribute strongly to training (e.g., advanced analysis of neuroimaging data) and communication of our research to the public, clinicians, psychologists and educators.

Our future ambitions focus on international leadership in fundamental neurocognitive science, and forward and reverse translation of theory to treatment of brain disorders and mental health, particularly in the context of transdiagnostic approaches that identify core cognitive deficits underlying multiple disorders. We will continue the maximal exploitation of our unique cohorts through frequent longitudinal assessment and harmonisation with other national (e.g. CPUK/BrainBank) and international (e.g. European) cohorts. Our research will continue to advance applications of neuroimaging methods, including high-field MRI, as well as interventional recording and stimulation during neurosurgery. We will continue to lead by example in sharing our science and data as part of the open science movement, and continue to grow our collaborations with other University Departments including Psychiatry, Psychology and Clinical Neurosciences.

Over the past 20 years, researchers at the Medical Research Council's Cognition and Brain Sciences Unit (CBU) have been developing mindfulness-based interventions (MBIs) - a form of psychological training - to prevent the onset and recurrence of common mental health problems, such as depression. The worldwide burden of these problems is alarmingly high, and efforts to expand the provision of clinical treatments for sufferers urgently need to be supplemented by preventative approaches for those who are currently well but at high risk.

MBIs target the maladaptive psychological processes that underpin such risk using a combination of education and systematic practice in attentional control and regulation. For example, Mindfulness-Based Cognitive Therapy (MBCT) can be used for the prevention of depressive relapse in those with a significant history of depression but who are currently not depressed. MBCT was developed at the CBU by John Teasdale and colleagues in the late 1990s. Recently, Dr Tim Dalgleish at the CBU, in collaboration with colleagues at the University of Exeter, reported the results of the first large scale treatment trial comparing the effects of MBCT to staying on anti-depressant medication: the NHSCR HTA funded 906/0107 trial. PREVENT showed that a single, 8-week course of MBCT was as effective in preventing depressive relapse as remaining on medication.

Subsequently, the data from PREVENT were merged with the data from all other published clinical trials of MBCT, and these synthesised data showed that MBCT might actually be better than medication in the prevention of depression. MBCT is now recommended by the National Institute for Health and Care Excellence (NICE) as a front-line intervention for depression prevention.

Following the success of PREVENT, Dr Dalgleish is now looking to establish the value of MBIs in preventing mental health problems in young people who have yet to experience difficulties. He is a Principal Investigator on a Wellcome Trust-funded Strategic Award, known as MYRIAD. The project is ongoing and investigates the effectiveness of introducing a schools-based MBI programme into mainstream secondary education in a trial involving over 80 UK schools.

Ma SH & Teasdale JD. JCCP 2004; 72(1):31

This work was supported by the Wellcome Trust, the National Institute for Health Research (NIHR) Healthy Technology Assessment program, the NIHR Collaboration for Leadership in Applied Health Research; the Care and Exeter National Health Service Foundation Trust; and the Medical Research Council.
RESEARCH SYNOPSIS
Housed over two sites, the Division has a laboratory block at Addenbrooke’s Hospital with the main Department of Pathology building being in central Cambridge. We combine research, teaching and diagnostic histopathology and provide important links between the School of Biological Sciences and the School of Clinical Medicine. Our research focuses on analysing the molecular and cell biology of disease and applying advances in this area to improving clinical practice. We are responsible for the clinical pathology course that is a central component of the curriculum at the Clinical School. We also teach basic pathology to undergraduates reading medical sciences and natural sciences, through the Biology of Disease and the Cellular and Genetic Disease courses. We have group leaders that are honorary consultant clinicians, and provide diagnostic services in the clinical specialties of molecular pathology, paediatric pathology, gastro-intestinal pathology and haematopathology. The Division also hosts the Addenbrooke’s solid tumour molecular malignancy laboratory.

MAIN RESEARCH THEMES
We combine the work of clinical and non-clinical scientists, studying the molecular mechanisms of disease. Our research ranges from basic cell biology and biochemistry, through to computational biology and clinical trials of new diagnostic tools. We interact widely with colleagues in the Cambridge Cancer Centre and the broader Biomedical Research Centre. Our work focuses on specific human diseases, particularly neoplasia (including lymphomas, squamous cell carcinomas and germ cell tumours), and neurodegenerative diseases.

Mammary gland development
We investigated mechanisms of stem cell commitment to luminal and basal cell lineages and the role of cell death and tissue remodelling during post-lactational regression.

Neurodegenerative disease and cancer
We investigate the biochemical pathways that are deficient in diseases characterised by deregulation of ubiquitin ligases, most notably in Parkinson’s disease and cancer. We also research the regulation of cytokinesis in cell division by mitotic kinases, and the significance of their deregulation in cancer.

Our research investigates the role of aberrant lipid processing in neurodegenerative disease and cancer, particularly how disruption to glycolipid and glycoprotein recycling in the lysosome alters the levels of bioactive lipids involved in regulating cell death pathways.

We look at the molecular pathogenesis of B and T cell lymphomas, including those of mucosa-associated lymphoid tissue (MALT lymphomas) and clinically aggressive diffuse large B cell lymphomas. We research the role of the AUK oncogene in paediatric malignancies, including gene rearrangements in anaplastic large cell lymphomas and activating mutations in neuroblastoma. We study tumour/stroma interactions in gastro-intestinal malignancy, particularly the role of cancer associated fibroblasts in influencing tumour progression. We identify mechanisms of squamous cell carcinogenesis, including local genomic instability caused by integration of human papillomavirus DNA into the host genome and the significance of tumour/stroma interactions in metastasis.

We work on the genetic and epigenetic contributions to purperal psychosis, using a porcine model of post-partum maternal aggression.

Our work also identifies the significance of microRNA deregulation in malignant germ cell tumours, including the value of microRNAs as disease markers (in serum, cerebrospinal fluid and other body fluids) and as therapeutic targets via inhibition or replenishment.

Inflammatory diseases
Our research uses RNA-based approaches to identify T cell clonality in neoplastic and inflammatory diseases.

Bioinformatics
We use computational biological analysis of the functional importance of regulatory RNAAs, including microRNA, piwi RNAs and long non-coding RNAAs, using bioinformatics approaches to combine target prediction, secondary effects and upstream regulation into complex regulatory networks.
**DIRECTOR AND PROFESSOR OF PUBLIC HEALTH MEDICINE**
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CAMBRIDGE INSTITUTE OF PUBLIC HEALTH (CIPH) is part of the School of Clinical Medicine at the University of Cambridge. It is a multidisciplinary partnership of public health researchers and professionals contributing to the improvement of the health and wellbeing of the global population. We believe that respecting and understanding the different types of contribution and knowledge, achieved through essential and equal partnerships, must underpin any chance of sustainable improvements in health and wellbeing.

**RESEARCH SYNOPSIS**
We are members, and our collective mission is to improve the health of the public through research, teaching and analysis to promote wellbeing, prevent disease and reduce health inequalities. In public health and population sciences, our members:

- Produce world leading research
- Educate scientists, clinicians and public health professionals
- Analyse and interpret population health evidence and data
- Lead the way with novel methodological approaches
- Inform and support health policy development and implementation

CIPH works to achieve our mission by acting as a Gateway to public health at Cambridge, providing an overview of what’s happening in public health across the University, highlighting our members’ research and latest discoveries.

**Facilitator of new research collaborations,** between our members, our cross-University Public Health@Cambridge Strategic Research Network and our locally and globally located partner institutions and systems.

**Supporter of research impact,** making sure our members’ research makes a difference in the real world through our work with public health stakeholders outside of academia, including policymakers and practitioners.

**Producer of future leaders in public health,** through our multi-disciplinary graduate teaching, supervision, mentorship and career development events for early to mid-career researchers.

**Resource Hub** for our members, providing them with funding guidance, communications and networking resources.

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**CASE STUDY**

**Collaboration**

A snapshot of Cambridge Institute of Public Health (CIPH)

CIPH aims to facilitate collaboration. It hosts the PublicHealth@Cambridge Network, a community of over 1000 Cambridge based researchers. The Network connects academics working across disciplines, from economics and engineering to computer science and law, to foster innovative collaborations that have the potential to tackle today’s most pressing public health issues. Members can find collaborators, publicise their expertise online, attend events, such as the annual Network conference, and access free resources like our funding hub and special interest groups.

Our international research collaborations include our partnership with the University of North Carolina’s Gillings School of Global Public Health, involving several academic members. To date, this has led to a variety of publications, new linkages with the continuation of eight ongoing collaborations.

We support research impact by providing resources such as best practice guides and case studies, and hosting events that connect researchers with regional, national and international stakeholders. CIPH has longstanding links to public health colleagues in the NHS, including Public Health England (PHE). These relationships provide an excellent vehicle for the development of strong strategic collaborations that will enable the direct engagement of public health researchers with key policymakers and advisors in government. Through our PHE Academic Liaison Committee and Dr Rosalind Parkes-Ratanshi, a PHE funded lecturer at CIPH, we aim to highlight and strengthen collaboration between these organisations.

The CIPH membership trains and develops future leaders in public health research and practice by offering multi-disciplinary graduate teaching, supervision, mentorship and career development events for early to mid-career researchers. In 2016, the Dennis and Mireille Gillings Fellowships in Global Public Health Leadership were established as a collaboration between the University of Cambridge and the Institute Pasteur in Paris. These fellowships aim to instil financial acumen and business entrepreneurship against a backdrop of research excellence, all at a formative stage in the careers of young scientists.

CIPH’s flagship Bradford Hill Seminars programme invites nine world leading public health academics a year to speak to and connect with our researchers and students.

We provide a resource hub, and benefits include our annual CIPH conference and lecture, an opportunity for public health researchers, policymakers and professionals to come together, discover and discuss the latest public health research breakthroughs at Cambridge. Each year we invite a leader in public health to deliver the keynote lecture, previous speakers include Dr Flavia Bustreo (former Assistant Director-General, Family, Women’s and Children’s Health, WHO) and Professor Dame Sally Davies (Chief Medical Officer for England).
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RESEARCH SYNOPSIS
As one of Europe’s leading university departments of population health sciences, our mission is to generate evidence to inform the prevention of premature death and disability, the promotion of health, and health policy.

Comprising over 400 researchers, we are distinctive for our multidisciplinary character and research strengths across quantitative and qualitative methods, cohort studies and randomised trials, genetic epidemiology, public health, primary care, and social and behavioural sciences. This diverse expertise is cross-linked in ‘team science’ efforts that tackle grand challenges in the understanding, prediction, prevention and control of common chronic diseases. Patient and public involvement and engagement are prioritised throughout.

We are home to enviable population research resources, including global consortia (such as the 2.5 million-participant Emerging Risk Factors Collaboration), multi-centre cohort studies (for example, the world’s largest cardiovascular disease case-cohort study, EPIC-CVD), which is embedded in the >520,000-participant pan-European EPIC cohort, unusually deeply-characterised cohorts (for example, the 50,000-participant INTERIMAL study), and a variety of community-based randomised trials.

We have strategic partnerships with external organisations, including NHS Blood and Transplant, Wellcome Sanger Institute, RAND Europe, Health Foundation, industry, and policy-makers at local, national and international levels. These partnerships facilitate multidisciplinary research projects, ensure relevance to population and health service need, and accelerate translation of findings into policy and practice.

MAIN RESEARCH THEMES
Biological basis of disease
Our goal is to identify and evaluate causal risk factors for selected major diseases, including cardiovascular diseases, cancer, neurodegenerative diseases, diabetes, and other age-related conditions, thus providing foundations for novel prevention, early detection and therapeutic strategies.

We have led discovery of hundreds of genetic risk factors for a range of common diseases (eg, breast, prostate, and ovarian cancers; coronary disease; type 2 diabetes) and thousands of genetic risk factors for intermediate traits (eg, blood lipids, proteins). These findings have opened new avenues of mechanistic understanding and helped industry prioritise novel therapeutic targets.

In an attempt to provide a more complete picture of the genetic basis of disease, our gene sequencing studies are being extended to >100,000 individuals, including tens of thousands with breast cancer or coronary disease as well as healthy controls. We have commenced large-scale ‘multi-omic’ studies of >30,000 molecular traits to identify and understand potential predictors and determinants of disease.

Early detection of disease, risk prediction and screening
We aim to develop and evaluate approaches that can cost effectively enhance the diagnosis, early detection, prediction and control of chronic disease outcomes.

Our studies have shaped clinical management guidelines by producing precise cancer risk estimates for women with genetic faults in major cancer susceptibility genes (eg, PALB2, CHEK2, BRIP1), and have shown that cancer risks for women with genetic faults in BRCA1 and BRCA2 depend on both the precise mutation and the woman’s family cancer history. We have developed widely used risk prediction and prognostic tools for breast and ovarian cancer that have been incorporated in several national clinical management guidelines, as well as electronic clinical decision support tools for general practitioners to help target cancer screening more accurately. Our work has also shaped >10 cardiovascular disease risk management guidelines, principally by suggesting approaches that simplify risk prediction without sacrificing accuracy. We have developed efficient strategies using routinely available general practice data to identify those at risk of type 2 diabetes, derivatives of which have been incorporated into prevention and screening programmes worldwide. Our trials have shown that early detection through screening those at risk is not associated with significant harms and translates into reductions in cardiovascular disease and prolongation of life among those with previously undiagnosed diabetes. We have shown that routinely available data can also predict cancer such as colorectal. We plan to evaluate the effectiveness and efficiency of varying screening programmes according to individuals’ modelled risk.

We plan to develop and implement improved cancer diagnostic testing strategies for general practitioners through the first ever Cancer
We plan further randomised controlled trails to test behavioural and policy interventions targeting people with type 2 diabetes and new ways of addressing the long-term consequences of stroke, through primary care based services, both preventing recurrence and improving quality of life of stroke survivors. We plan to identify the optimal way for primary care to manage people with a particular type of heart failure (Heart Failure with Preserved Ejection Fraction) and women with a history of gestational diabetes.

**Behaviour and health**

We aim to develop interventions that can be implemented at scale to target the four sets of behaviours that contribute most to premature, preventable death worldwide, years lived in poor health and health inequalities: excessive consumption of food and alcohol, smoking and low physical activity.

For interventions that target whole populations rather than specific individuals (e.g., changing cues in physical environments that shape our behaviour often without our awareness, also known as nudging), we have developed a classification of interventions for changing proximal physical environments to change behaviour, such as in relation to food portion size. For interventions that target specific individuals (e.g., using digital, automated text messaging and smartphone applications), we have developed and are evaluating an intervention for smoking cessation using tailored text messaging (iQuit in Practice) and a version for pregnant smokers (MiQuit).

We are planning a series of integrated field and laboratory studies to estimate the effect sizes of promising interventions to reduce food, alcohol and tobacco consumption. These studies will be conducted in supermarkets, bars and cafeterias; the interventions will be optimised through laboratory studies determining mechanisms.

**Health services research**

Our goal is to provide high quality evidence for making improvements in quality, safety, and experience of care.

We have conducted studies across a range of care settings, including general practice, hospital, mental health, and community care. These include an evaluation of a ‘telephone first’ approach in primary care, which showed that telephone consultations do not reduce GP workload or hospital referrals. Our studies of patients’ experiences of care have revealed how specific patient populations (such as those of minority ethnicity) may have poorer experiences than others. Our research has challenged current policy orthodoxy on people’s preferences for place of death, demonstrating that dying at home may not be the universal choice it is often portrayed.

The Healthcare Improvement Studies Institute

In 2018, we established The Healthcare Improvement Studies (THIIS) Institute, core-funded by the Health Foundation. Through collaborative partnerships across the UK and internationally, the Institute aims to create a world-leading scientific asset for the NHS by strengthening the evidence-base for improving the quality and safety of healthcare. The Institute’s work is defined by a highly inclusive approach that combines academic rigour with the real concerns of patients and staff. We will be bringing together multidisciplinary expertise, strengthening the science behind the study of improvement, evaluating interventions to assess their effectiveness and cost-effectiveness, and figuring out how successful improvements can be replicated and scaled and where disinvestment is warranted.

The Cambridge Centre for Health Services Research

The Cambridge Centre for Health Services Research (CCHSR) is a thriving collaboration between the University of Cambridge and RAND Europe. It aims to inform health policy and practice by conducting research and evaluation studies of organisation and delivery of healthcare, including safety, effectiveness, efficiency and patient experience.

**Global health**

We aim to help provide context-specific solutions to control the epidemic of chronic diseases in low- and middle-income countries, and to advance understanding of disease by leveraging the striking heterogeneity of environmental, lifestyle and genetic exposures in these populations.

We have established a portfolio of studies in various emerging economies, with a particular focus on settings with rapidly increasing rates of cardiometabolic conditions (e.g., heart disease and diabetes). They include BELIEVE (a 30,000-participant household survey in Bangladesh) and MAVEN (a 5,000-participant case-control study of myocardial infection in Malaysia). Initial findings have highlighted the important interplay of universal risk factors (e.g., blood lipids) and local factors (e.g., consanguinity, toxic metal exposure).

As part of a capacity-building effort funded by Research Councils UK, we are establishing a 100,000-person cohort in Bangladesh in urban, rural and slum contexts, using this study as a framework to develop and evaluate interventions that help control the complex set of risk factors for chronic disease.
In the regenerative medicine field, our researchers have shown that the effects of ageing on neuronal myelination are reversible, opening up the possibility for drug approaches to a range of malignancies.

Our researchers have extensive expertise across multiple haematological, malignancy and regenerative failure, in studies which are laying the foundation for translational aspirations requiring robust control of differentiation. We study the fundamentals of pluripotent and adult stem cells to understand the mechanisms by which they self-renew, maintain their states and commit to differentiate. We also demonstrated that electrical activity in demethylated arises governs the behaviour of brain stem cells.

We have pioneered methods to grow, characterise, differentiate and genetically manipulate normal and patient-derived pluripotent stem cells. Exploiting our knowledge of genome editing, we are developing forward programming approaches to generate functionally mature cells including brain, liver, heart and blood cells. In collaboration with bioengineers, we are growing these programmed stem cells on miniature scaffolds to promote tissue-specific cells growth and maturation, providing valuable disease models and offering new approaches to organ transplant and repair.

In addition to studying diseases using patient derived stem cells, we are developing stem-cell products to treat patients across a range of diseases. Over the last five years, our investigators have led the world on neural transplant trial in Parkinson’s disease, Huntington’s disease and Pelizaeus-Merzbacher disease. Stem cell therapies are also the subject of ongoing trials for heart and knee joint diseases, and are also the focus of forward programming research to mass produce blood platelets for transfusion.

"We study the fundamentals of pluripotent and adult stem cells to understand the mechanisms by which they self-renew, maintain their states and commit to differentiate."

"Stem cells have the extraordinary ability to develop into any type of cell in the body, and studying these cells provides new understanding of many fundamental biological questions. From a clinical perspective it is increasingly clear that stem cell dysfunction underlies many of the global health challenges that face us today. Our Institute brings together biological, clinical and physical scientists operating across a wide range of tissues and at multiple scales with a mission to transform human health through a deep understanding of stem and progenitor cells. This pioneering setup allows communalities and differences in stem cell biology to be explored in a cohesive and inter-disciplinary manner. In 2019, our investigators will come together in the Jeffrey Cheah Biomedical Centre, a new purpose-built home on the Cambridge Biomedical Campus. The proximity to the hospitals as well as industrial research partners are fundamentally important to realising the full therapeutic potential of stem cells."
The Wellcome – MRC Institute of Metabolic Science comprises the MRC Epidemiology Unit, the Metabolic Research Laboratories (with embedded MRC Metabolic Diseases Unit), and the IMS Clinical Care Centre of Cambridge University Hospitals NHS Foundation Trust.

Professor Sir Stephen O’Rahilly
TEL: 01223 336855
EMAIL: so104@medschl.cam.ac.uk

Professor Nick Wareham
TEL: 01223 330315
EMAIL: nick.wareham@mrc-epid.cam.ac.uk

www.ims.cam.ac.uk

RESEARCH SYNOPSIS
The Wellcome – MRC Institute of Metabolic Science (IMS) is a purpose-built centre dedicated to research, education, prevention and clinical care in the areas of obesity, diabetes and related diseases, all of which are major and increasing threats to public health, both in the UK and worldwide.

Almost a quarter of all adults and children in the UK are considered obese, and these numbers are predicted to increase. Obesity significantly increases the risk of developing life-threatening conditions such as type 2 diabetes, cardiovascular, gastrointestinal, osteoarticular and reproductive diseases, reducing both quality of life and life expectancy of affected individuals and adding significantly to healthcare costs.

Led by Professor Sir Stephen O’Rahilly and Professor Nick Wareham, the IMS provides state-of-the-art facilities for laboratory science, clinical and epidemiological research and promotes cross-fertilization of ideas between clinicians, laboratory scientists and clinical scientists. The goal of the IMS is to promote world-leading research, enabling rapid, effective ‘translation’ of fundamental advances in scientific and clinical research for patient benefit.

Diabetes, obesity and related metabolic and endocrine diseases are major and growing threats to public health worldwide. In recognition of this, the University of Cambridge, the Medical Research Council (MRC) and Cambridge University Hospitals NHS Foundation Trust joined in partnership to create this unique institute. The generosity of research funders, in particular the MRC and the Wellcome Trust, has allowed Cambridge to nurture a world class group of researchers who will greatly benefit from the close interactions provided by the IMS.

We are enormously grateful to the many organisations who continue to provide generous support for our ongoing research and facilities, including the Wellcome Trust, the MRC, the National Institute for Health Research, the British Heart Foundation, the Juvenile Diabetes Research Foundation, Diabetes UK and the Biotechnology and Biological Sciences Research Council.
RESEARCH SYNOPSIS
Obesity, type 2 diabetes and related metabolic disorders present a major and growing global public health challenge. These disorders result from a complex interplay between genetic, developmental and environmental factors that operate throughout life. Our goal is to investigate this interplay and to use the evidence to develop and evaluate strategies for the prevention of these diseases.

The MRC Epidemiology Unit comprises of an MRC core-funded unit and a department, supported through additional research grants, with connections to basic science, clinical medicine and public health. The Unit is embedded in the Wellcome Trust – MRC Institute of Metabolic Science (IMS), which is critical to our work examining the associations between potential exposures and disease outcomes. We are also a member of the Cambridge Institute of Public Health (CIPH), acting the translation of epidemiological observations into public health action.

MAIN RESEARCH THEMES
Our research is delivered by a number of interdependent programmes that work collaboratively across a series of studies. Specialist teams in data management, information technology, laboratory analysis, statistics, physical activity and anthropometric measurement, study coordination, field epidemiology, and communications, support the research.

MRC core-funded programmes
Our Aetiology of Diabetes and Related Metabolic Disorders programme aims to identify how genetic factors influence the risk of type 2 diabetes and related metabolic disorders, and examine how these associations are modified by environmental factors, such as diet and physical activity.

Childhood growth and reproductive ageing are associated with health outcomes that include type 2 diabetes and other obesity-related co-morbidities. Our Growth and Development programme seeks to describe and understand these mechanisms, in order to inform early-life preventive strategies.

Our Nutritional Epidemiology and Physical Activity Epidemiology programmes investigate the role that diet nutrition, physical activity and sedentary behaviour play in the risk of developing diabetes, obesity and obesity-related disorders.

The Prevention of Diabetes and Related Metabolic Disorders programme translates knowledge gained from epidemiological studies into individual health-sector approaches to prevent diabetes, obesity and related disorders.

Our Behavioural Epidemiology programme investigates the key factors influencing physical activity behaviour in young people with the aim of developing, evaluating, and targeting interventions to promote physical activity.

Focusing on the physical environment and wider determinants of active living, our Physical Activity and Public Health programme evaluates the effects of environmental and policy interventions on physical activity behaviours.

Centre for Diet and Activity Research (CEDAR)
We lead the CEDAR, which studies the population-level influences on diet and physical activity. CEDAR has active collaborations with public health organisations, schools, charities and policy bodies through which it is helping to shape public health practice and policy.

The Food Systems and Public Health programme is building understanding of the relationships between consumer food markets and food behaviours, developing our understanding of the key levers for change within food systems, and identifying and evaluating interventions in this area.

The Evaluation of Population Interventions in Dietary Public Health programme studies the factors influencing the effectiveness, equity and acceptability of interventions in dietary public health.

The Public Health Modelling programme combines evidence from primary studies, plus insights from experts and stakeholders, to create simulations of systems to answer questions in physical activity and diet that cannot be addressed by individual studies.

Global Public Health Research
We lead the NIHR Global Diet and Activity Research Group and Network (CEDAR), a new international research partnership to help combat poor diet and physical inactivity in order to reduce the risk of non-communicable diseases. The partners in the CEDAR network include Universities in South Africa, Cameroon, Kenya and the West Indies.

NIHR Biomedical Research Centre
We also lead the NIHR Biomedical Research Centre theme in Nutrition, Diet and Lifestyle, a key element of which is a platform for the measurement of diet, nutrition and physical activity in observational studies, trials, and real-world intervention studies.

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Cambridge Epidemiology and Trial Unit (CTU)
CTU is an NIHR accredited Clinical Trials Unit (CTU) and focuses on investigator led randomised controlled trials (RCTs) and other well designed studies that evaluate interventions to improve health care and public health. We have expertise in evaluating interventions ranging from individual- and group-level behavioural interventions, through to policy interventions.

CASE STUDY
A road to impact
Generating the evidence for effective healthy transport policies
Dr David Ogilvie and Dr James Woodcock
Medical Research Council Epidemiology Unit

The MRC Epidemiology Unit’s research into physical activity, travel and health is having a significant impact on transport policy in the UK. Our researchers have developed relationships with policymakers, contributed evidence to policy development and created resources to help planners best target cycling investment.

Switching more of our everyday travel choices to walking and cycling could bring benefits in physical activity and health, as well as reducing pollution and congestion and improving the liveability of our cities. However, making the case to transport policymakers for appropriate interventions can be a challenge, because health may not be a priority topic, and links with public health researchers have not historically been widespread.

Unit research in this area has been cited in reviews and guidance produced by a wide range of parliamentary and public bodies, including the House of Commons Health Committee, House of Lords committee, and NICE. Building on Unit-led epidemiological work on the importance of physical activity for chronic disease health outcomes, researchers in two of our programmes – Physical Activity and Public Health (Dr David Ogilvie), and Public Health Modelling (Dr James Woodcock) – have developed relationships with governments locally, nationally and internationally, as well as a range of other agencies and partners.

A particularly productive relationship has been forged with senior civil servants at the UK Department for Transport (DfT). Activities have included contributing to workshops and policy round-tables, supporting professional development of civil servants, and providing advice to the Department. For instance, our evidence has increased understanding about the need and opportunities for better evaluation, and has helped quantify the potential health benefits from increases in walking and cycling, particularly for older people.

The Unit’s relationship with DfT contributed to the commissioning of the Propensity to Cycle Tool (PCT) – a project led by Dr Woodcock, in collaboration with the Universities of Leeds and Westminster, to help planners prioritise cycling investment. The PCT is an online, interactive planning support system that allows for the exploration and mapping of cycling potential across England and Wales. It helps allocate and prioritise where cycling investment and policy interventions are most needed, and shows the potential reductions in premature mortality that might be achieved. The DfT is now recommending the tool for use in developing the new Local Cycling and Walking Investment Plans. The tool and the best is being used in policy and practice by local and regional governments, and commercial organisations.

Pauline Reeves, the DfT’s former Deputy Director for Sustainable Travel and Equalities, has summarised our work with the department: “Direct impacts of research on policy making are not always easy to identify, but CEDAR’s work on physical activity... is having a clear impact on DfT’s cycling policy development.”

Ogilvie, D et al. 2018 BMJR Journals library. DOI: 10.1136/bmjgh-2018-000870

This research was funded through a variety of core MRC programme funding and other project-specific funding sources.

www.mrc-epid.cam.ac.uk
RESEARCH SYNOPSIS
Our research focuses on how the body normally controls its metabolism and energy balance and how these systems go wrong in disease. As hormones play such a crucial regulatory role in these processes we have a major interest in endocrinology, the science of hormones. We use the results of our research to aid the development of better approaches to classifying, treating and preventing obesity, type 2 diabetes and other related endocrine and metabolic disorders.

Our Principal Investigators apply a broad range of technologies to studies in cells, animal models, and humans to better understand how metabolic and endocrine systems function in health and disease. In addition, we have a particularly close relationship with the MRC Epidemiology Unit, which takes a population science-based approach to disorders such as obesity and type 2 diabetes.

The MRL benefits from high quality core facilities provided by the University in partnership with the MRC and Wellcome Trust. The MRL and MDU are based at the Wellcome-MRC Institute for Metabolic Science (IMS), a purpose built centre on the Addenbrooke’s Biomedical Campus. The building is shared with the MRC Epidemiology Unit and with the ambulatory care services in endocrinology and metabolism of Addenbrooke’s Hospital.

MAIN RESEARCH THEMES
All of the themes use a multi-disciplinary approach which encompasses studies in cells including stem cell derived human neurons and other cell types, murine and other animal models and human participants. Our research has long been a strong component of many of our programmes.

Neuroscience of appetite
We aim to better understand how key areas of the brain control hunger and satiety and how dysfunction of these contribute to conditions such as obesity and cachexia/anorexia.

Energy expenditure
We investigate how the body controls its expenditure of energy through thermogenesis in brown fat and other tissues and its control by the nervous system.

Entero-endocrinology
We study the hormones of the gastro-intestinal tract, the location of the largest volume of endocrine cells in the body, how they are produced and controlled and how they influence other organs.

Insulin action and resistance
We investigate how insulin works at the cellular level and how defects in insulin signalling (both loss and gain of function) can lead to disease.

Adipocyte function and dysfunction
Our work has helped establish how important fat cells are in maintaining overall metabolic health. We aim to build on this body of work to better understand fat cell function in health and disease.

Lipotoxicity
It is clear that one of the major mechanisms of insulin resistance and fatty liver and type 2 diabetes is the metabolic damage wrought by the presence of inappropriate amounts of particular lipids in certain key tissues, we wish to understand more about the nature of these lipid species and how we might prevent them accumulating and causing damage.

Developmental endocrinology
Events occurring in utero and in early life can have profound influences on metabolic health. We aim to study the nature of such developmental events and how they might be manipulated for health benefit.

Inherited endocrine disorders
We investigate inherited disorders of thyroid hormone synthesis and action including those involving a primary impairment of selenoprotein production.

Diabetes technology
We use mathematical modelling of human physiology to aid the development of artificial pancreatic technology to aid glucose control in a range of clinical situations.

Endocrine tumours/Imaging
We aim to find clinical solutions using novel imaging technologies to improve the diagnosis and management of tumours of the adrenal and pituitary glands.
### Composition of the School of Clinical Medicine

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<th>Building</th>
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<td>• Clinical Neuroscience • Medicine • Radiology • Surgery • Addenbrooke’s Hospital – MRI • Oncology • MRC Epidemiology Unit (CEDAR) • Clinical Biochemistry • Paediatrics • Pathology (SBS) • Psychiatry • Obstetrics &amp; Gynaecology</td>
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<td><strong>2</strong> ADDENBROOKE’S HOSPITAL</td>
<td>• Medical Genetics</td>
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<td><strong>3</strong> PROPOSED SITE FOR THE HEART AND LUNG RESEARCH INSTITUTE</td>
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<td><strong>6</strong> KEITH PETERS BUILDING</td>
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<td>A. Herchel Smith Building – Clinical Neurosciences/Psychiatry/Experimental Psychology B. West Forvie Building – Clinical Neurosciences C. John Van Geest Centre for Brain Repair D. Institute of Public Health - Public Health and Primary Care/MRC Biostatistics Unit</td>
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<td><strong>9</strong> WELLCOME-MRC INSTITUTE OF METABOLIC SCIENCES</td>
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<td><strong>12</strong> ROSIE HOSPITAL AND MATERNITY CENTRE</td>
<td>• Obstetrics &amp; Gynaecology</td>
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<tr>
<td><strong>13</strong> CAMBRIDGE CLINICAL RESEARCH CENTRE</td>
<td>• Sir Patrick Sissons Building • NIHR/Wellcome Clinical Research Facility • Clinical Investigation Ward • Experimental Medicine Research Facility</td>
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<td><strong>14</strong> DEAKIN CENTRE AND CLINICAL SKILLS UNIT</td>
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<td><strong>16</strong> MRC LABORATORY OF MOLECULAR BIOLOGY</td>
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<td><strong>17</strong> ROYAL PAPWORTH HOSPITAL</td>
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<td><strong>18</strong> ISLAND RESEARCH BUILDING</td>
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<td><strong>19</strong> CLIFFORD ALLBUT T BUILDING</td>
<td>• Clinical Neuroscience • MRC Epidemiology Unit • Cancer Molecular Diagnostics Lab • Radiology</td>
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<td><strong>21</strong> ASTRazeneca HEADQUARTERS</td>
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<td><strong>22</strong> ASTRazeneca ENERGY CENTRE</td>
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<td><strong>23</strong> ABCAM</td>
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The School of Clinical Medicine – Administration

The School of Clinical Medicine is led by Professor Patrick Maxwell, Regius Professor of Physic. He is supported by Professor Peter Jones, Deputy Head of School and Dr Caroline Edmonds who leads the Clinical School Office and is overall head of administration for the School. Support is also provided by Dr Diana Wood, the Director of Medical Education, who is responsible for all aspects of undergraduate medical education in the School, Professor Fiona Gribble, Director of Graduate Education and Professor Fiona Karet, Director of Organisational Affairs.

The School Office is organised into three teams – the Resources Division, the Education Division and the General Division. This is complemented by Human Resources, the Clinical School Computing Service and the Research Governance Officer and other research support services.

RESOURCES DIVISION
Robin Uttin
Responsible for the finances of the Clinical School Departments, Institutes, Units and Centres.

EDUCATION DIVISION
Dr Litsa Biggs
Administrative coordination of the clinical component of the Cambridge Medical student programme and higher degrees.

GENERAL DIVISION
Jackie Hall
Responsible for efficient operation of the Estates and University buildings on the Cambridge Biomedical Campus. Provides oversight of Departments including the REF.

HUMAN RESOURCES
Caroline Newman

COMPUTING SERVICES
Martin Keen

RESEARCH GOVERNANCE
Carolyn Read

PROFESSOR PATRICK MAXWELL
Regius Professor of Physic and Head of School

PROFESSOR ED BULLMORE
Deputy Head of School

DR CAROLINE EDMONDS
Secretary of School

DR PAUL WILKINSON
Director of Medical Education

PROFESSOR FIONA GRIBBLE
Director of Graduate Education

PROFESSOR NITA FOROUHI
Director of Organisational Affairs

The School of Clinical Medicine – Research support

THE RESEARCH OPERATIONS OFFICE – CLINICAL SCHOOL

The Clinical School Research Operations Office (ROO) offers expert guidance and support in securing and administering research funding. There are two divisions within the team: the Grant Team provides both pre- and post-award support, administering over 500 applications per annum and managing over 1,200 live awards. The Contracts Team negotiates and executes all the Clinical School research agreements (over 1,400 per annum), ranging from confidentiality agreements to framework agreements with industrial partners.

THE RESEARCH OPERATIONS OFFICE – CLINICAL SCHOOL

PROFESSOR PATRICK MAXWELL
Regius Professor of Physic and Head of School

PROFESSOR ED BULLMORE
Deputy Head of School

DR CAROLINE EDMONDS
Secretary of School

Dr Litsa Biggs

www.admin.cam.ac.uk/offices/research

THE RESEARCH OPERATIONS OFFICE – CLINICAL SCHOOL

CAMBRIDGE CLINICAL TRIALS UNIT (CCTU) AND CLINICAL RESEARCH FACILITY (CRF)

The Office for Translational Research (OTR) is led by Dr Anita Marguerie de Ratrou and the Director, Professor Ian Wilkinson. Its remit is to support investigators in their efforts to convert findings from their basic biological, biomedical or clinical research into interventions, therapies and diagnostics that will improve human health. Translation requires connecting the right expertise with the right funding at the right time within the project for the best outcome whether it is a clinical trial in the NHS setting, a commercialised product through licensing or a spin-out.

The OTR also provides expert support throughout your project life cycle in the form of project management.

The Office supports researchers from Cambridge University Health Partners (CUHP) and acts as a contact point for industrial partners (together with Cambridge Academy of Therapeutic Sciences (CATS) and the Milner Therapeutics Institute) who would like to develop translational research collaborations with investigators. The OTR also provides expert support throughout your project life cycle in the form of project management.

General enquiries:
translation@medschl.cam.ac.uk

Website:
https://otr.medschl.cam.ac.uk

CAMBRIDGE CLINICAL TRIALS UNIT (CCTU) AND CLINICAL RESEARCH FACILITY (CRF)

The CCTU is part of the NIHR UKCRC CTU network working with investigators across CUHP and beyond in the design, set-up and conduct of clinical trials. Situated beside the entrance to the Addenbrooke’s Treatment Centre (ATC), and adjoining the Sir Patrick Sissons Building, this new building provides the Cambridge Biomedical Campus with additional capacity and enhanced capability to translate fundamental biomedical research into clinical research that benefits patients.

General enquiries:
cctu@addenbrookes.nhs.uk

The NIHR / Wellcome Trust Clinical Research Facility is a joint venture between the Wellcome Trust, Cambridge University Hospitals and the University of Cambridge, housed in the Sir Patrick Sissons Building. Any member of the local research community holding an honorary contract with Addenbrooke’s can use the facilities of the Centre. The research projects are patient or volunteer based with a peer reviewed protocol and research ethics approval.

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Website:
https://cambridge.crf.nihr.ac.uk

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By inspiring and organising collaboration, CUHP aims to ensure that patients reap the benefits of the world class research, clinical service and industry based in Cambridge and the surrounding area.

Malcolm Lovel, Executive Director, explains how Cambridge University Health Partners (CUHP) delivers increasing collaboration, economic growth and patient benefit: “Our mission to turn possibilities into better healthcare has been supported by a strategic effort to concentrate on four domains.

"First, we maximise the benefit of co-location on the Cambridge Biomedical Campus (CBC) by promoting close partner working. The CBC is a hive of activity which will see the completion of four major capital projects by 2020. To locate Abcam, AstraZeneca, Royal Papworth Hospital along with The Jeffrey Cheah Biomedical Centre, the Wellcome-MRC Cambridge Stem Cell Institute, the Cambridge Institute for Immunotherapeutics and Infectious Disease and the Milner Therapeutics Institute all on one site is a staggering prospect."

“This combined with the clinicians, researchers and industry already on the Campus in a variety of forms and organisations demonstrates why Cambridge is now known as the Capital of UK Sciences.

“This takes us neatly to the second domain which is the development and growth of the CBC in line with CUH’s strategy. We signed an agreement with Cambridge Mediparks Ltd in 2017 for CUH to carry out pre-commercial marketing activities relating to the development of the CBC Phase 3 land. This is a mutually beneficial relationship which provides a strategic control for both parties on how the CBC will expand, driven by facilitating interaction between clinicians, researchers and potential new occupiers. This is clearly an exciting opportunity to shape our future – delivering growth and jobs to not just Cambridge but potentially the wider region.

“This is why strengthening regional and national links to encourage clinical research adoption, health education and economic growth is our third area of promotion of cancer, digital and medtech, but we are broadening this to link in specific themes on mental health and cardiothoracic research.”

Finally we are focused on maximising opportunities for CUHP and the wider region arising from the Life Sciences Industrial Strategy (LSIS). We have created the Cambridge narrative, a document developed in response to the LSIS to demonstrate how Cambridge has a key part to play in developing the UK economy. For instance, 431 life sciences companies are based in the city and employ 13,000 people, while Cambridge files more patents per 100,000 people than any other city in the UK. Our work initially focused on key strengths in cancer, digital and medtech, but we are broadening this to link in specific themes on mental health and cardiothoracic research.”

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**CUH HOSPITAL TRUSTS**

CUH creates a partnership between one of the world’s leading universities and three NHS Foundation Trusts. CUH delivers world-class excellence in healthcare, research, clinical education and improves the health of people across Cambridgeshire and the wider region.

**CAMBRIDGE UNIVERSITY HOSPITALS NHS FOUNDATION TRUST (CUH NHSFT)**

CUH NHSFT consists of Addenbrooke’s Hospital and the Rosie Hospital, both of which are recognised as centres of medical excellence and innovation. The Trust’s role in CUH-P makes it one of the richest pools of clinical and scientific knowledge and expertise in the NHS.

Addenbrooke’s Hospital provides specialist services dealing with rare or complex conditions and it is a centre of excellence for regions specialist services like paediatrics, neurosciences, organ transplantation, cancer and genetics.

**ROYAL PAPWORTH HOSPITAL NHS FOUNDATION TRUST**

Royal Papworth Hospital is the UK’s leading heart and lung hospital, treating more than 100,000 patients each year from across the UK. Since carrying out the UK’s first successful heart transplant in 1979, the hospital has established an international reputation for excellence in research and innovation.

As well as performing more heart and lung transplants than any other UK centre, Royal Papworth Hospital has the UK’s largest Respiratory Support and Sleep Centre (BSSC). It is the only centre in the UK for a number of specialist services including Pulmonary Endarterectomy and Balloon Pulmonary Angioplasty (BPA).

The Trust is moving Royal Papworth Hospital to a brand new state-of-the-art facility on the Cambridge Biomedical Campus in 2019.

**CAMBRIDGESHIRE AND PETERBOROUGH FOUNDATION TRUST (CPFT)**

CPFT is a partnership organisation providing mental health and specialist learning disability services and statutory social care services across Cambridgeshire and Peterborough, and children’s community services in Peterborough. There are two main facilities at the Cavell Centre Peterborough and Fulbourn Hospital Cambridge and staff are based in around 50 facilities.

The Trust provides nationally recognised specialist services in many areas including; specialist eating disorders services for adults and young people, specialist learning disability services and child and adolescent in-patient services. It is the biggest provider of psychological therapies in the East of England, as well as being a partner in the local Collaborations for Leadership in Applied Health Research and Care (CLAHRC) and a partner in the first national consortium of leading mental health trusts providing secondary mental health services to serving Ministry of Defence and USAF staff.

**“We are at the beginning of a very exciting journey for CUHP and the Cambridge Biomedical Campus – there may be challenges ahead but the opportunities before us are huge and very exciting.”**

**EXECUTIVE DIRECTOR**

Kristin-Anne Rutter

**TEL:** TBC

**EMAIL:** pippa.tomlin@cuhp.org.uk

www.cuhp.org.uk
AstraZeneca
In 2020, AstraZeneca will move its corporate headquarters and global R&D centre to the Cambridge Biomedical Campus. This new, iconic development will bring over 2,000 new scientists from other AstraZeneca sites around the world to Cambridge, and will provide vital late-phase drug development capacity to complement the existing pre-clinical and early phase infrastructure on the Campus.

GlaxoSmithKline (GSK)
The GSK Cambridge Clinical Unit is a clinical research facility embedded in the heart of Addenbrooke’s Hospital and maintained by GSK. The Unit specialises in innovative Phase 1 and early Phase 2 studies across a broad range of therapeutic areas, exemplified by recent studies on atherosclerosis, type 2 diabetes, obesity, cognitive impairment, and various aspects of inflammation.

The Babraham Institute
The Babraham Institute is an international leader in research focusing on basic cell and molecular biology with an emphasis on healthy ageing through the human lifecycle. The Institute is supported by strategic funding from the Biotechnology and Biological Sciences Research Council (BBSRC) which funds the four core areas of research in epigenetics, lymphocyte signalling, nuclear dynamics and signalling.

The European Bioinformatics Institute (EBI)
The EBI aims to make the world’s public biological data freely available to the scientific community via a range of services and tools, performs basic research and provides professional training in bioinformatics. The EBI is part of the European Molecular Biology Laboratory (EMBL) and is situated on the Wellcome Genome Campus.

The MRC Laboratory of Molecular Biology (LMB)
The MRC LMB is dedicated to understanding important biological processes at the levels of atoms, molecules, cells and organisms. In doing so, the MRC LMB provides knowledge needed to solve key problems in human health and tackles fundamental research questions. Revolutionary contributions include pioneering X-ray crystallography to determine protein structures, the sequencing of DNA and the development of monoclonal antibodies.

The Wellcome Sanger Institute
The Wellcome Sanger Institute is a world leader in genome research, which concentrates on the study of genome variation: naturally occurring and engineered, inherited and somatic, in humans, pathogens, human cells and mice. Studies provide insights into human, pathogen, cellular evolution, the phenotypic and hence biological consequences of genome variation and the processes that cause mutations.

The Health Foundation
The Health Foundation has chosen to invest in an Improvement Studies Institute on the Cambridge Biomedical Campus. Established in 2018, The Health Foundation Improvement Studies Institute (THS Institute) creates an enabling infrastructure to make the NHS the world’s largest producer of systematic learning about how to improve healthcare. THS Institute uses crowd sourcing and citizen science to create a distributed learning network, coordinating national programmes of research and capability building.

The PHG Foundation
The PHG Foundation is a non-profit think tank with a special focus on how genomics and other emerging health technologies can provide more effective, personalised healthcare and deliver improvements in health for patients and citizens. In April 2018 the PHG Foundation became wholly owned by the University of Cambridge as a linked exempt charity. Their mission is to make science work for health.

NHS Blood and Transplant
The Cambridge Blood Centre, part of NHS Blood and Transplant (NHSBT), helps to provide a blood and transplantation service to the NHS, looking after blood donation services in England and transplant services across the UK. This includes managing the donation, storage and transplantation of blood, organs, tissues, bone marrow and stems cells, and researching new treatments and processes.

The Cambridge Academy of Therapeutic Sciences (CATS)
CATS has created a structure that transcends traditional boundaries between disciplines and between academics and industrialists, providing a unique outwardly-focused mechanism in which fundamental and applied research into therapeutics and diagnostics can flourish and be translated into patient treatments with maximum efficiency.

The Milner Therapeutics Institute
The Milner Therapeutics Institute, at the University of Cambridge, is dedicated to the conversion of ground-breaking science into therapies. This is delivered by connecting academic institutions with pharmaceutical and biotech companies, enabling collaborative research projects throughout Cambridge and by accelerating the formation of new biotech companies with a therapeutic outlook.