Cambridge Offered Projects for 2022 Entry in NIH OxCam Scholars Programme

Category	Project	Project_Listed_Date	Institute_Center	NIH_Mentor	UK_Mentor	University	Project_Details
Genetics & Genomics	Using population genomic approaches to evaluate Anopheles gambiae	2019-09	National Human Genome Research Institute (NHGRI)	Adam Phillippy	Mara Lawniczak	Cambridge	investigate population structure and signatures of selection. In the recent past, long reads are more traditionally used to build reference genomes to which the short read data can be aligned and evaluated. However, the cost of long read sequencing as well as the DNA input required to generate high quality long read data is dropping rapidly. We foresee a future where population genomics transitions to long read data. Using these emerging technologies, this project will begin to evaluate what new insights are gained for the Anopheles gambiae species complex, a set of mosquito species famous as the vector of malaria and known to exhibit porous species boundaries and abundant structural variation. We anticipate that long-read approaches for haplotype phasing and structural variant discovery will enable much clearer resolution of gene flow within species, introgression between species, and alleles under directional or balancing selection. Insights gained from this project are likely to influence approaches taken for other species that are known to have similar complexities (e.g.,
Developmental Biology	Effects of obesity on maternal metabolism and fetal growth	2020-10	N/A	N/A	Amanda Sferruzzi-Perri	Cambridge	Obesity during pregnancy affects maternal and infant health both during pregnancy and for long afterwards. It raises the risk of health complications like maternal diabetes during pregnancy, and increases the susceptibility of the mother to develop metabolic syndrome in the years after delivery. It also leads to neonatal and later life health complications in their infants, such that infants are more prone to develop metabolic impairments themselves in later life. Despite this, the mechanisms operating during pregnancy that lead to these poor pregnancy outcomes in obese women, remain unknown. The placenta is the organ that produces hormones responsible for changing the metabolism of the mother to ensure sufficient nutrients are available for fetal growth during pregnancy. However, to date, little is known about the role of placental hormone production in the development of maternal metabolic complications in pregnancies where the mother is obese. This study aims to identify the importance of placental hormone production for maternal metabolism and fetal growth in pregnancies where the mother is obese. It will use samples from pregnant mice that are lean or obese (due to a diet high in sugar and fat) and omic approaches (RNAseq/mass spec) on fluorescence-activated sorted placental endocrine cells to identify the hormones disrupted by maternal obesity with metabolic effects. It will also use metabolic, molecular, mitochondrial and biochemical assays to assess the mother€™s ability to use glucose and respond to insulin in obese mice with and without a genetic defect in the placenta that disrupts placental hormone production. Finally, hormones identified to be importance in maternal metabolic regulation in mouse pregnancies will be quantified in the plasma of lean and obese women to determine if they relate to pregnancy outcome.
Microbiology and Infectious Disease	Forward and reverse genetic screening of macrophages and epithelial cells to identify host factors controlling nontuberculous mycobacterial infection.	2020-10	National Heart, Lung, and Blood Institute (NHLBI)	Ken Olivier (NHLBI) & Steve Holland (NIAID)	Andres Floto	Cambridge	Nontuberculous mycobacteria (NTM) represent the most common mycobacterial infection in the developed world and are often difficult or impossible to treat. While exposure of humans to NTM is almost universal (most species are ubiquitous in the environment), pulmonary infection only occurs in certain individuals, suggesting a strong genetic contribution to host susceptibility. Nontuberculous mycobacteria (NTM) represent the most common mycobacterial infection in the developed world and are often difficult or impossible to treat. While exposure of humans to NTM is almost universal (most species are ubiquitous in the environment), pulmonary infection only occurs in certain individuals, suggesting a strong genetic contribution to host susceptibility. Our proposal aims to use both forward and reverse genetics to define and characterise host restriction factors for NTM infection. The project will employ the following orthogonal experimental approaches: 1) We will functionally test the impact of genetic polymorphisms, identified through the NIH whole exome sequencing study of NTM-infected individuals and family pedigrees (Ref) using CRISPR-Cas9 genomic editing of macrophages and IPSC-derived epithelial cells. 2) In parallel, we will undertake an unbiased forward genetic screen using an established and validated genome-wide CRISPR-Cas9 macrophage library to phenotypically screen for mutants with defective restriction of intracellular NTM. Validated hits from both approaches will be prioritised, based on novelty and effect size, for further analysis to examine (a) their molecular mechanism of action (using advanced cell imaging and biochemical techniques), (b) their effect on in vivo infection (using established fly, fish, and mouse models); and (c) the impact of potential therapeutic manipulation of implicated pathways as host-directed therapy.
Virology	HIV-1 assembly and release, and Env incorporation	2020-10	National Cancer Institute (NCI)	Eric Freed	Andrew Lever and John Briggs	Cambridge	The Freed lab is interested in the assembly and release of HIV-1 from infected cells, Env incorporation, the host factors that both promote and restrict the late events in HIV-1 replication, and virus maturation. The lab has a long-term program focused on developing maturation inhibitors, and has recently discovered a role for the HIV-1 envelope glycoprotein in conferring broad antiretroviral drug resistance. A new project is focused on cellular factors that block the function of a range of viral glycoproteins, including the spike protein of SARS-CoV-2.

Microbiology and Infectious Disease	Mechanisms underlying DNA replication and cell cycle control in Plasmodium	2020-10	N/A	N/A	Catherine Merrick	Cambridge	My group studies the human malaria parasite Plasmodium falciparum. Collaborative PhD projects can be offered in research areas centered around Plasmodium DNA biology: we are particularly interested in the molecular mechanisms underlying DNA replication and cell cycle control in Plasmodium, which replicates by an unusual method called schizogony. We are also interested in mechanisms for silencing and promoting the recombination of a family of key virulence genes called var genes - particularly the role that G-quadruplex DNA structures may play in var gene control. In fact, we have recently discovered that G-quadruplexes and their helicases have more general roles in genome stability and evolution in the malaria parasite as well.
Molecular Biology and Biochemistry	Molecular Mechanism of the Integrated Stress Response	2020-10	National Institute of Child Health and Human Development (NICHD)	Alan Hinnebusch	David Ron	Cambridge	A signalling pathway linking nutrient availability to changes in gene expression that hinges on the phosphorylation of translation initiation 2 (eIF2) has long been known to exist. Recognized initially as the yeast General Control Response, recent convergent lines of research have implicated its metazoan counterpart, the Integrated Stress Response, in diverse physiological processes ranging from immunity to memory formation. This PhD programme will exploit our emerging detailed understanding of translation initiation and termination to shed light on unanticipated mechanistic aspects of the ISR. An understanding of these details may inform efforts to target the ISR to therapeutic ends.
Molecular Biology and Biochemistry	Characterizing the MPC complex structure and mechanism	2020-10	National Institute of Neurological Disorders and Stroke (NINDS)	Lucy Forrest	Edmund Kunji	Cambridge	The mitochondrial pyruvate carrier (MPC) is critical for cellular homeostasis, as it transports pyruvate, the end product of glycolysis, from the cytosol into the mitochondrial matrix, where it enters the Krebs cycle. Dysfunction of MPC has been implicated in many diseases and MPC is being investigated as a drug target for the treatment of cancer, non-alcoholic fatty liver disease, Parkinson€™s disease and diabetes, because of its central role in metabolism. MPC is a heterodimeric complex of two small homologous membrane proteins, called MPC1 and MPC2 (1, 2). There is currently no structure and the molecular transport mechanism has not been elucidated. The aim of this project is to characterise the MPC complex with respect to its structure and mechanism, and to develop it further as a drug target. The Forrest lab (NIH-NINDS) uses bioinformatics, structural modelling, and molecular simulations to study integral membrane proteins. The lab focuses on transporters, and in particular, those that harbour mechanistically-relevant symmetries, and has successfully predicted important functional properties of many different transport proteins (3-5). The lab also develops novel bioinformatic tools, such as the sequence alignment software, AlignMe, aimed at improving structural modelling approaches for membrane proteins (6). The Kunji lab (University of Cambridge) has developed methods to purify the MPC complex, to reconstitute it into liposomes, and to study its transport properties (1, 2). In addition, it has developed methods to study the binding of small molecules to the MPC complex, opening the way to find specific inhibitors, which could be developed further as drug leads. The lab also uses advanced x-ray crystallography and cryo-EM techniques to obtain the structures of highly dynamic mitochondrial transporters, for example the mitochondrial ADP/ATP carrier (7).
Neuroscience	Molecular studies of excitatory and inhibitory CA1 synapses in synaptic plasticity	2020-10	National Eye Institute (NEI)	Wei Li	Ingo Greger	Cambridge	A balance between neuronal excitation and inhibition is crucial for normal brain physiology; upsetting this balance underlies various brain pathologies. To shed light on the molecular underpinnings of this regulation at the synapse level, this project will investigate the dynamics of glutamate- and GABA-A synapses and receptors in CA1 hippocampus under baseline conditions and in response to synapse potentiation. Specifically, using structural, functional and imaging approaches we will study both, spiny glutamatergic and aspiny GABA-ergic CA1 synapses and associated receptor complexes (AMPA-type glutamate and GABA-A) and how these change at the synapse- and receptor levels in response to LTP (long-term potentiation) induction. Our aim will be to monitor changes of glutamatergic and GABAergic synapses and receptors at pyramidal neurons (glutamate) and/or parvalbumin-positive (PV+) interneurons at various points after LTP induction. We will monitor changes in synapse size and receptor composition using advanced imaging and electrophysiological approaches.

Microbiology and Infectious Disease	Understanding natural immunity to malaria for better vaccine design	2020-10	National Institute of Allergy and Infectious Diseases (NIAID)	TBC	Julian Rayner	Cambridge	There are more than 200 million clinical cases of malaria each year, leading to nearly half a million deaths, primarily among children in Africa. The two major tools for malaria control, antimalarial drugs and insecticides, are both seriously threatened by resistance, making the search for a highly effective malaria vaccine more urgent than ever. My lab focuses on the malaria parasite blood stages, during which parasites invade, multiply inside and consume human erythrocytes. The process of erythrocyte invasion represents a brief extracellular window in the parasite life cycle when parasites are exposed to the antibody-mediated immune system, making it a potential vaccine target. A number of vaccine-related projects are available that intersect with the interests of NIH collaborators in the NIAID Malaria Research Program, from systematic screening of new potential vaccine candidates, to deep structural understanding of current high-profile candidates, to understanding natural immunity to malaria in order to inform better vaccine design. All could involve a mix of new technologies, cutting edge experimental genetics, parasite biology and the opportunity to contribute to the long-term battle against one of humanities oldest and most persistent infectious disease foes.
Microbiology and Infectious Disease	Understanding genetic susceptibility to nontuberculous mycobacterial infections	2020-10	National Institute of Allergy and Infectious Diseases (NIAID)	Steve Holland	Lalita Ramakrishnan	Cambridge	TB remains the biggest infectious killer in the world despite >50 years of antimicrobial therapy. 10 million people get TB each year of whom nearly 2 million succumb to it. Yet this burden represents only 5-10% of those who get infected; 90% clear the infection on their own. Both the Ramakrishnan and the Holland labs are trying to solve the puzzle of why some individuals get TB disease. The two labs take different and complementary approaches to the problem. Holland runs an internationally known referral service that takes care of a unique cohort of patients with genetic susceptibility to nontuberculous mycobacterial infections. In the lab, they have mapped these susceptibilities to varied immune genes €“ IRF8 and GATA-2, myeloid growth factors, IL-12R, the GTPase Rac2, to name only a few. How and whether deficiencies in these genes causes susceptibility to TB remains a black box. Ramakrishnan€™s approaches afford the opportunity to open this black box. Her group has pioneered the optically transparent and genetically tractable zebrafish infected with Mycobacterium marinum as a model for TB. The use of the zebrafish has enabled discoveries about TB immunopathogenesis and the genetic basis of susceptibility to TB which has led to the discovery of a variety of inexpensive, approved drugs that can be used to treat TB, often in a patient genotype-directed manner. Through this joint project, the two labs will work together to harness the power of the zebrafish to understand the molecular and cellular basis of the human susceptibilities identified by Holland. The student will move between humans and fish (and Bethesda and Cambridge) to uncover fundamental mechanisms of mycobacterial disease pathogenesis while acquiring mastery over the disciplines immunology, infectious diseases, genetics, molecular biology and cell biology.
Pharmacology	Self-assembling multi-functional biomolecular condensates for targeted degradation of disease-associated proteins	2020-10	N/A	N/A	Laura Itzhaki/ Janet Kumita	Cambridge	We are developing artificial multi-valent proteins capable of liquid-liquid phase separation (LLPS) with the aim of building multi-functional biomolecular condensates and thereby harnessing specific cellular enzymes to target disease-associated proteins for destruction. We propose to design condensates that contain a class of proteins known as tandem-repeat proteins (RPs). We have shown that RPs are strikingly amenable to rational design and can be engineered to simultaneously bind multiple proteins, bringing them into specific spatial proximity in such a way as to enable a chemical modification of the target protein. The rational design of LLPS systems capable of selectively recruiting client proteins into them to drive specific biological reactions would enable both a deeper understanding of the role of biomolecular condensates in nature as well as the exploitation of their remarkable physico-chemical properties for therapeutic effect. Key areas of interest include: 1) Understanding the molecular grammar of protein phase separation to define rules for creating designer LLPS systems. 2) Developing novel hetero-bifunctional phase-separating proteins to recruit disease-associated targets to the protein degradation machinery. 3) Translating the designed LLPS proteins into biomolecular condensates in the cell capable of enhancing targeted protein degradation.

Neuroscience	Developing novel treatments for children with inherited neurological diseases	2020-10	National Institute of Neurological Disorders and Stroke (NINDS)	Dr. Carsten Bonnemann	Rita Horvath	Cambridge	Inherited neurological disorders are disabling, progressive, often fatal conditions, representing an enormous unmet medical need with devastating impacts on affected families, the healthcare system, and the economy. There are no cures and the limited therapies available treat symptoms without addressing the underlying disease. Next-generation sequencing has facilitated a molecular diagnosis for many inherited neurological disorders, such as mitochondrial diseases and other neuromuscular diseases, which are the focus of this research. The development of targeted therapies requires detailed laboratory investigation of molecular and mutational mechanisms, and a systematic evaluation of well-chosen agents as well as gene and transcript directed strategies using standardized experimental systems. Our research is focusing on understanding the molecular pathogenesis of childhood onset inherited neurological diseases, such as mitochondrial disease and other neuromuscular diseases to develop targeted therapies. Using a translational approach, we aim to 1. understand the clinical course of patients in relation to the underlying disease mechanism 2. delineate the mutational and molecular mechanisms of the molecular defect in the appropriate cell types by developing model systems such as induced neuronal progenitor cells (in vitro) and zebrafish (in vivo) 3. improve the treatment options for patients by developing novel therapies that are directed at these mechanisms, including directly at the genetic mutation or resulting transcript. We use a combination of exome sequencing, genome sequencing, and other omics technologies to identify novel disease genes and disease mechanisms. By functional evaluation in vitro (induced neuronal progenitor cells) and in vivo (zebrafish) we confirm pathogenicity and uncover molecular mechanisms of disease. To address the mutational mechanisms, we use gene transfer, splice modulation, allele silencing and CRISPR/cas systems.
	Characterisation of parasite cell proteomes	2020-10	National Institute of Allergy and Infectious Diseases (NIAID)	Michael Grigg	Ross Waller	Cambridge	Apicomplexan pathogens are highly-adapted intracellular parasites of humans causing disease including malaria, toxoplasmosis and cryptosporidiosis. These parasites actively confront, subvert and defend themselves against host immune attack using a complex suite of parasite surface and secreted proteins that hijack immune signalling pathways. Moreover, transmission and generation of genetic novelty occurs in definitive hosts where differentiation into sexual parasite forms occurs. Relatively little is known, however, of the molecules and processes that drive these events, particularly during the sexual stages of parasite development.Â This project will use new methods in in vitro culture of sexual development in Toxoplasma, advanced methods for global spatial characterisation of parasite cell proteomes in order to identify specific proteins thought to be implicated in these interactions, and then utilise CRISPR/cas9 mutagenesis tools to engineer pools of strains deficient in these specific proteins.Â By assaying mutant pools both in vitro, and through the definitive host we will identify proteins and processes required for sexual stage conversion.
Neuroscience	Ultra-high field imaging of adaptive brain circuits	2020-10	National Institute of Mental Health (NIMH)	Peter Bandettini	Zoe Kourtzi	Cambridge	The human's brain capacity for sensory plasticity has been studied mainly in the context of neurodevelopment (i.e. critical periods) and pathology (e.g. amblyopia) with interventional approaches (e.g. sensory deprivation) that result in drastic brain re-organisation. Yet, understanding the brain plasticity mechanisms that mediate subtler changes in perceptual judgments through shorter-term experience and training remains a challenge. This project focuses on the brains ability to improve perceptual skills at the core of visual recognition through training; that is, the ability to detect the features of an object from cluttered backgrounds and discriminate whether they belong to the same or different objects. Learning and experience have been suggested to facilitate this ability to translate complex patterns of visual information into perceptual decisions. We will exploit methodological advances in high-field (7T) brain imaging to investigate functional and neurochemical brain plasticity mechanisms at finer-scale. We will test the hypothesis that perceptual learning is implemented by feedback and inhibitory mechanisms that re-weight sensory information across stages of processing (from early to higher visual cortex). In particular, the high resolution of 7T imaging allows us to measure functional signals in different cortical layers. We will test whether learning alters fMRI activation patters in deep rather than middle layers in the visual cortex, consistent with feedback processing. Further, advances in MR Spectroscopy enable us to test the role of GABA the primary inhibitory neurotransmitter for brain plasticity in perceptual learning. We will test whether learning-dependent changes in GABA relate to changes in functional brain activity and improved behavioural performance in perceptual tasks. Investigating these core mechanisms of brain plasticity will advance our understanding of how the brain optimises its capacity to support adaptive behaviour through learning and experience.

Genetics & Genomics	Understanding how germ cells ensure genome integrity and the survival of future generations	2020-11	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	Astrid Haase	Felipe Karam Teixeira	Cambridge	Germline genomes are immortal. Their genetic information is transmitted to the next generation and ensures that continuation of life. To protect the integrity of their genomic information, germ cells employ a specialized small RNA-based defense system, PIWI-interacting small RNAs (piRNAs) and their PIWI protein partners. The interest of the Karam Teixera lab in germ cell biology and evolution and the focus of the Haase lab on mechanisms of small silencing RNAs converge on piRNA-guided surveillance of genome integrity. The collaborative project of an OxCam Scholar is designed to combine strength of both labs in genetics, biochemistry and genomics, and offers training in experimental techniques and basic computational analyses of next-generation sequencing data. Results from this graduate study will further our understanding of how germ cells ensure genome integrity and the survival of future generations.
Neuroscience	Stem cells of the aging MS brain	2020-11	National Institute on Aging (NIA)	Isabel Beerman	Stefano Pluchino	Cambridge	Primary progressive multiple sclerosis (PPMS) is a chronic demyelinating disease of the central nervous system, which currently lacks restorative therapies. Transplantation of neural stem cells (NSCs) has been shown to promote healing of the injured CNS, but previous work has demonstrated that NSCs from patients with PPMS are prematurely senescent. Cellular senescence causes a pro-inflammatory cellular phenotype that impairs tissue regeneration. Senescence in PPMS NSCs was found to be associated with increased secretion of HMGB1, a pro-inflammatory alarmin found to inhibit oligodendrocyte differentiation, and also found increased within white matter lesions of PPMS autopsy tissue. This project aims to understand the role of HMGB1 in PPMS NSC senescence using techniques such as CRISPR-Cas9, RNA sequencing, and functional NSC assays. The longterm goal of this project will be to determine the cause of senescence in NSCs from patients with PPMS and if these cells are suitable for therapeutic use.
Cancer Biology	The role of tumor suppressor, adenomatous polyposis coli (APC) inactivation in colorectal cancer	2021-05	National Heart, Lung, and Blood Institute (NHLBI)	John Hammer	Marc de la Roche	Cambridge	The tumor suppressor adenomatous polyposis coli (APC) is at the nexus of cellular homeostasis, controlling microtubule and actin dynamics and regulating the Wnt pathway, a cell-to-cell communication system that specifies stem cell identity. Mutational inactivation of APC in colorectal epithelial stem cells drives malignant transformation. Colorectal cancer is the second leading cause of cancer-related deaths in the Western world, and greater than 90% of all cases harbor oncogenic mutations in APC. The molecular contribution that APC inactivation makes to the development of lethal metastatic colorectal cancer is unclear. We hypothesize a direct connection between APC inactivation, the aberrant transmission of chromosomes in dividing cancer cells (i.e. aneuploidy), and a defect in the extrusion of aneuploid cells from the epithelium leading the dissemination by metastasis of the primary gut tumor. The research interests of the Hammer lab (NIH) and the de la Roche lab (Cambridge) intersect with a goal of understanding the fundamental basis by which cells regulate their organization and shape. This project will exploit the power of the intestinal organoid system, an in vitro model of intestinal epithelia that recapitulates the morphology, cellular complexity and organization of the gut epithelium in vivo. One major goal of this project is to use genetically engineered organoids (GEOs) to determine how oncogenic mutations in APC contribute to the generation of aneuploid cells and the subsequent development of colorectal cancer. Overall, this project offers numerous exciting training opportunities, including CRISPR/Cas9-based genetic engineering of organoids and state-of-the-art super-resolution imaging technologies, and focuses on biological questions that have major implications for human health.
Developmental Biology	Understanding the self-organization of morphogenesis and collective cell migration in the zebrafish embryo	2021-08	National Institute of Child Health and Human Development (NICHD)	Ajay Chitnis	Alexandre Kabla	Cambridge	The posterior Lateral Line primordium is a group of about a hundred cells that migrates under the skin, from the ear to the tip of the tail, periodically forming and depositing sensory organs called neuromasts, to spearhead formation of the zebrafish Lateral Line sensory system. In recent years, this relatively simple and accessible system has emerged as an attractive model for understanding various aspects of morphogenesis in the developing embryo, including the guidance of cell migration, tissue patterning and organ formation. The goal is to use a combination of cellular, molecular, genetic and biomechanical manipulations coupled with live imaging, image processing and the development of multi-scale computational models to understand the self-organization of cell-fate, morphogenesis and migration of the lateral line primordium. Specific focus will be on developing tools and methods for investigating, imaging, quantifying and modelling the mechanics of collective migration, morphogenesis of epithelial rosettes and the intercellular and intracellular signaling networks that coordinate lateral line primordium development.
Cancer Biology	Using targeted immune regulation of the brain to treat traumatic brain injuries	2021-09	N/A	N/A	Adrian Liston	Cambridge	The brain is a site of relative immune privilege, long considered isolated from the peripheral immune system. We recently identified a population of resident T cells in the healthy mouse and human brain, important for the maturation of microglia (Pasciuto et al, Cell 2020). By analysing the kinetics of migration between the blood and brain, we found that the key bottleneck controlling the number of anti-inflammatory regulatory T cells in the brain was the high rate of cell death the cells exhibit when housed within the brain. Through developing a unique tool, with potential therapeutic application, we were able to deliver a biologic directly to the brain and enhance the size of the regulatory T cell population. The approach protects mice from brain damage following traumatic brain injury, stroke and multiple sclerosis. In this project we wish to explore the immunological processes that drive damage during neuroinflammation, and to harness immune-modulating biologics to prevent damage to the brain.

Biomedical Engineering & Biophysics	Ultra-High Field (7T) Magnetic Resonance Imaging (MRI) Development	2021-09	N/A	N/A	Chris Rodgers	Cambridge	I lead the ultra-high field (7T) MRI physics group at Cambridge University. We develop new MRI approaches to studying the human brain and body using our state-of-the-art Siemens Terra 7T MRI scanner. My group have active collaborations with clinicians in clinical neurosciences, psychiatry, oncology, and cardiology (Papworth), and with experts in cognitive neuroscience. I welcome PhD students to join the group. The following are areas of strong interest from our community, which would be suitable to develop a PhD project in discussion with me. (i) Developing new spectroscopic imaging pulse sequences to map neurochemical profiles across the whole brain in a single scan. A particular focus is on cerebral energy metabolism as measured by phosphorus 31P MRI (to probe PCr, ATP, in vivo pH mapping) and the new approach of deuterium 2H metabolic imaging (to probe glucose uptake and metabolism) for applications in patients with brain tumours or dementias. (ii) Developing new metabolic imaging methods to track the processes of energy metabolism in the human heart and how it changes in heart failure (a major disease that kills half of patients within 5 years). This is a collaboration with clinical colleagues at Royal Papworth Hospital and Addenbrooke's Hospital using new custom MRI coils and pulse sequences and analysis approaches to be created by the student. (iii) Developing new methods for neuroimaging, particularly for imaging blood flow in small vessel disease, or for rapid, motion-corrected fMRI in deep brain nuclei. (iv) Developing new approaches to interpret and analyse ultra-high resolution 7T neuroimaging data to extract information on the cortical laminar structure to understand neurodegeneration.
Molecular Pharmacology	Life will find a way….'	2021-09	N/A	N/A	Martin Welch	Cambridge	In a now famous quote from the 1993 movie Jurassic Park, the "chaotician" Ian Malcolm nicely captures the essence of adaptation through evolution. But series evolutionary change often requires multiple mutations to arise – the changes arising from SNPs and indels in single genes usually amount to little more than phenotypic "tinkering". So what would happen if we could "step on the evolutionary gas pedal" and accelerate the pace of change? Or alternatively, what would be the consequences of "slamming on the evolutionary brakes" to prevent adaptation? Well, these are just the kind of approaches that we have developed in the Welch lab, and we are applying these to look at how the opportunistic bacterial pathogen, Pseudomonas aeruginosa, adapts to the presence of infection-relevant selection pressures. Essentially, we've engineered the mismatch-repair system to come under the control of an inert chemical inducer, and so can "rheostatically" modulate the rate of mutation from very high (1000 x the wild-type level) to very low indeed (eliciting a state of "hypomutation" in which evolutionary change essentially grinds to a halt). Using this system, we aim to investigate the evolutionary trajectories of P. aeruginosa when challenged with intense selection pressures e.g., in a polymicrobial environment, or upon exposure to antimicrobial agents or nutrient limitation. Project will involve elements of synthetic biology, microbiology, evolutionary biology, modelling and genomics. A stable polymicrobial culture system has recently been developed by the lab and is available for use.
Neuroscience	Regulation of neuronal plasticity by synaptic signalling pathways	2021-09	National Institute of Child Health and Human Development (NICHD)	Mihaela Serpe	Matthias Landgraf	Cambridge	Neuronal plasticity is fundamental to nervous system development and function. We recently discovered that reactive oxygen species (ROS) are generated in response to neuronal activity and function as signals for adaptive/homeostatic plasticity. This is contrary to a commonly held view of ROS as destructive agents during ageing and diseased brains. Moreover, we find that different sources of ROS (cytoplasmic vs mitochondrially generated) regulate distinct aspects of synapse development, such as cellular growth vs synapse number. Now we need to understand the molecular mechanisms by which ROS regulate neuronal plasticity. Do ROS act as metabolic signals that link activity of neurons to their metabolic state? And how do ROS mediate change – by modulating other pathways known to shape synaptic plasticity, such as BMP and Wnt signalling? This project will combine biochemical and genetic approaches with electrophysiology and methods for live and super-resolution imaging. We expect this project to redefine our understanding of how multiple signalling pathways, each regulating distinct elements of plasticity, integrate at the synapse.

Radiology	Artificial intelligence in diagnostic prostate MRI to improve outcomes	2021-09	National Cancer Institute, NIH	Baris Turkbey	Tristan Barrett	Cambridge	There has been increasing interest in applying computational methods in medicine, to make sense of cancer's 'big data' problem by exploiting recent advances in data-processing and machine learning to capture and integrate clinical, genomic, and image data collated from hundreds of cancer patients in real-time. Such methods can be applied to digital clinical images to extract image information about patterns of pixels that are not perceivable to the human eye, allowing characterisation of tumour. Prostate cancer is the 2nd commonest male cancer worldwide, and MRI is the diagnostic tool of choice, however, MRI can miss 10% of significant tumours and leads to unnecessary (invasive) biopsy in around 1/3rd patients who do not have cancer. We will use a prototype AI system (Pi) developed with Lucida Medical on retrospective data, in a prospective clinical study. We plan to link histological data to imaging features derived from MRI (including texture analysis) to identify predictors of lesion aggressiveness and need for sampling, using biopsy cores and surgical specimens from the prospective cohort. Further work will link biopsy tissue to MRI data to identify radiogenomic markers of disease aggressiveness. The project presents an opportunity for AI to answer key clinical questions at the intersection of interpretation, imaging and biopsy. The project will involve working with an established interdisciplinary programme of researchers and help in the assessment of cross-cutting "multi-omic" approaches to cancer assessment, involving integration of advanced image analysis, transcriptomic, genomic, tissue, and patient outcomes to inform the design of diagnostic strategies
Toxicology	Metabolic regulation of gene expression in the context of cancer	2022-02	National Cancer Institute, NIH	Len Neckers	Ritwick Sawarkar	Cambridge	Emerging evidence suggests an exciting link between metabolism, chromatin and transcription. Metabolism can regulate post-translational modifications of histones which in turn regulate transcription of target genes. Highly proliferative cancer cells re-wire their metabolism to fuel growth, and in turn modify histones to alter gene expression. Identifying mechanisms by which cancer cells re-wire their metabolism and gene expression will identify key vulnerabilities to target using small molecule therapeutics. Our recent work at NIH has demonstrated links between histone lactylation, gene expression and cancer metabolism (histone lactylation depends on elevated cellular lactate, the end product of glycolysis – a preferred metabolic pathway in cancer). Work in Cambridge has further linked the molecular chaperone HSP90 with gene expression and metabolism in the context of cancer. Harnessing the complementary strengths in the two labs at NIH and Cambridge, the collaborative work will delineate molecular pathways linking small-molecule therapeutics targeting the chaperone HSP90 with cancer metabolism and with specific small-molecule inhibitors of glycolysis. The data we obtain delineating the metabolic dependence of gene expression in cancer will uncover novel and exciting treatment strategies to treat cancers' metabolic vulnerabilities.