



Principal Investigators

Name	Research	Email
Dr Clemence Blouet	<p>Human obesity is predominantly a disease of brain pathways regulating appetite. Our aim is to help characterize these pathways to eventually develop safe and efficient therapies promoting satiety.</p> <p>Although protein is known to be the most potent appetite suppressant among all macronutrients, little is known about how the mammalian brain senses protein availability to create neural representations that guide behaviour and modulate metabolism. Data obtained across taxa from flies to humans indicate that evolutionary-conserved homeostatic mechanisms tightly control protein intake, and that this control is prioritized over the control of carbohydrate, fat or energy intake. Targeting protein-sensing mechanisms could therefore represent a novel avenue for the development of anti-obesity drugs.</p> <p>The Blouet Lab employs a multi-disciplinary approach coupling calcium imaging to characterize the neurophysiology of metabolic-sensing neurons, discrete manipulations of brain neurocircuits and nutrient sensing pathways using cutting-edge molecular genetics, and refined functional assessments in behaving rodents to characterize how proteins are detected by the brain to maintain energy homeostasis in health and disease.</p> <p>Our current research focuses on the following questions:</p> <p>Can we target hypothalamic protein-sensing cells to produce satiety and improve energy balance?</p> <p>What is the neuronal representation of central protein abundance?</p> <p>Are protein-sensing circuits integrated with neurocircuits sensing gut-derived and adiposity signals? Can we target the integration mechanisms to maximise beneficial outcomes on appetite and weight control?</p>	csb69@medschl.cam.ac.uk
Professor Krishna Chatterjee	<p>Our principal research interests are in genetic and molecular endocrinology, with particular emphasis on disorders nuclear hormone synthesis and action. We study several human disorders: Resistance to Thyroid Hormone (RTH), defined broadly as abnormal circulating thyroid hormones with tissue refractoriness to hormone action; and PPARgamma gene defects associated with lipodystrophic insulin resistance. Candidate gene and whole exome approaches are used to identify novel genetic aetiologies mediating defective hormone action. Human phenotypic studies elucidate mechanisms whereby thyroid hormones alter physiological processes acting via receptor subtypes in tissues. In a multisystem selenoprotein deficiency disorder including thyroid deiodinase enzymes, we are investigating features (cardiovascular, metabolic, photosensitivity) attributable to elevated ROS and the roles of selenoproteins of unknown function. Finally, we translate our research into technologies (biochemical, genetic) that comprise our national diagnostic laboratory service, develop</p>	tdw30@medschl.cam.ac.uk

	<p>biomarkers of hormone action and trial therapies (e.g. selective thyromimetics) that are applicable to commoner thyroid dysfunction or metabolic disorders.</p>	
<p>Dr Maria Chondronikola</p>	<p>Human physiology and experimental medicine</p> <p>Obesity and its related metabolic diseases (i.e., type 2 diabetes, cardiovascular disease, hepatic steatosis, etc) are major public health problems worldwide. Although an armamentarium of pharmacologic approaches is available for the treatment of those conditions, many patients fail to achieve their treatment goals suggesting that there is a need for more effective approaches for the prevention and treatment those conditions.</p> <p>I have a longstanding interest in understanding the mechanisms involved in the regulation of metabolic function and energy homeostasis in people. The overall goal of my research is two-fold to: 1) understand the mechanisms underlying the pathophysiology of the obesity related metabolic complications and 2) develop and evaluate interventions (nutritional, lifestyle, pharmacological, etc.) aiming to improve metabolic function and determine their underlying mechanisms. My primary research involves the use of both basic and clinical research tools to evaluate cellular, regional, and whole-body substrate metabolism to test physiologically and clinically relevant hypotheses in people in vivo.</p> <p>Our current research focuses on:</p> <ul style="list-style-type: none"> • understanding the role of the brown and white adipose tissue function in health and disease • examining the role of the temporal distribution of food intake (chrononutrition) on cardiometabolic health in high-risk populations for cardiometabolic disease <p>I am always happy to hear from enthusiastic PhD and postdoctoral candidates with strong background in nutrition, exercise physiology, metabolic science.</p>	<p>mc2425@medschl.cam.ac.uk</p>
<p>Dr Anthony Coll</p>	<p>Diseases of human metabolic health where energy balance is disordered are significant medical and socioeconomic problems. Meaningful intervention requires an understanding of the processes involved. My research aims to investigate how disorders of energy balance can result from disruption of the pathways that control how we eat, how we metabolise fuel and how we store excess energy in tissue. The basis of these studies comes primarily from studies of human disease, including rare genetic forms of obesity and larger population-based genetic studies.</p> <p>In collaboration with colleagues in the IMS (O’Rahilly, Yeo) my work aims to gain a more mechanistic understanding of how pathways highlighted by these human genetic studies can malfunction and result in disorders of energy balance and metabolism</p> <p>Our current understanding of the central control of appetite has relied heavily upon mouse models and I combine murine genetics and whole animal physiological studies to address these issues, in particular how signals from peripheral organs</p>	<p>apc36@medschl.cam.ac.uk</p>

	<p>are integrated within the brain to change appetitive behaviour. Through an evolving interaction with colleagues at CRUK , I am also interested in determining how resources and skills developed in the study of obesity can be employed to understand the body composition and metabolic phenotypes seen in cachexia.</p>	
<p>Dr Miguel Constância</p>	<p>Epigenetics is an exciting and rapidly moving field that impacts basic biomedical research and clinical medicine. Epigenetic mechanisms such as DNA methylation, histone modifications and non-coding RNAs provide dynamic, heritable and reversible ways of modulating genome function. They affect a number of processes such as chromosome architecture, chromatin function and gene expression.</p> <p>We are interested in understanding how epigenetic mechanisms regulate gene activity and how they respond to environmental cues (e.g. nutrition), with a focus on imprinted genes and developmental pathways that link growth with metabolic function.</p> <p>The work in the lab is divided into two related areas:</p> <p>1- Genomic imprinting and fetal growth</p> <p>Genomic imprinting is a form of epigenetic regulation in mammals which results in the silencing of one of the two gene copies, according to parental origin. Imprinted genes have key roles in maternal allocation of resources that affect the development of the placenta, fetal and infant growth, glucose and fat metabolism as well as adult behaviours. We are studying how imprinted genes control fetal growth and placental function and their roles in metabolic functions using genetically engineered mouse models, in vivo physiological assays, and cell based systems.</p> <p>2- Epigenetics and gene-environment interactions</p> <p>Epigenetics may underpin interactions between the genome and the environment. Environmentally-induced changes to the epigenome that may occur during the “waves” of genome-wide epigenetic reprogramming in early development are likely to have long term health consequences. We aim at finding key genes that, when epigenetically de-regulated by sub-optimal nutrition in early development, may contribute to onset and risk of diabetes and obesity phenotypes in later life. We use a combination of (epi)genomic-wide screens and in vitro manipulation of epigenetic machinery, in rodent and human biological materials, to detect loss of epigenetic cellular memory.</p>	<p>jmasmc2@cam.ac.uk</p>
<p>Dr Laura Dearden</p>	<p>The aim of our research is to find out how obesity during pregnancy alters development of the offspring’s hypothalamus- an area of the brain that is essential for regulating food intake- and leads to increased food intake and obesity later in life.</p> <p>Our research will help us understand the molecular mechanisms that mediate the effects of maternal obesity on offspring hypothalamic development and function. If we understand the mechanisms at play during a pregnancy with obesity, we can try and intervene in the inter-generational transmission of obesity risk. We are particularly interested in the role of insulin, as this is one of the main factors altered in both the mother and baby during a pregnancy complicated by obesity. We are using mouse models to define how the increased insulin levels in a pregnancy with obesity alters hypothalamic</p>	<p>ld454@medschl.cam.ac.uk</p>

	<p>development in the baby. In addition to direct effects on brain development insulin can regulate expression of miRNAs, which are small RNAs that control gene and protein expression. Insulin-mediated changes in miRNA levels are a likely cause of the lasting changes in gene expression in the hypothalamus that lead to feeding pathway dysfunction and thus obesity.</p> <p>Working in a mouse model, we can experimentally manipulate insulin and miRNAs in the fetal brain so that we can examine the consequences for hypothalamic development and later feeding behaviour when these factors are altered (as they are in a pregnancy with obesity). We are also investigating translatable interventions strategies that will correct maternal and fetal insulin levels in a more physiological way- such as exercise, or drugs that are given to women with gestational diabetes.</p> <p>This research will address an important gap in our knowledge of how it is that obesity during pregnancy affects the long-term metabolic health of offspring. It is currently not feasible to ensure all women enter pregnancy with a healthy BMI, so interventions to improve the health of offspring exposed to obesity in pregnancy may need to occur after birth. An understanding of the mechanisms at play during pregnancy will enable us to a) better advise individuals who have obesity during pregnancy and b) develop intervention strategies to stop the inter-generational transmission of obesity risk.</p>	
<p>Professor Mark Evans</p> <hr/>	<p>I am interested in (1) how brain detects changes in blood glucose and how this glucose-sensing interacts with peripheral metabolism (2) how defences against hypoglycaemia (low blood sugar) may become abnormal in diabetes (3) the short and long term effects of episodes of hypoglycaemia on brain (4) new and innovative technology for monitoring and managing diabetes, including the development of closed loop insulin pump systems (the “artificial pancreas”).</p>	<p>mle24@cam.ac.uk</p>
<p>Professor I. Sadaf Farooqi</p> <hr/>	<p>Research Vision</p> <p>Our goal is to develop new treatments for people living with severe obesity by delivering a step-change in our understanding of the control of human energy balance.</p> <p>Severe Childhood Obesity</p> <p>Previously, we have demonstrated that mutations disrupting the hormone leptin and its downstream neural targets cause severe childhood obesity. In clinical studies, we have demonstrated the critical role of this pathway in food intake, food reward and fat preference. Our current work builds on this framework to obtain a deeper understanding of the genetic, molecular and physiological mechanisms that control human energy homeostasis.</p> <p>With the help of many international collaborators, we have recruited over 7000 people with severe childhood onset obesity to the Genetics of Obesity Study (GOOS) (www.goos.org.uk). We use a number of genetic approaches to identify networks of genes and the molecular mechanisms they perturb. We undertake physiological studies in patients and volunteers to examine the role of the relevant molecules in eating behaviour, energy expenditure and peripheral metabolism. In this work, we benefit hugely from the Translational Research Facility (TRF)</p>	<p>isf20@medschl.cam.ac.uk</p>

	<p>Thinness</p> <p>We are also interested in understanding how and why some people remain thin in an obesogenic environment. Thinness (BMI<18kg/m²) is as heritable as severe obesity. We have recruited a UK cohort of 4000 thin people (STILTS cohort; www.stilts.org.uk) in whom we are undertaking genetic and physiological studies.</p> <p>Translational Research</p> <p>Our aim is to deliver treatments that will benefit people with severe obesity and use new knowledge to reduce weight stigma and discrimination. To that end, we work with a patient advocacy group, Obesity Empowerment Network (https://oen.org.uk/) and other partners. We developed new diagnostics for a range of obesity syndromes and an NHS Obesity Gene Panel is now available for use by Physicians in the UK (https://www.england.nhs.uk/publication/national-genomic-test-directories/). We treat patients with congenital leptin deficiency from around the world. We are running clinical trials administering Setmelanotide (a melanocortin 4 receptor agonist) in patients with several genetic obesity syndromes and work with other companies in drug discovery and trials.</p> <p>We are working with colleagues at the MRC Toxicology Unit, Dept of Medicine and Babraham Institute to study immune responses to the SARS CoV-2 vaccine in people with severe obesity (https://scorpiostudy.org.uk/).</p>	
<p>Dr Daniel Fazakerley</p>	<p>Research Interests</p> <p>We are interested understanding how insulin stimulates glucose transport into fat and muscle cells, and how this process breaks down in disease.</p> <p>One of the ways in which insulin lowers blood glucose is through stimulating glucose transport into adipose and muscle tissue. Insulin activates a signal transduction cascade in these tissues to promote the translocation of the glucose transporter GLUT4 from specialised intracellular storage vesicles to the plasma membrane, facilitating glucose uptake. We currently have an incomplete understanding of the signalling events and trafficking processes that control the redistribution of GLUT4. One of the objectives of our work is to fill in these knowledge gaps.</p> <p>The reason we want to increase our understanding in this area is that impaired insulin-stimulated glucose transport in muscle and fat is a major contributor to whole body insulin resistance – a state where insulin no longer efficiently lowers blood glucose and a risk factor for type II diabetes. There is currently no consensus on the molecular basis for impaired insulin responses in these tissues. We aim to shed light on how the insulin signalling network and GLUT4 trafficking apparatus are altered in insulin resistance.</p> <p>Research Approach</p> <p>We take an interdisciplinary approach using cell culture and in vivo models to study insulin action, GLUT4 trafficking and glucose metabolism. We design and perform unbiased mass spectrometry-based proteomics studies to uncover proteins</p>	<p>djf72@medschl.cam.ac.uk</p>

	<p>or protein post-translational modifications (e.g. phosphorylation) that may play a role in insulin-stimulated GLUT4 trafficking and/or insulin resistance.</p> <p>A current focus of our work is to develop techniques that allow us to screen many genes-of-interest for a role in insulin-stimulated GLUT4 trafficking, and that allow us to study distinct aspects of GLUT4 trafficking in cells (e.g. delivery to the cell surface, internalisation). We use our expertise in cell biology (e.g. microscopy) and biochemistry (e.g. subcellular fractionation, immunoprecipitation) techniques to study the role that proteins-of-interest play in the insulin signalling-GLUT4 pathway in health and disease.</p>	
<p>Professor Paul Fletcher</p> <hr/>	<p>I am interested in higher level perceptual and learning processes, and how these shape decision-making and behaviour. In particular, I try to understand how individual variability in such processes may contribute to seemingly irrational choices that may have health-harming consequences. This is relevant not just to an array of mental disorders but also to over-consumption and obesity. I think that it is very important that we do not consider the brain in isolation from either the body or from its external environment and that the study of high level cognitive processes must be shaped by close consideration of underlying metabolic and endocrine signals. This work benefits from collaboration with Professors Steve O’Rahilly and Sadaf Farooqi.</p> <p>In addition, the study of fundamental reward-related processes in the human brain benefits from close links with basic neuroscientists at the Behavioural and Clinical Neuroscience Institute, notably Professor Wolfram Schultz. And in attempting to extend the work beyond the laboratory to larger samples in naturalistic settings, I work closely with Professor Theresa Marteau at the Behaviour and Health Research Unit (http://www.bhru.iph.cam.ac.uk/).</p> <p>My work has focused on how combined functional neuroimaging, behavioural and pharmacological studies can elucidate brain processes involved in responding to environmental stimuli and determining food choice. Pharmacological perturbations, for example with dopamine agonists and antagonists, can be used to explore the neurotransmitter basis for these processes and ensuing measures of food-related behaviours are set up to determine the relevance of these lab and imaging-based measures to real-world choice and consumption. These studies have formed the basis for targeted assessment of brain structural changes associated with obesity.</p> <p>The overall aim, through systematic exploration of these processes, is to understand choice and behaviour in detail and to determine the basis for marked variability in susceptibility to internally- and environmentally-driven consumption. Through this understanding, a fuller comprehension of the multiple factors contributing to obesity will be possible.</p>	<p>pcf22@cam.ac.uk</p>
<p>Professor Fiona Gribble</p> <hr/>	<p>Hormones from the gut are central to the control of appetite and insulin release. Drugs based on the gut hormone glucagon-like peptide-1 (GLP-1) have proved highly successful for treating type 2 diabetes, and also suppress food intake. In collaboration with Frank Reimann our group researches how gut hormones are released and their actions on target tissues. We hope this will lead to the development of new drugs or diets that treat diabetes and obesity by targeting gut hormone release.</p>	<p>fmg23@cam.ac.uk</p>

	<p>The release of gut hormones such as GLP-1 and PYY after a meal conveys signals to the brain to stop eating, to the pancreas to produce insulin and to the gut to coordinate digestion. We are particularly interested in establishing how gut hormones are released after food ingestion, and how the gut endocrine system is affected after gastric bypass surgery.</p> <p>Our research encompasses a range of experimental approaches, from physiological studies in humans to analysis of single cells <i>in vitro</i>. We use optical and electrophysiological recording techniques to monitor stimulus detection and vesicle release from endocrine cells in primary intestinal cultures, intestinal organoids and immortalized cell lines. To identify living gut endocrine cells, we have generated transgenic models in which hormone producing cells, or cellular targets of gut hormones, are labelled by cell-specific fluorescent markers and reporters of cytoplasmic signalling pathways. The mechanisms by which cells detect stimuli are identified by combining methods such as live cell imaging, electrophysiology, transcriptomics and measurements of hormone secretion using immunoassays and LC-MS.</p>	
<p>Professor Mark Gurnell</p> <hr/>	<p>Although typically benign, tumours of the pituitary and adrenal glands are often associated with significantly increased morbidity and mortality – reflecting the primary disorder (e.g. cardiometabolic dysfunction in acromegaly and Cushing’s; hypertension in primary aldosteronism), or its treatment (e.g. hypopituitarism after pituitary surgery or radiotherapy). Our research is focussed on optimising the diagnosis and treatment of these conditions, to allow more patients to access specific, and potentially definitive interventions in a timely manner. For example, we have developed, and introduced into clinical practice, novel PET imaging techniques, which are transforming the care of a subgroup of patients with pituitary and adrenal tumours – individuals previously deemed unsuitable for surgery, and consigned to a lifetime of expensive/poorly tolerated medical treatment, are, in many instances, undergoing curative surgery. In parallel studies, we perform detailed phenotyping of patients with (i) acromegaly, (ii) TSH-secreting pituitary adenomas and (iii) primary aldosteronism.</p> <p>Together with Professor Chatterjee and Drs Moran, Oddy and Halsall, we also provide a UK national thyroid function test referral service, offering specialised clinical, biochemical, molecular and radiological phenotyping.</p> <p>In cross-disciplinary work (with Judge Business School), we are studying the endocrine and neural basis of financial decision-making. We have shown that human physiology is a powerful influence on the behaviour of those working on the world’s trading floors.</p>	<p>mg299@medschl.cam.ac.uk</p>
<p>Professor Roman Hovorka</p> <hr/>	<p>Diabetes Technology</p> <p>We are interested in using diabetes technology to improve life in people with diabetes and related conditions. Specifically we are developing and clinically testing the artificial pancreas in various populations. The artificial pancreas consists of a subcutaneous glucose monitor, a control algorithm, and an insulin pump. Our work includes the development of computer-based simulations for pre-clinical evaluation and optimisation of the artificial pancreas.</p>	<p>rh347@cam.ac.uk</p>
<p>Dr Albert Koulman</p>	<p>My main research involves developing cutting-edge analytical methods to measure specific metabolites and nutrients, and using these methods to facilitate the further understanding of our metabolism and of the role of metabolism in disease.</p>	<p>ak675@medschl.cam.ac.uk</p>

	<p>The current technical challenge is to comprehensively analyse all metabolites and lipids (aka metabolomics and lipidomics), which demands developments in experimental design, sample preparation, analysis, data processing and bioinformatics. I have been responsible for the development and application of novel analytical pipelines. These methods enables us to measure metabolites (fatty acids, lipids, etc.) in very large population studies, some of which are still the largest in the world, as well as to measure lipids in single cells (single cell lipidomics). We are currently using these results to understand how genetics and diet are associated with disease risk through metabolism. This has resulted, for example, in new understanding of the metabolism of odd chain fatty acids and their relation to diabetes risk. I was the first to adapt lipid-profiling methodology to use dried blood spots to measure lipid metabolism in healthy infants, leading to the development of biomarkers for infant nutrition. My research is divided into three key areas.</p> <ul style="list-style-type: none"> • Metabolism in pregnancy and early life. Early life exposure is associated with lifelong changes in disease risk. In collaboration with Sue Ozanne we study lipid metabolism during pregnancy and early life. This has led to development of biomarkers of gestational diabetes, infant nutrition and candidate markers of future childhood obesity. Furthermore, there are collaborations with different teams worldwide to study lipid metabolism of severely malnourished children. • Technological developments in metabolomics and lipidomics Our lab forms a technology ‘hub’, working on technological advances in metabolomics and lipidomics measurement. Together with the team of Dr Emmanouil Metzakopian we have developed a complete pipeline to use lipidomics to study single cells (Single cell Lipidomics) and we use to study the role of lipids in Parkinson’s disease, funded by the Michael J Fox Foundation. Our methods and analyses contribute to biomedical innovation in diseases where metabolism is perturbed. My lab works collaboratively to identify and validate metabolic markers that can be used in diagnosis and prognosis of disease and treatment, providing the complete pipeline from experimental design, sample preparation, analysis, data processing and bioinformatics. • Developing, validating, applying and disseminating methods for blood sample collection and nutritional biomarker analysis(supported by the MRC Epidemiology Unit) We will facilitate the application of nutritional biomarker analysis in (clinical) research, surveillance and experimental medicine, allowing objective measurement of dietary and nutritional status and identification of new nutritional biomarkers. <p>The combination of these research areas makes it possible to maintain the critical mass required to develop analytical methods and approaches with a high level of quality control and assurance. This provides the IMS with a centralised knowledge hub for analytical chemistry to drive forward our understanding of the role of metabolism in disease.</p>	
<p>Dr Florian Merkle</p>	<p>The Merkle laboratory aims to uncover the mechanistic basis of human neurological diseases using human pluripotent stem cell (hPSC)-derived culture systems in order to facilitate the development of effective treatments. We use a variety of techniques including CRISPR/Cas9-based genome engineering, single-cell transcriptomics, high content imaging,</p>	<p>fm436@medschl.cam.ac.uk</p>

electrophysiology and calcium imaging, and organoid and other co-culture systems. Our research focuses on three main areas:

1) Cellular models of obesity

Obesity leads to millions of premature deaths each year and lacks broadly effective treatments. It has a strong genetic basis and is caused in part by the abnormal function of cell populations in the hypothalamus that regulate appetite. We generate these human hypothalamic neurons from hPSCs to take advantage of the fact that can be produced in large numbers, are functionally responsive, have a human genome that can be readily edited, and are in culture environment that can be readily controlled. These advantages provide an unprecedented opportunity to study the genetic and environmental factors underlying obesity, and we are using the system to ask several questions: A) how do human neurons respond to metabolic factors and what role do primary cilia play in this process?, B) which genes associated with obesity act in hypothalamic neurons, and how does their dysfunction lead to cellular phenotypes? C) can we develop the hPSC-derived neuronal model system into a cellular platform for drug screens, e.g. for compounds that can promote the production of appetite-suppressing neuropeptides such as beta-MSH?

2) Metabolic and neurodegenerative disease

Mid-life obesity and diabetes has been identified as is a potential risk factor for dementia later in life, and certain anti-obesity drugs are neuroprotective. We are exploring the hypothesis that there are shared mechanisms between these diseases in a new line of investigation for our group, using a combination of *in vitro* co-culture models and *in vivo* models. In particular, we are using a prion model of neurodegeneration to understand how diet and/or drugs traditionally used to treat obesity and diabetes mechanistically act to alter disease severity and time course. We are also pursuing targeted CRISPR screens of genes associated with neurodegeneration and/or metabolic disease across a range of cell types to gain insight into cell type-specific cellular phenotypes that could contribute to these disease types. Our ultimate aim is to identify drug treatments that are more potently neuroprotective and could be given to at large scale to human populations.

3) Rational pluripotent cell line selection and genetic stability

HPSCs are widely used to study development or model disease *in vitro*, and to generate cellular products for human transplantation to restore function lost in disease. However, hPSCs accumulate mutations in culture that could compromise both the reproducibility of *in vitro* studies and the safety of regenerative medicine approaches. For example, hPSCs recurrently acquire cancer-associated mutations in the tumour suppressor *TP53* (p53) that promote growth in culture and would increase the risk of cancer formation from transplanted cells (Merkle et al., *Nature*, 2017). It is therefore critical to understand which mutations are likely deleterious, and to reduce the rate at these mutations accumulate in culture. In collaboration with the [UK Regenerative Medicine Platform](#) we are systematically testing the selective pressures hPSCs experience under different growth conditions, in order to identify conditions to optimise their genomic stability. In

	<p>parallel with these efforts we are working collaboratively to identify lead cell lines to underpin large-scale collaborative studies, which we hope will lead to greater reproducibility in the field.</p> <p>I am always happy to hear from outstanding graduate and postdoctoral candidates via email.</p>	
<p>Professor Sir Stephen O’Rahilly</p>	<p>I am interested in the aetiology and pathophysiology of human metabolic and endocrine disease and how such information might be used to improve in the diagnosis, therapy and prevention of these diseases. One major area of continuing interest is to better understand why some people are very susceptible to obesity and others seem resistant. We can learn quite a bit about this from human genetics but those discoveries need to be better integrated with growing fundamental knowledge regarding processes controlling energy intake and expenditure. I am also very interested in why people, particularly those who become obese, become resistant to the glucose lowering effects of the hormone insulin. Again the integration of human genetics with basic studies in cells and disease models will be necessary to advance our understanding. I am lucky to work in an environment where I can collaborate freely with a wide range of Principal Investigators, a subset of whom are previous trainees from my lab, who have complementary interests and expertise.</p> <p>I co-direct the Institute of Metabolic Science (IMS) with my colleague Professor Nick Wareham. Within the IMS, I direct the MRC Metabolic Diseases Unit. I am also Head of the University Department of Clinical Biochemistry. On the wider Cambridge Biomedical Campus, I am Scientific Director of the NIHR Biomedical Research Centre. I am also a Fellow of Pembroke College.</p>	<p>so104@medschl.cam.ac.uk</p>
<p>Professor Susan Ozanne</p>	<p>Early Programming of Obesity, Type 2 Diabetes and Ageing</p> <p>The major focus of our research is to understand the mechanistic basis of the relationships between sub-optimal early life nutrition and subsequent increased risk of type 2 diabetes, obesity, and premature death. There are a large number of epidemiological studies suggesting that such relationships exist- for example from children exposed to maternal obesity or under-nutrition- however the molecular mechanisms mediating such phenomena are not understood. Our goal is to define these mechanisms and to use this understanding to develop rational intervention strategies.</p> <p>Cardiovascular health: We have shown that the offspring of obese mothers develop cardiac hypertrophy, and this is associated with impaired cardiac function. These impairments in cardiac function could lead to increased risk of heart disease in later life. This phenotype is associated with alterations in cardiac microRNAs and a molecular switch in substrate utilization in fetuses that are exposed to an obese <i>in utero</i> environment. Recently, our studies have extended to incorporate echocardiographic imaging of cardiac function, which allows us to carry out non-invasive longitudinal assessments of cardiac function in parallel with blood pressure measurement in the offspring of obese mothers.</p> <p>We have recently developed models of both pharmacological (administration of metformin) and lifestyle (peri-gestational exercise) interventions during obese pregnancy. These intervention studies have provided vital clues as to the mechanism underlying the programming of offspring cardio-metabolic disorders in maternal obesity and we have shown rescue of some of the detrimental phenotypes in the offspring.</p>	<p>seo10@cam.ac.uk</p>

	<p>miRNAs as mediators of early life nutrition: We have a strong interest in defining the role of miRNAs as potential mediators of the effects of early life nutrition on gene expression and organ function. We use a range of molecular techniques to determine whether microRNAs in tissues such as the pancreas, liver and adipose tissue may be epigenetic regulators that are sensitive to programming by the nutritional environment associated and thus contribute to the dysfunction observed in these tissues. We have recently identified a subset of hepatic microRNAs sensitive to programming by maternal obesity, and used <i>in vitro</i> techniques to show a role for one of these microRNAs in development of early hepatic steatosis.</p> <p>Control of food intake: We have shown that increased weight gain observed in offspring exposed to maternal obesity is associated with hyperphagia, implicating altered central regulation of food intake as an underlying cause. Our research shows that exposure to maternal obesity results in disruption of early hypothalamic development, and altered anatomy and the expression of key feeding pathways in adulthood. We are using a combination of molecular and physiological techniques to define the metabolic parameters that mediate the effects of maternal obesity on hypothalamic development, and establish whether this disrupted development underlies the hyperphagia- and ultimately obesity- we observe in the offspring of obese mothers.</p> <p>Oxidative Stress, Senescence and Ageing: One of our most striking observations in offspring exposed to sub-optimal early life nutrition has been that life span can be increased or decreased by restricting growth either during suckling or fetal life, respectively. These differences in lifespan are associated with differences in telomere length in a number of organs. We are investigating whether the rate of early growth may affect degrees of oxidative damage, which in turn affect organ function leading to altered longevity.</p>	
<p>Dr Zahid Padamsey</p>	<p>Our aim is to understand how nutrition impacts brain function and energy use. We focus on how dietary manipulations (e.g. calorie restriction, high fat diet, etc) affect the cortex, which we probe <i>in vivo</i> using two-photon imaging and electrophysiology techniques in mice. We additionally carry out dietary manipulations and fMRI work in humans in collaboration with other labs (Farooqi, Fletcher).</p> <p>We have previously demonstrated that calorie restriction reduces cortical function in mice to save energy, resulting in impaired behavioural function (Padamsey et al., 2022; PMID: 34741806). Mechanistically, these changes depend on diet-induced reductions in the levels of leptin, a hormone that is secreted by adipose tissue in proportion to fat mass. These findings reveal that peripheral metabolic state and brain function are intimately coupled.</p> <p>Current we have three aims:</p> <ul style="list-style-type: none"> • Investigate how obesogenic, high-fat diets impact cortical function and energy use in mice and humans. • Investigate the role different metabolic hormones, such as leptin and insulin, play in influencing cortical function, including in the context of obesity and type 2 diabetes, which are associated with leptin and insulin resistance. 	<p>zp278@cam.ac.uk</p>

	<ul style="list-style-type: none"> Investigate the molecular mechanisms through which metabolic hormones exert their impact on cortical function and energy use. <p>To address these aims we use a range of techniques. We employ genetic and dietary manipulations in mice, accompanied by detailed investigations of function and energy use in mouse cortex using two-photon calcium and ATP imaging, <i>in vivo</i> and <i>ex vivo</i> patch clamp electrophysiology, and combined laser doppler and haemoglobin spectroscopy <i>in vivo</i>. We complement these techniques with behavioural assays, RNA sequencing, molecular biology approaches, and investigations in primary neuronal culture. For experiments in humans, we employ fMRI and cognitive testing before and after dietary manipulations in collaboration with other labs.</p> <p>I am always happy to hear from passionate PhD and postdoctoral candidates coming from either a neuroscience or metabolic science background.</p>	
<p>Professor John Perry</p> <hr/>	<p>My research is focused on using human genetics to identify genes and biological mechanisms underlying susceptibility to metabolic disease, with an emphasis on early-life exposures and reproductive ageing. This is achieved through large-scale population studies where we perform genome-wide genetic screens for naturally occurring alleles influencing phenotype. Identifying genetic determinants of health and disease states has the potential to both highlight the underlying biology and inform epidemiology. For example, we can use genetic risk scores to predict individuals at high risk of common disease or infer causal relationships between diseases and modifiable risk factors. To advance biological understanding, my team collaborate with colleagues in the IMS-MRL and elsewhere to experimentally characterise identified genes in cellular and animal models.</p> <p>In addition to my position in the IMS-MRL, I am an MRC programme leader in the MRC Epidemiology Unit and associate group leader at the Gurdon Institute.</p>	<p>jrbp2@cam.ac.uk</p>
<p>Professor Frank Reimann</p> <hr/>	<p>Intestinal hormone secretion and action</p> <p>The intestinal epithelium is scattered with enteroendocrine cells (EECs), which, although only accounting for less than 1% of this tissue, can be considered the biggest endocrine organ in the body. Some of the peptides secreted have important regulatory roles for metabolism; glucagon-like peptide-1 (GLP-1) for example boosts postprandial insulin secretion and is the basis for mimetics with improved plasma half-life now widely used in the treatment of diabetes. GLP-1 and the co-secreted polypeptide YY also reduce food intake, and elevated plasma levels of these hormones correlate with the positive effects of gastric bypass surgery for the treatment of obesity.</p> <p>Our lab, which works in close collaboration with Fiona Gribble's group, has in recent years made a number of transgenic mice in which cells expressing specific hormones are tagged by fluorescent reporters or Cre-recombinase, allowing identification and/or manipulation of EEC-subsets. We have established intestinal organoids – intestinal epithelial stem cells giving rise to all derived cells including EECs <i>in vitro</i> – from different intestinal sections from these mice and similar organoid cultures derived from human intestinal tissue. We use electrophysiological and live-cell imaging techniques to identify the</p>	<p>fr222@cam.ac.uk</p>

	<p>mechanisms underlying the secretion of GLP-1, glucose-dependent insulinotropic peptide (GIP) and other hormones, with the aim eventually to manipulate their release therapeutically for the treatment of diabetes and obesity. We are developing LC-MS/MS based methods for simultaneous and sensitive detection of gut hormones in biological matrices, which we hope will extend our understanding of integrated EEC-responses to different nutrient challenges and after intestinal surgery. To better understand the targets recruited by these gut hormones we have made mice tagging cells expressing the receptors for some of the secreted peptides, e.g. GLP1R, GIPR and Rxfp4, the receptor for insulin-like peptide-5 (InsI5), which is co-secreted with GLP-1 in the distal colon. Ongoing research focuses on the expression of these receptors in several different nuclei of the central nervous system regulating food intake and energy homeostasis.</p>	
<p>Professor David Savage</p>	<p>Insulin resistance and type 2 diabetes are quintessential complex diseases involving hormone action or resistance in several different target tissues. Unravelling this complexity is impossible in cultured cells alone and unfortunately whilst many disorders can be reliably modelled in rodents, this is not always the case in insulin resistance where my own work has already highlighted some key interspecies differences (Embo Mol Med 2009). Many different approaches are therefore needed to tackle this complex metabolic problem.</p> <p>Our work is currently focussed in three areas, all of which relate to lipodystrophy, a rare cluster of disorders, characterised by too little rather than too much fat (obesity). Remarkably, lipodystrophy is associated with all the features of the metabolic syndrome. Within the past decade we identified four novel subtypes of partial lipodystrophy; two caused by mutations in adipocyte lipid droplet proteins, one caused by loss-of-function mutations in Pcyt1a, the rate limiting enzyme in Kennedy pathway phosphatidylcholine synthesis, and one caused by mutations in MFN2, a key regulator of mitochondrial fusion. The group is actively engaged in studies aimed at understanding the key cell biological roles of these and other proteins involved in energy storage (see below).</p> <p>Within the past 2 years, in collaboration with colleagues in the MRC Epidemiology Unit in Cambridge, we have provided compelling human genetic evidence suggesting that subtle forms of lipodystrophy are a prevalent cause of human insulin resistance (Lotta et al, NG 2017).</p> <p>Specific research programmes:</p> <p>1) The molecular basis of human lipodystrophies</p> <p>Understanding the molecular basis of rare human inherited diseases has, over many decades, provided key insights into both the pathophysiology of disease and more fundamental understanding of cell biology and human physiology. We have access to a unique population of patients with extreme insulin resistance/lipodystrophy. Mutations detected in candidate gene studies are explored further for their role in human disease by linkage studies in pedigrees, functional studies of the properties of the mutant variant and detailed in vivo studies in humans. More recently, we have switched from a candidate based approach to the use of next generation whole exome/genome sequencing in efforts to identify novel genetic causes of severe insulin resistance.</p>	<p>dbs23@cam.ac.uk</p>

	<p>Having recently shown that subtle forms of lipodystrophy contribute to prevalent human insulin resistance, we are also increasingly involved in characterising coding (missense) variants which affect fat mass/ distribution in the general population.</p> <p>2) Lipid droplets (LDs)</p> <p>LDs are unique organelles in being surrounded by a phospholipid monolayer and, presumably related to the unique biophysical properties of this monolayer and the underlying hydrophobic neutral lipid core, are targeted by a specific set of proteins. Our recent discoveries of genetic mutations in LD proteins have led us to explore the fundamental biology underpinning the targeting and subsequent requirement of CIDEC for the formation of a unilocular LD in white adipocytes and also to explore the way in which perilipin1 co-ordinates the sequential activity of triacylglycerol lipases. This work is leading us in entirely new and fascinating directions.</p> <p>3) In vivo models</p> <p>Ectopic fat accumulation is strongly linked to insulin resistance although mechanistic details remain incomplete. In order to understand the metabolic pathways responsible for ectopic fat accumulation, a prominent feature in all severe forms of lipodystrophy, we undertake a combination of detailed mouse and human physiological studies.</p>	
<p>Dr Nadia Schoenmakers</p>	<p>My principal research interest lies in elucidating the genetic and environmental determinants of congenital hypothyroidism (CH), the commonest neonatal endocrine disorder, due either to failure of thyroid gland development (dysgenesis) or function (dysmorphogenesis). Central hypothyroidism, a rarer entity, is due to impaired thyrotropin (TSH) production by the pituitary gland.</p> <p>I use candidate gene, gene panel and whole exome sequencing technologies to identify known and novel genetic causes of CH. I then undertake phenotyping of genetically ascertained individuals with parallel molecular and murine studies, aiming to gain new insights into thyroid biology and associated extra-thyroidal phenotypes.</p>	<p>naaa2@cam.ac.uk</p>
<p>Professor Antonio Vidal-Puig</p>	<p>Molecular Mechanisms of Energy Balance</p> <p>Our program of research explores the molecular mechanisms involved in controlling energy expenditure, fat deposition, and the mechanisms controlling the partition of energy towards oxidation or storage.</p> <p>Specifically we are interested in the following interrelated questions.</p> <ol style="list-style-type: none"> 1. How the expansion of adipose tissue typically associated with obesity relates to the development of the Metabolic Syndrome. More specifically we are exploring whether lipotoxicity and/or changes in adipokines secreted by adipose tissue affect insulin sensitivity in other organs (skeletal muscle, heart, liver, brain, beta cells and macrophages). 	<p>ajv22@medschl.cam.ac.uk</p>

	<ol style="list-style-type: none"> 2. Whether modifications in adipogenesis and remodeling of adipose tissue may be good strategies to ameliorate the metabolic effects associated with obesity. 3. The molecular mechanisms that control energy expenditure and brown fat activation. 4. Whether modulation of partitioning of nutrients towards fatty acid oxidation in skeletal muscle and away from storage in adipose tissue may prevent the devastating metabolic effects of obesity. <p>To address these challenges is a daunting task that requires the modulation of highly integrated and complex mechanisms of energy homeostasis designed to prevent negative energy balances. According to this integrated concept of energy homeostasis, my laboratory is using an Integrated Physiology approach that relies greatly upon the generation and detailed <i>in vivo</i> phenotyping of genetically modified organisms. Together with Systems Biology approach integrating transcriptomic and lipidomic analysis, using bioinformatics to identify organ specific lipid metabolic networks relevant for insulin resistance and metabolic disease.</p>	
<p>Professor Giles Yeo</p>	<p>We aim to identify new molecules and pathways that play a role in the brain control of energy homeostasis, and thus reveal new potential therapeutic targets to tackle obesity.</p> <p>The approaches we have taken include:</p> <p>Mapping the human hypothalamic functional architecture underlying appetitive control using both single nucleus RNA sequencing (NucSeq) and single molecule fluorescent in situ hybridization (smFISH).</p> <p>Genetic studies point to the brain, and in particular the hypothalamus, as having a crucial role in modulating appetitive behaviour, which has limited the mechanistic insights achievable from human research. The inaccessibility of the human hypothalamus has, to date, meant our understanding of circuitry controlling food intake has emerged primarily from murine studies. For example, arcuate proopiomelanocortin (POMC) and NPY/AgRP neurons are critical nodes in the control of body weight. Often characterised simply as direct targets for leptin, recent data suggest a more complex architecture. Using single cell RNA sequencing, we have generated an atlas of gene expression in murine POMC and NPY/AgRP neurons. These data reveal murine arcuate POMC neurons to be a highly heterogeneous population (<i>Lam et al, Mol Met 2017</i>). Now, a collaboration with the Cambridge Brain Bank, has provided us access to frozen human donor brain samples. In a BBSRC funded project grant we are transcriptionally profiling >500,000 human hypothalamic cells using NucSeq, as well as mapping the feeding circuitry onto human hypothalamic sections using smFISH. In addition, in a BBSRC CASE PhD studentship together with Novo Nordisk, we are characterising human neurons expressing the GLP1-R. Mechanistic studies on the brain will naturally, still require mouse models. However, comparing and contrasting the human and mouse architectures will allow us, and others in the field, to refine our approach and focus our efforts on only the relevant appetitive circuitry that exists in both species.</p> <p>Molecularly characterizing, in human neurons, genes associated with severe obesity identified from consanguineous pedigrees. 10% of severe human obesity currently has a monogenic cause. Thus, much of the genetic aetiology of severe obesity remains unknown. In an MRC funded collaborative project grant with Philippe Froguel (Imperial/Lille), we are</p>	<p>gshy2@cam.ac.uk</p>

studying the disease in consanguineous pedigrees. Froguel has recruited a cohort of >400 severely obese children from consanguineous families in Pakistan, in which homozygous mutations in the leptin-melanocortin pathway, identified by whole exome sequencing, explain ~30% of cases. We are currently molecularly characterizing emerging candidate genes that emerge from the screen in human neurons and mapping their expression in the human hypothalamus. In addition, we plan to explore the functional consequences of mutations in these candidate genes in hypothalamic neurons derived from human stem cells.

Understanding the physiological role of known genetic modifiers influencing food intake and body-weight

The first and most robust of the genes identified by GWAS is FTO (fat mass and obesity related transcript) and we have taken a number of different approaches to studying its biology. We have contributed to characterizing its enzymatic function as a demethylase (*Gerken et al, Science 2007; Ma et al, Biochem J 2012*), as well as identifying and characterizing loss-of-function human mutations (*Boissel et al, AJHG 2009; Meyre et al, Diabetes 2010*). Whatever the explanation for the effects of intronic polymorphism on human adiposity, studies of humans and mice indicate that FTO itself is an important regulator of body size and composition. We have demonstrated a role for FTO in the cellular sensing of amino acids, linking levels to mTOR signalling (*Cheung et al, IJO 2013; Gulati et al, PNAS 2013*), and that FTO links high-fat feeding to leptin resistance through activation of hypothalamic NFκB-related signalling pathways (*Tung et al, Mol Met 2016*).

However, as FTO has demonstrated, the speed of translating these obesity GWAS genes into insightful biological knowledge has been disappointing for two reasons: (1) the vast majority of the identified obesity susceptibility variants are located in intronic or intergenic regions, making the identification of the 'causative' gene difficult to establish; and (2) the investigation of the involvement of the 'proposed' genes have so far been addressed in more complex model organisms such as mice. There is therefore an unmet need for validation of this GWAS data. *Drosophila melanogaster*, a key model for research in developmental biology, cell biology and neurobiology, has recently been demonstrated to be an excellent model for dissecting metabolic homeostasis and nutrient sensing pathways.