Summer Project List 2024

Supervisor Details:	Project Details:
Project 1: Prof Torsten Baldeweg t.baldeweg@ucl.ac.uk https://profiles.ucl.ac.uk/3788-torsten-baldeweg	Project title: Brain plasticity in children with focal epilepsy Project outline: The student will join a team of scientist who are investigating functional MRI data from children with focal epilepsy. We have observed that about 40% of children have evidence of atypical language representation, e.g. right-sided dominance or crossed lateralisation – evidence of neuroplasticity to developmental insults. However, the factors that contribute to these atypical patterns have not been identified. Furthermore, the impact of surgical treatment on cognitive outcomes can be highly variable and difficult to predict for individual patients (1). We now wish to harness the power of our extensive clinical and neuroimaging dataset (n>400), the largest of any paediatric epilepsy programme in the world, to answer these important questions. Project outcomes: The student will be learning modern methods of brain image analysis and will be embedded in a clinical academic team who are working closely with the neurosurgery service at Great Ormond Street Hospital.

Supervisor Details:	Project Details:
Project 2: Prof John Christodoulou j.christodoulou@ucl.ac.uk https://profiles.ucl.ac.uk/4210-john-christodoulou	**Project title:** Structural characterisation of co-translational folding intermediates by ^{19}F NMR spectroscopy **Project outline:** Most proteins must fold into their specific, biologically active conformation, and avoid misfolded and aggregated conformations implicated in a host of human diseases. Protein folding can occur during biosynthesis on the ribosome, providing an essential means to maintain cellular homeostasis. Indeed, co-translational folding energetics, pathways, and outcomes have been found to differ significantly from those in in vitro unfolding/refolding studies. However, a detailed structural understanding of co-translational folding and misfolding is lacking because the experimental means to examine such dynamic processes remains inaccessible. The human glycoprotein alpha-1-antitrypsin (AAT) is a serine protease inhibitor, whose pathological variants misfold and form self-associated polymers, associated with the disease AAT deficiency. Biochemical assays have shown that AAT naturally stalls during translation on the ribosome, and forms an obligate compacted intermediate, which completes its folding post-translationally but is prone to misfolding in the presence of the Z-mutation (1). In this project, we aim to characterise the structure of AAT intermediates on the ribosome using 19F NMR spectroscopy. Currently, 19F NMR is the only experimental technique that is able directly observe co-translational folding intermediates (2), and site-specific labelling permits the acquisition of both short- and long-range structural information through chemical shift analysis and paramagnetic relaxation enhancement measurements respectively. The project will begin with testing and screening 19F-labelling sites on AAT, each rationally designed using molecular dynamics simulations and AlphaFold predictions; this will involve introducing amber codons into DNA constructs for site-selective incorporation of 19F-labels, expression of recombinant, isotopically labelled AAT, and 19F-NMR of the purified protein. Successful 19F labelling sites will then introduced into translation-stalled ribosome-nascent chain complexes (RNCs) to begin to a detailed structural characterisation of the co-translational folding intermediate of AAT. References (1) Plessa et al, Nascent chains can form co-translational folding intermediates that promote post-translational folding outcomes in a disease-causing protein, Nat Com (2021) (2) Chan et al, The ribosome stabilizes partially folded intermediates of a nascent multi-domain protein, Nat Chem (2022)

	Project outcomes: This project will provide a hands-on introduction to a wide range of structural biology techniques, both computationally and experimentally, the latter including molecular biology, preparative/analytical biochemistry, and NMR spectroscopy. The project forms one part of a wider ongoing study on the folding/misfolding of AAT, and successful outcomes will therefore result in publication.

Supervisor Details:	Project Details:
Project 3: Dr Arnd Roth arnd.roth@ucl.ac.uk https://profiles.ucl.ac.uk/10134-arnd-roth	**Project title:** Localizing axonal and dendritic signals in Neuropixels extracellular recordings from the International Brain Laboratory **Project outline:** Neuropixels (https://www.ucl.ac.uk/neuropixels/neuropixels-0) are modern high-density silicon probes, developed with support by the Wellcome Trust, that are being used by many neuroscience laboratories to record extracellular voltage signals from populations of neurons. Since signals arising from the activity of many neurons are superimposing on each recording site on Neuropixels, localizing the different sources of these signals is a nontrivial problem. In this project we will use the single-cell kernel Current Source Density method (skCSD; https://elifesciences.org/articles/29384) to untangle the sources of extracellular signals detected by Neuropixels and map them to the cell bodies, dendrites and axons of identified and morphologically reconstructed neurons. The method works by defining spatial basis functions along the dendrites, cell body and axon of a reconstructed neuron, and using them to numerically reconstruct the spatial combination of sources that gave rise to the extracellular signals recorded by the probe. We will perform this analysis using a recently published Python implementation of skCSD (https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1011941). We will first test our software pipeline on ground truth data obtained by simulating extracellular signals arising from model neurons in LFPy (https://www.frontiersin.org/articles/10.3389/fninf.2018.00092/full). This will answer questions regarding the accuracy and reliability of the skCSD method, and allow us to optimize its parameters. Next, we will apply the tested analysis pipeline to a collection of curated experimental data from the International Brain Laboratory (https://www.internationalbrainlab.com), a consortium that our laboratory is part of. We will use spike-triggered average extracellular waveforms as the starting point for skCSD. This will reveal the spatial distribution of membrane current sinks and sources along the axon, cell body and dendrites of neurons during an action potential. Finally, we will apply this analysis to individual action potentials, aiming to identify synaptic input currents preceding these action potentials, and to detect local spikes in the dendrites of neurons in vivo. **Project outcomes:** This project will yield software pipelines that will be published in a code repository, and scientific results that will be publishable as an article in a peer-reviewed journal. It will be attractive to students from many fields who are interested in neuroscience and have good programming skills in Python.

Supervisor Details:	Project Details:
Project 4: Dr Gabriella Heller g.heller@ucl.ac.uk https://profiles.ucl.ac.uk/81817-gabriella-heller	**Project title:** Characterisation of Monomeric Amyloid-β 40 using Molecular Dynamics Simulations **Project outline:** Alzheimer's disease, a leading cause of death in the UK, represents an increasingly untenable load on healthcare systems worldwide, particularly in developing countries unprepared for fast-growing elderly populations. Dubbed the "twenty-first century plague," an estimated 40 million people currently suffer, with numbers expected to rise to 140 million by 2050 unless a cure is found. The aggressive aggregation of amyloid-β (Aβ) peptide is at the heart of this illness, which is progressive, incurable and eventually fatal. Aβ belongs to a class of proteins, known as intrinsically disordered proteins, which lack a single, rigid tertiary structure, and instead exist as an equilibrium of conformationally distinct states. The highly dynamic nature of these proteins makes them extremely challenging to study experimentally. Aβ exists in several variations; The 40-residue variant, Aβ40, is predominantly found in biological fluids. In contrast, the 42-residue variant, Aβ42, is more commonly found in Alzheimer's disease plaques and has a higher propensity for aggregation. The most striking difference in aggregation rates between the two peptides is found in primary nucleation, where only the monomeric form is involved. This suggests fundamental differences in the disordered, monomeric forms of Aβ40 and Aβ42, but structural studies of the two peptides have found very little differences in monomeric states. The aim of this project is to provide a complete understanding of the differences in the structures adopted by the Aβ40 and Aβ42 peptides associated with Alzheimer's disease, which exhibit markedly different toxicities. The student will perform all-atom simulations on Aβ40 and compare these to existing simulations of Aβ42. The student will validate their simulations with advanced Nuclear Magnetic Resonance Spectroscopy (NMR) data (preliminary data already collected, further studies on-going). Such insight into the monomeric differences between these two peptides has the potential to create novel therapeutic strategies against Alzheimer's disease. **Project outcomes:** The student will learn how to perform all-atom molecular dynamics simulations (using metainference metadynamics). The student will perform simulations of Aβ40 and compare their results to simulations that have already been performed in Aβ42. This data will be combined with existing NMR data from the lab for publication.

Supervisor Details:	Project Details:
Project 5: Dr Liam Browne liam.browne@ucl.ac.uk https://profiles.ucl.ac.uk/40022-liam-browne	**Project title:** Probing Neural Circuits That Detect Compromised Sensory Information **Project outline:** The brain can detect when sensory information becomes unreliable, thus maintaining effective interactions with the environment, ensuring safety, and optimising behaviour. Although the thalamus is known to monitor sensory information in the cortex, the precise mechanisms by which cortico-thalamic circuits detect compromised sensory information are unclear. This project will explore the role of these circuits by examining their anatomy and their function using computational approaches. We will trace the projections from different areas of the cortex to the thalamus across the mouse brain using serial two-photon tomography, which involves using brains expressing fluorescent tracers to map projections between cortical and thalamic areas of interest. Behavioural datasets will be analysed to examine how exploration in novel environments is affected by disturbances in peripheral sensory input and by closed-loop optogenetic manipulation of cortico-thalamic circuits. We predict that mice will adopt different exploratory strategies when certain peripheral inputs are compromised and that these strategies are expected to be replicated during the manipulation of cortico-thalamic circuits. To test this hypothesis, we will use pose estimation (DeepLabCut) and motion sequencing (MoSeq) to decompose and analyse the structure of exploratory behaviour. Overall, this project aims to impose key constraints on the neural mechanisms that monitor sensory fidelity. **Project outcomes:** The student will see a wide range of systems neuroscience approaches conducted in the laboratory: behavioural tasks, optogenetic manipulations, whole-brain anatomy, and analysis using supervised and unsupervised approaches. The student will conduct the anatomical and computational analyses. Data generated will provide new insights and support future grant applications.

Supervisor Details:	Project Details:
Project 6: Dr Pilar Acedo p.nunez@ucl.ac.uk https://profiles.ucl.ac.uk/55574-maria-del-pilar-acedo-nunez	**Project title:** Characterising clinically relevant in vitro models mimicking pancreaticobiliary diseases **Project outline:** Pancreatic and bile duct malignancies are amongst the deadliest diseases due to late diagnosis and lack of effective therapies. These diseases are characterised by an aggressive, invasive and migrative potential, which is regulated by the crosstalk between malignant epithelial cells and neighbouring cells, such as immune cells and fibroblasts. However, the exact mechanisms regulating disease development and progression are not fully understood yet. A key issue in this field of research is the lack of human models that recapitulate tissue complexity, organisation and physiology, compromising the translatability of preclinical results to the clinical setting. Pancreaticobiliary diseases are commonly associated with inflammation and fibrosis, leading to disease progression and resistance to therapy. Thus, the aim of this project is to decipher the key role of the tissue microenvironment in the physiology and behaviour of pancreaticobiliary malignant epithelial cells. To achieve this aim, the student will develop and characterise clinically relevant 3D models containing cancer cells and stromal components (e.g. fibroblasts, stellate cells and/or immune cells). We will decipher changes induced in cancer cells by this complex crosstalk at the transcriptome (e.g. RT-qPCR) and proteome (e.g. western blotting) levels. This will accelerate the discovery of prognostic and diagnostic biomarkers, by identifying specific gene signatures while considering cell-to-cell interaction and paracrine crosstalk. This will also increase accuracy for the identification of novel therapeutic targets and potential markers associated with disease progression and aggressiveness of pancreaticobiliary diseases, highly expressed in disease cases but almost absent in healthy individuals. We will build on our experience in biomarker discovery and organoid/spheroid establishment to unravel immuno-inflammatory markers differently expressed in these models. The student will join our multidisciplinary team formed by basic and clinical scientists. We aim to improve the outcome of patients with pancreatic and biliary diseases. **Project outcomes:** Outcomes for the student: • Understanding of pancreas and bile duct biology • Techniques: cell culture, viability assays, fluorescence microscopy, western blotting, qPCR

	Outcomes for the project: • Data for inclusion in planned conference submissions • Pilot data for future applications • New insights: tumour microenvironment in pancreaticobiliary diseases, in vitro models

Supervisor Details:	Project Details:
Project 7: Prof James Cox j.j.cox@ucl.ac.uk https://profiles.ucl.ac.uk/16510-james-cox	**Project title:** Exploring the dark genome for novel long non-coding RNAs that are important in chronic pain **Project outline:** The dark genome, the non-protein coding part of the genome, is replete with long non-coding RNAs (lncRNAs). These functionally versatile transcripts, with specific temporal and spatial expression patterns, are critical gene regulators that play essential roles in health and disease. In recent years, FAAH-OUT was identified as the first lncRNA associated with an inherited human pain insensitivity disorder. Several other lncRNAs have also been studied for their contribution to chronic pain. Furthermore, genome-wide association studies are frequently identifying single nucleotide polymorphisms that map to lncRNAs. Chronic pain is a major clinical problem with millions of people living with severe, debilitating and poorly treated pain. It has been more than 20 years since a new class of analgesic medicine has been licensed, with many seemingly excellent validated targets yet to be successfully drugged, such as the NaV1.7 voltage-gated sodium channel blockers and nerve growth factor neutralizing antibodies which are yet to be approved for clinical use. With the added problems of current painkillers also contributing to the opioid crisis, new analgesic medicines are therefore urgently needed. The main aim of this project will be to identify and clone a new lncRNA(s) that is important in chronic pain. Using a dataset of dysregulated genes expressed in dorsal root ganglia from pain models, non-coding RNAs will be computationally prioritised using web-based genome browsers and gene expression databases. Candidate genes will then be PCR-amplified, cloned, sequenced and tested using transfection of cell lines and/or CRISPR-based approaches. The tissue expression profile of the novel non-coding RNA will also be explored. If successful, this work could lead to the development of an RNA therapeutic for the treatment of chronic pain. **Project outcomes:** Submission of cloned gene sequence(s) into GenBank; a better understanding of the dark genome which could be applied to many diseases; if successful, inclusion of data in a publication; pilot data for future grant applications; potentially provide data that could lead to a new way to treat chronic pain.

Supervisor Details:	Project Details:
Project 8: Prof Matilda Katan m.katan@ucl.ac.uk https://profiles.ucl.ac.uk/33964-matilda-katan	**Project title:** Characterisation of novel inhibitors for selectivity among different, disease-linked phospholipase C families **Project outline:** The specific project proposed for this studentship is part of our ongoing efforts to address a major gap related to studies phospholipase C (PLC) enzymes in health and disease, namely, a discovery of selective inhibitors targeting these signal transduction proteins. So far, there are no reports of compounds that are fully validated as their direct pharmacological inhibitors or that can be utilized /developed into drug molecules (Katan and Cockcroft (2020) Prog Lipid Res 80:101065). Current interest in targeting PLCγ in disease is based on recent evidence linking genetic changes in these enzymes with processes implicated in disease development. PLCγ is implicated in several types of disease with the unmet clinical need; these include T cell malignancies and other types of cancer (PLCγ1 in ATL and angiosarcoma), cancer drug resistance (PLCγ2 in ibrutinib resistant CLL), rare immune disorders (PLCγ2 in APLAID) and neurodegeneration (protective role of PLCγ2 in Alzheimer's). New structural and mechanistic insights and development of assays suitable for HTS accompanied these discoveries, including work from our team (Liu et al. (2020) EBioMedicine, 51, 102607; Le Huray et al. (2022) Sci Adv, 8, eabp9688; Prawiro et al. (2023) BBA Mol Basis Dis, 1869, 166601). Recently, we discovered new PLC inhibitors from a HTS of over 1 million compounds and are working to further develop the most promising candidates. This proposed project is part of our programme to optimise and characterise PLCγ inhibitors and aims to assess our new compounds for their selectivity for different PLC families and elucidate whether they are pan-PLC or family-selective. During the six-week period, the student will be trained to perform various in vitro and cellular PLC-assays and use them to generate IC50 values for a selected panel of PLC inhibitors. All required PLC proteins and protocols are in place. Wellcome remit: complexities of human health and disease **Project outcomes:** The main outcome for this project is to provide initial data related to selectivity of PLC inhibitors (PLCγ-selective or pan-PLC). This will help us to prioritise compounds for our further optimisation. The student will learn many laboratory techniques/methods, including planning and preforming assays in a format used for drug discovery.

Supervisor Details:	Project Details:
Project 9: Prof Marco Endrizzi m.endrizzi@ucl.ac.uk https://profiles.ucl.ac.uk/35538-marco-endrizzi	**Project title:** Lab-based imaging at tigh-resolution of spinal cord tissue three-dimensional Architecture with X-ray phase-contrast tomography **Project outline:** Central nervous system in adult mammals does not have healing capability, in the event of a tissue loss it is unable to form new neural tissue. In this type of tissue, the reaction to an insult typically results in scar-like environment that does not lead to repair. Understanding these mechanisms and developing way to support neural tissue healing suffer the lack of an imaging modality capable of representing the tissue morphology with microscopic resolution, in three dimensions. In the context of a Wellcome Trust Technology Development Grant, 'A multi-contrast X-ray nanoscope for multidisciplinary research' 221367/Z/20/Z, this project will focus on high-resolution X-ray phase-contrast imaging of mice models' spinal cords (6 samples, 3 controls, already harvested and used for a study currently under review. 100% reuse of animal tissue) for assessing the feasibility of micron-scale-resolution three-dimensional imaging of neural tissue and lesions. The unique ability of X-ray to provide quantitative volumetric images will enable characterizing the tissue and lesion properties in a way that is simply not achievable by the current standard, namely histology. Histology has high specificity, thanks to a variety of staining protocols, however it inherently lacks the capability of imaging in three-dimension as only a few slices are typically extracted from a volume and undergo the entire process, from preparation to image analysis. Spinal cord tissue is complex, and its function is intimately related to its three-dimensional structure. Current imaging methods that rely on histology protocols are inadequate for providing statistically relevant insights on structures that are inherently three-dimensional and whose function cannot be understood by sparse two-dimensional sampling. Moreover, the approach proposed here does not rely on staining, it has therefore the potential to reports the tissue morphology in a state that is as close as possible to its native state. **Project outcomes:** Research: assessment of feasibility for volumetric, non-destructive imaging, on spinal cord tissue at the micron scale, and the subsequent morphological analysis. (part development of a new laboratory-based imaging workflow, planned publication). Student: will learn, hands-on learning of system set-up, data acquisition, reconstruction and analysis; low-level coding/programming for quantitative analysis tasks

Supervisor Details:	Project Details:
Project 10: Prof Isaac Bianco i.bianco@ucl.ac.uk https://profiles.ucl.ac.uk/7550-isaac-bianco	**Project title:** Development and function of the high acuity area in the larval zebrafish retina **Project outline:** In humans, our conscious visual perception is dominated by high acuity vision mediated by a small, specialised region in the centra retina called the fovea. Many ocular diseases affect foveal function, including age-related macular degeneration as well as congenital defects that impact foveal development. In fact, it is estimated that up to 3% of children with clinically normal eyes may suffer from foveal hypoplasia and consequent visual dysfunction. The molecular-genetic pathways that control foveal development are very poorly understood and in this project, the student will contribute to our ongoing research efforts which are taking advantage of the experimental accessibility of the larval zebrafish to understand foveal development and function. Zebrafish possess a high acuity area (HAA) in their ventro-temporal retina which, like the human fovea, has specialized cone photoreceptors and retinal circuitry enabling high acuity vision. We have recently identified a number of candidate genes, in particular involved in FGF and retinoic acid signaling, that are well placed to control aspects of foveal specification and differentiation. During the BVS project, the student will test the function of 2-3 of these genes. First, they will microinject CRISPR-Cas9 reagents into fertilized eggs to efficiently knock-down the candidate gene. Next, they will use 3rd generation fluorescent in situ hybridization and confocal microscopy to examine the expression of various foveal marker genes in intact eyes. This will reveal which aspects of foveal patterning as disrupted in the Crispant embryos. Finally, they will work alongside other members of our group to test specific aspects of visual function in Crispant larvae, using a panel of quantitative behavioural assays. Overall, by characterizing these molecular-genetic and behavioural phenotypes, the project will provide valuable information about the pathways that control specific aspects of foveal development in vertebrates. **Project outcomes:** Student: (1) Training in state-of-the-art techniques in development neurobiology and systems neuroscience, including CRISPR-Cas, confocal and 2-photon imaging, image analysis, high-speed behavioural tracking, MATLAB programming. (2) By joining our lab meetings and our joint zebrafish floor meeting, they will gain a broad understanding of the field. Research programme: This project will contribute to our work on foveal development, funded by Fight for Sight; our work on eye development, funded by MRC; and our work on the circuit basis of visually guided behaviour, funded by Wellcome.

Supervisor Details:	Project Details:
Project 11: Dr Johnathan Labbadia j.labbadia@ucl.ac.uk https://profiles.ucl.ac.uk/61349-john-labbadia	Project title: Establishing how loss of DNA helicase activity impacts protein homeostasis in aged tissues Project outline: Generating and maintaining an optimal proteome is central to the proper function of all cells. However, as cells age, their ability to maintain proteome integrity declines, leading to the appearance and persistence of misfolded, mislocalised and aggregated proteins. This phenomenon, often referred to as “Protein homeostasis (proteostasis) collapse”, leads to cell and tissue dysfunction, and the onset of multiple age-associated diseases. Therefore, understanding how cells maintain proteostasis throughout life, and maintaining or activating these pathways in old age, has the potential to simultaneously suppress multiple age-associated diseases. To this end, we recently discovered that the expression of the DNA helicases, Werner syndrome helicase (WRN) and Bloom’s syndrome helicase (BLM), declines prior to the onset of age-related proteostasis collapse in the nematode worm Caenorhabditis elegans. This observation raises the tantalising possibility that DNA helicase activity is important for cells to maintain proteostasis with age. This summer project will address the hypothesis that reduced WRN/WRN-1 and BLM/HIM-6 activity promotes age-related proteostasis collapse across tissues. The student will use RNA interference and tissue-specfic proteostasis sensors to: Aim 1. Determine whether knockdown of WRN/wrn-1 or BLM/him-6 early in life accelerates age-related proteostasis collapse in muscle cells Aim 2. Ascertain whether knockdown of WRN/wrn-1 or BLM/him-6 early in life accelerates age-related proteostasis collapse in neurons The short lifespan of C. elegans (2-3 weeks) and the early onset of phenotypes associated with loss of proteostasis (4 – 8 days) means that we expect these experiments to be completed within the following timeframe: Weeks 1 & 2: Learn C. elegans husbandry and prepare wrn-1 and him-6 RNA interference reagents (plates, bacteria, etc) Weeks 3 & 4: Perform and analyse muscle proteostasis experiments (and make figure). Weeks 5 & 6: Perform and analyse neuronal proteostasis assays (and make figure).

	Project outcomes: We expect the data generated by this work to be used in a planned publication. In addition, the student will learn how to: (1) use C. elegans as a model system, (2) design and run phenotypic readouts of tissue health, and (3) analyse data, make figures and present findings.

Supervisor Details:	Project Details:
Project 12: Prof Paolo De Coppi p.decoppi@ucl.ac.uk https://profiles.ucl.ac.uk/915-paolo-de-coppi	**Project title:** Derivation and Characterisation of Human Mesenchymal Cells for Oesophageal Tissue Engineering **Project outline:** Oesophageal atresia (OA) is a rare congenital condition where the oesophagus, instead of connecting normally from the gullet to the stomach, ends in a blind pouch. This means that affected babies cannot feed until surgical intervention joins the disconnected ends. In some cases, the gap between the ends is too extensive for direct connection. Current treatment options involve complex oesophageal replacement procedures using the patient's own organs (e.g. the stomach, colon, or small bowel). However, these often lead to complications and a diminished quality of life. Our groundbreaking solution involves personalized, size-matched, tissue-engineered oesophageal grafts. We achieve this by injecting biological scaffolds with mesenchymal cells, effectively bridging the gap in OA patients. In successful minipig transplantations, we demonstrated proof-of-concept, showing both deliverability and safety. Complications observed were comparable to those typically seen in OA patients and were managed with standard clinical treatment. Within six months, the implanted grafts developed muscle, allowing the transplanted oesophagus to contract alongside the native counterpart. This breakthrough enables animals to feed and grow normally during the study period. Our construct holds promise as a potential treatment for Long-Gap OA. To further advance this innovative approach, we have secured funding from GOSHCC/LifeArc Research Accelerator Grant. This grant will allow us to optimize graft preparation to meet good manufacturing practice standards by: 1) Producing Grafts: We will create grafts (including scaffolds and human cells) exclusively using reagents approved for patient use, adhering to clinical safety standards (GMP-compliant). 2) Enhancing Cell Delivery: We aim to standardize cell distribution within the scaffold by utilizing a robotic microinjector. We invite a dedicated student to join our team, contributing to the derivation, characterization, and expansion of human mesenchymal cells from muscle biopsies. This exciting research will compare cells derived using two distinct protocols, ultimately advancing the treatment landscape for OA patients. **Project outcomes:** The student will acquire foundational skills in primary mesenchymal cell derivation and culture under R&D and GMP-like conditions. They will learn protocol design, analytical techniques (including immunofluorescence, cytofluorimetry, and real-time qPCR), and effective experiment planning. These skills prepare them for potential future work in research or biotechnology industries.

Supervisor Details:	Project Details:
Project 13: Mr Liam Barrett l.barrett.16@ucl.ac.uk https://profiles.ucl.ac.uk/74186-liam-barrett	**Project title:** Automatic Digitisation of Audiogram Data **Project outline:** Hearing loss is the most common sensory disorder in humans, has far-reaching effects on health and quality of life, and has been identified as a strong risk factor for dementia. The development of preventive and curative treatments, while in the pipeline, are hampered by difficulties in clinically identifying (phenotyping) the patient populations that may benefit from these highly targeted treatments. Currently, there are no UK and international patient databases large and accurate enough for deep phenotypical analysis. Methods to phenotype patients require, in the least, clustering analyses across a large repository of hearing and patient variables. The spine of this dataset is pure tone audiometry – an internationally agreed method that records the basic thresholds of sound detection across 6 sound frequencies. Audiogram data is recorded in the patients' medical records. Most audiograms, especially before 2005 in the UK or any from low- and middle-income countries have been hand-drawn onto graph paper. Without an electronic database that holds the raw values these hand drawn results are excluded from analyses. This has considerable implications in the UK population as hand drawn historical data is omitted from analyses and limits our ability to predict hearing loss progression over only 15 years of digital data capture. It has even farther-reaching implications internationally, since the populations that suffer the greatest burden of hearing loss, in LMICs, will not be included in research that is generalisable to their populations. Therefore, it is essential that a reliable and valid method is developed that can rapidly digitize hand-drawn audiograms and therefore allow the inclusion of historic hearing data as well as that from LMICs. The aim of this project is to assess the reliability of a tensor based computational method to digitise audiograms. **Project outcomes:** The student will develop algorithms to estimate audiogram values from hand-drawn copies, gaining experience in scientific coding and data analysis. This foundational work will support future research and publications, with the students receiving appropriate credit.

Supervisor Details:	Project Details:
Project 14: Dr Aswin Chari Aswin.chari.18@ucl.ac.uk https://profiles.ucl.ac.uk/71578-aswin-chari	Project title: Thalamic volumetrics in focal and generalised epilepsies in children Project outline: Epilepsy is one of the most common neurological diseases of childhood and affects 100,000 children in the UK. One in three children will develop drug resistance, meaning they continue to have seizures despite being on medication to try and stop them. Novel treatments for these children are needed and one such emerging treatment is deep brain stimulation of the thalamus, a deep structure in the brain. However, there is no consensus as to which nucleus in the thalamus to target. It is thought that thalamic nucleus volumes may help us understand which nuclei are preferentially affected in children with epilepsy, forming the basis for DBS targeting. As part of this study, the student would work with an existing imaging dataset to analyse differential volumes of thalamic nuclei in children with drug-resistant epilepsy, compared to healthy controls to understand whether certain nuclei may be preferentially affected by the epilepsy. The dataset has already been collated and image processing has largely been carried out by an existing PhD student, making this a feasible project in a 6 week timeframe. Project outcomes: The student would develop a deeper understanding of epilepsy, the thalamus, neuroimaging and statistical analysis as a result of this project. The data and results would contribute to our ongoing scheme of work to develop deep brain stimulation for children with epilepsy

Supervisor Details:	Project Details:
Project 15: Prof Michael Duchen m.duchen@ucl.ac.uk https://profiles.ucl.ac.uk/3559-michael-duchen	**Project title:** Impact of the 'MELAS' associated mtDNA mutation on cellular redox state and bioenergetic function **Project outline:** Mutations of mitochondrial DNA (mtDNA) cause a wide range of devastating diseases which are very poorly understood and for which there is currently no treatment. The most prevalent of these diseases is known as MELAS (mitochondrial encephalomyopathy lactic acidosis and stroke like episodes), usually caused by the m.3243A>G mutation which affects a mitochondrial tRNA and therefore affects multiple mitochondrial encoded proteins. As it has not been possible to generate animal models with these mutations (we cannot reliably yet manipulate the mitochondrial genome) so far we know almost nothing about the impact of the mutation on the terminally differentiated tissues most affected in the disease – neurons, muscle and vascular system. We have therefore generated induced pluripotent stem cells (iPSCs) from patient derived fibroblasts and we are differentiating these into these three terminally differentiated cell types of interest. As we know nothing about the underlying mechanism driving the 'stroke like episodes' which are profoundly debilitating and progressive, the current project will focus on the impact of the mutation on vascular endothelial cell function. To date, we have generated viable endothelial cell models and now we wish to establish the impact of the mutation on endothelial cell function. In particular we have found that bioenergetic defects vary between cell types, and so we need to establish the bioenergetic consequences of the mutation for bioenergetic function in the endothelial cells. We will culture the endothelial cells and measure mitochondrial membrane potential, redox state and rates of free radical generation using confocal microscopy and respiratory rate using the 'Seahorse' instrument. We will compare these with the native fibroblasts used to generate the iPS cells to ask how function compares depending on cellular specialisation. **Project outcomes:** The student will learn to culture fibroblasts and will receive training in confocal microscopy and respirometry and will thus develop core lab skills, learn about mitochondrial cell biology and fluorescence microscopy. The work will likely be incorporated into a planned publication.

Supervisor Details:	Project Details:
Project 16: Prof Oliver Robinson o.robinson@ucl.ac.uk https://profiles.ucl.ac.uk/40163-oliver-robinson	Project title: The impact of cognitive behavioural therapy on the neural circuits of anxiety Project outline: This study will aim to test whether neural circuitry changes, specifically within the circuit between the prefrontal cortex and amygdala, constitute a mechanism of action for CBT interventions in anxiety. The primary objective is to test whether this circuit responds to a course of CBT, by demonstrating disengagement of the circuit following CBT. Secondary objectives are to relate this change in circuit function to behaviour through cognitive measures of emotional processing, to explore the neurobiological features that distinguish patients who respond to CBT and those who do not, and also to compare the data from this study to another on-going study assessing the impact of pharmacological interventions for anxiety, allowing for the comparison of neurobiological mechanisms of psychological vs. pharmacological treatments in anxiety. This study will employ a randomised, single-site, case-control study in patients with anxiety-related mental health disorders. Project outcomes: -learning about clinical research -learning how to liase with NHS clinical services -learning how to screen participants -learning how to recruit participants -learning how to collect fMRI data -learning how to collect behavioural data -the project will result in publications that the intern will have the opportunity to be an author on.

Supervisor Details:	Project Details:
Project 17: Dr Stephanie Koch s.koch@ucl.ac.uk https://profiles.ucl.ac.uk/26387-stephanie-koch	Project title: AI-facilitated analysis of pain and movement in patients with juvenile idiopathic arthritis Project outline: Movement defines our life experience, so much so that walking is one of the most evolutionarily conserved behaviours across living species. As such, it provides an exquisitely sensitive measure of the health and wellbeing. This measure is all the more important as patients suffering from chronic pain will often describe the motor deficits associated with their pain condition as the primary factor restricting their quality of life. In this summer project, the student will use machine learning to analyse the gait of young patients suffering from Juvenile Idiopathic Arthritis (JIA) to determine how we can identify those at risk of high pain in the future. We aim to identify key motor patterns underlying chronic pain and outline diagnostic biomarkers of future pain trajectory. Project outcomes: The selected student will gain interdisciplinary knowledge in kinematic computer-based behavioural analysis. They will also participate in journal clubs and lab meetings, helping develop critical analytical and presentation skills. The data produced will be critical in generating data for future grant applications, which we are planning for submission in January.