Experimental and Translational Medicine

Project Booklet 2024-25

Professor Frederik Barkhof

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Theme: Experimental and Translational Medicine

Research overview

Neuroimaging analysis using brain MRI and PET to monitor disease progression in Alzheimer's disease and multiple sclerosis. We develop novel image endophenotypes using segmentation and AI-techniques that will help to prognosticate and monitor patients and understand disease mechanisms though linkage with genetic, laboratory and cognitive data

Rotation project **(including a brief outline of how this will develop into a PHD project)**

MRI is essential to diagnosis of multiple sclerosis by showing disseminated in the CNS. The number and location of lesions have prognostic information and monitoring of new lesions in brain and spinal cord are widely used to monitor treatment. Within the MS population, there is marked heterogeneity and using machine-learning we can derive clusters of patients with a different prognosis and response to therapy. There are also more extreme phenotypes, including patients with almost exclusive spinal cord involvement who will develop (motor) disability, whereas others are dominated by cortical involvement and cognitive impairment. We expect that the geographical pattern of CNS involvement is determined by genetic make-up of the immune system and the central nervous system (e.g. myelin genes). In this rotation project we will focus on the imaging-genetic interactions and examine how genetic factors affect lesion distribution. We have a large and well-curated dataset (n=850) from the PITMS project (Predicting Individual Treatment response in MS) with available MRI scans of the brain and spinal cord that have already been analysed for lesion number and distribution. Whole genome analysis has already been performed using peripheral bloods cells. You will focus on polygenic risk scores from genome-wide association studies to examine the impact of known risk variants for MS on lesion distribution using an extreme phenotype approach (i.e. those with exclusively spinal cord or supratentorial lesions). Potential (PhD) extensions include looking at atrophy subtypes and examine genes from other pathways (e.g. myelin genes such as MOG and PLD-1).

Relevant publications 1

https://pubmed.ncbi.nlm.nih.gov/33824310/

Relevant publications 2

https://pubmed.ncbi.nlm.nih.gov/33880511/

Professor Paola Bonfanti

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Theme: Experimental and Translational Medicine

Research overview

Our multidisciplinary research addresses fundamental questions related to human T-cell development and central tolerance with the aim to develop translational approaches for congenital and acquired immune disorders. We combine stem cell biology, microfluidics, next generation sequencing and molecular analysis of T-cell development. Lab is based at both UCL/Crick.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

During the rotation project the student will learn how to culture and analyse thymic progenitors and will be trained in clonal tracking technologies. This short-term project will aim to validate novel candidate surface markers for the isolation of potential long-term lymphoid progenitors (LtLPs) from donors' tissues. Isolated cells will be seeded in 3D co-culture as well as microfluidic systems to assess their maturation and functionality. Single-cell RNA-sequencing datasets are available and bioinformatic analysis will be conducted in parallel to the wet lab work. This short-term project has the potential to develop into a PhD project focusing on identification and functional characterization of unprecedented human LtLPs and study their development during the negative and positive selection in human thymus with a focus on the interaction with the antigen presentation pathways of stromal thymic cells. In fact, hematopoietic stem cells constitute fundamental cell products for treating a variety of blood disorders including immunodeficiencies and cancer. The PhD project will be supported by the technology development in Bonfanti lab for the ex vivo isolation of human thymic cells, in vitro expansion and development of human thymic epithelial cells and the development of 3D-engineered thymic organoids. The exploitation/engineering of putative LtLPs could have a broad impact on next-generation cell and gene therapy approaches for treating a variety of T cell defects and for cancer immunotherapies. The student will be trained and conduct the research project in Bonfanti lab and in collaboration with the group of Dr Luca Biasco (secondary supervisor) at UCL GOSH/ZCR.

Relevant publications 1

Ragazzini R, Boeing S, Zanieri L, Green M, D'Agostino G, Bartolovic K, Agua-Doce A, Watson SA, Batsivari A, Ariza-McNaughton L, Gjinovci A, Greco M, Scoville D, Han A, Hayday AC, Bonnet D, and Bonfanti P. Defining the identity and the niches of epithelial stem cells with highly pleiotropic multilineage potency in the human postnatal thymus. Developmental Cell 2023 doi: org/10.1016/j.devcel.2023.08.017

Relevant publications 2

Izotova N, Rivat C, Baricordi C, Blanco E, Pellin D, Watt E, Gkazi AS, Adams S, Gilmour K, Bayford J, Booth C, Gaspar HB, Thrasher AJ, Biasco L. Long-term lymphoid progenitors independently sustain naïve T and NK cell production in humans. Nat Commun. 2021 Mar 12;12(1):1622. doi: 10.1038/s41467-021-21834-9. PMID: 33712608; PMCID: PMC7954865.

Professor Benny Chain

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Theme: Experimental and Translational Medicine

Research overview

The immune system is a key determinant of protection against infectious disease and cancer. Our group applies mathematics and artificial intelligence to construct quantitative and predictive models of T cell adaptive immunity, which can be used for diagnosis, disease monitoring and to drive novel strategies for prevention or therapy.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

As part of a large project funded by the Alliance for Early Cancer Detection, we have sequenced the T cell receptor (TCR) repertoire of a large set of blood, primary tumour and metastatic samples from patients with non-small cell lung cancer. During the rotation the student will apply SCEPTR, a novel deep neural network algorithm which we have developed, to the analysis of these sequences. SCEPTR uses architecture developed for natural language processing to convert TCR protein sequences into numerical representations. By combining SCEPTR with statistical machine learning, we will identify sets of related T cell receptors which we hypothesise recognise shared tumor antigens. This rotation project would form an introduction to a PhD focused on using artificial intelligence to detect patterns of T cell receptor sequences which are associated with cancer, and explore their use in early diagnosis. The PhD offers several potential avenues of exploration. These include modelling the relationship between blood and tumor TCR repertoires, exploring the relationship between repertoire and clinical outcome, and the potential links between TCR sequence and cell function. The project is intended for students interested in mathematics/computation, but could offer wet lab options of cloning and expressing specific T cell receptors in order to explore antigen specificity and function. The project will provide a strong grounding in computational immunology, covering bioinformatics and newer AI-derived approaches. It will also provide training more broadly in the exciting field of cancer immunity as part of one of the UK's strongest cancer immunology centres.

Relevant publications 1

Contrastive learning of T cell receptor representations. Nagano et al. 2024 https://arxiv.org/abs/2406.06397

Relevant publications 2

Joshi K, Milighetti M, Chain BM. Application of T cell receptor (TCR) repertoire analysis for the advancement of cancer immunotherapy. Curr Opin Immunol. 2022 Feb;74:1-8. doi: 10.1016/j.coi.2021.07.006. Epub 2021 Aug 25. PMID: 34454284.

Professor Olga Ciccarelli

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Theme: Experimental and Translational Medicine

Research overview

Smartphone-based monitoring tool in multiple sclerosis: It is essential to track the mental and physical performance of patients with Multiple Sclerosis (MS). The Neurokeys phone App tracks "how" a patient is typing their messages. We aim to validate this App by comparing it with conventional methods for monitoring patients and investigating changes over time in MS.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

MS is a chronic neurological disease which causes severe disability and patients need to be monitored over time. A new technology, called Neurokeys App, analyses keystroke measures during typing of texts (number of errors, speed of typing, length of time, etc) in an unobtrusive way. We aim to examine changes in the keystroke dynamics over time and correlate them with changes in standard clinical scores and brain MRI measures in English-speaking individuals. We have just started to study a longitudinal cohort of 50 patients with MS and 25 healthy controls who are being assessed at baseline and over time. During the rotation project the student will learn: the principles of keystroke dynamics; assessment of physical and cognitive disability using standard measures; imaging analysis of lesions and brain atrophy; statistical tests for data analysis; writing abstracts and presentations at conferences. This rotation project will develop into a PhD by following patients and healthy controls longitudinally (the study schedule includes 3 visits: baseline, 6 and 12 months). The aim of the PhD project is to investigate the clinical responsiveness of the Neurokeys App by answering the following questions: (1) Is the App responsive to small changes recorded with other clinical scales and MRI? (2) Does the App predict cognitive and physical changes so that it can used as early warning system? This technology offers the possibility to track MS and predict its impact on cognition and physical abilities by analysing 'how' a patient is typing (and not what is typing, respecting privacy).

Relevant publications 1

Real-world keystroke dynamics are a potentially valid biomarker for clinical disability in multiple sclerosis. Lam KH, Meijer KA, Loonstra FC, Coerver E, Twose J, Redeman E, Moraal B, Barkhof F, de Groot V, Uitdehaag B, Killestein J. Mult Scler. 2021 Aug;27(9):1421-1431. doi: 10.1177/1352458520968797. Epub 2020 Nov 5.

Relevant publications 2

Wearable technologies to measure clinical outcomes in multiple sclerosis: A scoping review. Alexander S, Peryer G, Gray E, Barkhof F, Chataway J. Mult Scler. 2021 Oct;27(11):1643-1656. doi: 10.1177/1352458520946005. Epub 2020 Aug 4.

Professor James Cox

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Theme: Experimental and Translational Medicine

Research overview

The dark genome, the nonprotein-coding part of the genome, is replete with long noncoding RNAs. These functionally versatile transcripts, with specific temporal and spatial expression patterns, are critical gene regulators that play essential roles in health and disease. This project will identify, characterize and drug ncRNAs important in chronic pain.

Rotation project (including a brief outline of how this will develop into a PHD project)

The genetics revolution has led to significant advances in our understanding of pain at the molecular and cellular levels. Key pain genes have been identified from studying individuals with painless and painful genetic disorders; and single cell RNA sequencing of dorsal root ganglia damage-sensing neurons has identified genetically distinct populations with diverse functional properties. However, deep sequencing has also led to the remarkable finding that the majority of genes in the human genome are not in fact protein-coding, but instead specify regulatory non-coding (nc) RNAs. These genes, which can be subclassified into long ncRNAs (lncRNAs), long intergenic non-coding RNAs (lincRNAs), microRNAs (miRNAs), piwi-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNAs), circular RNAs (circRNAs), and other small non-coding RNAs, have diverse functions but have been largely underexplored in the pain field. The main aim of the project is to identify, characterise and drug key ncRNAs that are important in chronic pain. The first stage of the project will be computational, whereby gene expression datasets from mouse pain models will be analysed to see whether novel lncRNAs are up or down-regulated together with nearby protein-coding genes. Dysregulated ncRNAs will be cloned and expression activated or repressed using CRISPR-based assays in cell lines. This will lead to the development of gene therapy approaches to drug the key ncRNAs in mouse pain models. The project will provide experience of bioinformatics together with molecular and cell biology assays.

Relevant publications 1

Out of the dark: the emerging roles of lncRNAs in pain. https://pubmed.ncbi.nlm.nih.gov/38926010/

Relevant publications 2

Distinct transcriptional responses of mouse sensory neurons in models of human chronic pain conditions.
https://pubmed.ncbi.nlm.nih.gov/30079380/

Associate Professor Alice Davidson

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Research overview

Developing a framework to identify genetic variants amenable to nucleic acid therapies (NATs) for rare diseases. This project will be embedded within an MRC/NIHR Rare Disease Node on establishing a UK Platform of Nucleic Acid Therapy for rare diseases (UPNAT, https://rd-research.org.uk/node/upnat/), a national translational programme led by researchers at UCL.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Nucleic acid therapies (NATs) have been proven to treat broad ranging categories of disease-associated variants including splice-site altering, intronic, regulatory and coding mutations via mechanisms of RNA degradation, steric hindrance, or splicing modulation. The rotation project will require the student playing a pivotal role in the development of a strategic framework and guidelines to assess and prioritise both pathogenic genetic variants for NAT design and development, and the patients who might benefit from such treatments as part of the wider UpNAT network (https://rd-research.org.uk/node/upnat/). This will involve them leveraging large genomic datasets under the guidance and supervision of expert scientists and bioinformatics at UCL and across the UPNAT network. In addition to the mutation type, other factors require consideration including target cell/tissue-type, disease onset, severity and progression, model system availability, targetability with existing chemistries, informative functional analysis and biomarker(s), opportunistic funding scenarios, and available capacity to conduct a future clinical trial in an established UK clinical research facility. To validate the framework the appointed student will retrospectively assess variants that have already been extensively proven to demonstrate amenability to NATs (Kim 2023), in addition to prospective candidates identified as part of the UpNAT node. For the PhD project, the student will get the opportunity to select promising variants, associated with inherited forms of ocular disease, for NAT strategy design and pre-clinical development at UCL institute of Ophthalmology within the Davidson lab. This will comprise a diverse range of molecular and cell biology approaches utilising patient-derived cell systems and functional assays.

Relevant publications 1

Kim J, Woo S, de Gusmao CM, Zhao B, Chin DH, DiDonato RL, et al. A framework for individualized splice-switching oligonucleotide therapy. Nature. 2023 Jul;619(7971):828-836.

Relevant publications 2

Christina Zarouchlioti , Beatriz Sanchez-Pintado , Nathaniel J Hafford Tear et al. Antisense Therapy for a Common Corneal Dystrophy Ameliorates TCF4 Repeat Expansion-Mediated Toxicity American Journal of Human Genetics. 2018. Apr 5;102(4):528-539.

Professor Robertus de Bruin

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Theme: Experimental and Translational Medicine

Research overview

Cancer cells experience high levels of replication stress (RS) and becoming increasingly dependent on the RS-response. The PhD project will test and exploit the potential of our novel degradation technology, AutoCure, to allow targeting RS-response proteins for degradation to selectively kill cancer cells without affecting healthy tissue.

Rotation project (including a brief outline of how this will develop into a PHD project)

We have the unique opportunity to use a novel chemical biology platform named AUTINC1 (Autophagy-Initiating Chimera), developed by our collaborator Professor David Selwood (UCL), that utilizes the autophagy-lysosome for targeted protein and protein complex degradation. This provides an alternative, cost- and time-efficient, drug development pipeline, for targeting protein complexes in a titratable manner. This is an exciting opportunity for us and the cancer field to harness the huge potential of AUTINC1 in cancer therapy and the elucidation of cancer biology. As part of the rotation project, we will use this novel technology to develop prototype molecules targeting the Replication Stress Response master regulator ATR. Via click chemistry, using existing small molecule inhibitors of ATR, we will create ATR-AUTINCs. These compounds will be tested for their ability as protein degraders of ATR, and its interactors, via western blot analysis and immunofluorescence microscopy. This will involve testing the optimal dose and time to maximise degradation of its targets to provide quantitative analysis of the potential of ATR-AUTINCs to degrade ATR. This will establish first in class compounds to test the degradation potential of ATR-AUTINCs and their anti-cancer efficacy in the PhD project.

Relevant publications 1

Cell cycle control in cancer HK Matthews, C Bertoli, RAM de Bruin Nature Reviews Molecular Cell Biology 23 (1), 74-88

Relevant publications 2

Development of the ULK1-Recruiting Chimeras (ULKRECs) to enable proximity-induced and ULK1-dependent degradation of mitochondria Niyaz Zaman, Natasha Aley, Valeria Pingitore, David L Selwood, Robin Ketteler bioRxiv 2024.04.15.589474; doi: https://doi.org/10.1101/2024.04.15.589474

Professor Pietro Fratta

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Theme: Experimental and Translational Medicine

Research overview

The lab aims to develop novel treatments for ALS and neurodegenerative diseases. We focus on RNA mis-processing events in disease pathogenesis using molecular biology, iPSC-derived neurons, mouse models and human brain samples. Our work has led to advanced pre-clinical stage therapeutics. The lab is based at UCL-ION and the Crick.

Rotation project (including a brief outline of how this will develop into a PHD project)

TDP-43 pathology is the hallmark of amyotrophic lateral sclerosis (ALS; motor neuron disease), and a key event in other forms of common dementias as Alzheimer's disease. TDP-43 pathology induces the appearance of hundreds of novel mis-splicing events called cryptic exons. It has now been established that cryptic exons play a crucial role in disease pathogenesis and progression, and numerous companies are attempting to rescue these cryptic splicing events one at a time, predominantly with ASO approaches. We have developed a novel technology, TDP-REG, that limits expression of gene therapies specifically to the diseased cells. This is a transformational improvement as it enables the delivery of splice-rescue therapies that would not have been safe if expressed in all neurons. We have proven the specificity of TDP-REG both in vitro and in vivo, and have shown that it can be coupled with splice-rescue approaches to correct multiple cryptic exons at once. We now aim to refine this approach and provide compelling evidence of its ability to rescue ALS functional deficits in iPSC neurons and in vivo. This technology also holds enormous potential for designing better high-throughput screens to identify novel therapeutic targets. During the rotation the student will acquire skills in construct design, cloning, nanopore sequencing and analysis and cell culture.

Relevant publications 1

TDP-43 loss and ALS-risk SNPs drive mis-splicing and depletion of UNC13A. Brown AL, Wilkins OG, Keuss MJ, Hill SE, Zanovello M, Lee WC, Bampton A, Lee FCY, Masino L, Qi YA, Bryce-Smith S, Gatt A, Hallegger M, Fagegaltier D, Phatnani H; NYGC ALS Consortium; Newcombe J, Gustavsson EK, Seddighi S, Reyes JF, Coon SL, Ramos D, Schiavo G, Fisher EMC, Raj T, Secrier M, Lashley T, Ule J, Buratti E, Humphrey J, Ward ME, Fratta P. Nature. 2022 ;603(7899):131-137. doi: 10.1038/s41586-022-04436-3. PMID: 35197628

Relevant publications 2

Creation of de novo cryptic splicing for ALS/FTD precision medicine. Wilkins OG, Chien MZYJ, Wlaschin JJ, Pisliakova M, Thompson D, Digby H, Simkin RL, Diaz JA, Mehta PR, Keuss MJ, Zanovello M, Brown AL, Harley P, Darbey A, Karda R, Fisher EMC, Cunningham TJ, Le Pichon CE, Ule J, Fratta P. bioRxiv. 2023 doi: 10.1101/2023.11.15.565967.

Professor Franca Fraternali

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Theme:	Fundamental Mechanisms of Disease

Research overview

Fraternali's research group focuses on molecular determinants in the functioning or mis-functioning of protein structures and protein interactions by analysis of high-dimensional molecular data to understand their dysregulation in diseases. The group develops computational methods for modelling, simulations and characterization of antibody diversity in response to vaccination, cancer and other contexts.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Background As we age, our immune system becomes less effective, leading to higher morbidity and mortality. Elderly individuals produce less specific antibodies and more autoreactive antibodies, therefore their vaccine response is altered. Research in immunology often relies on protein markers to classify B-cells, but these groups are typically heterogeneous due to the limited panel of markers to define phenotypes and the use of bulk measurements of B-cell samples. Rotation The student will analyze single-cell transcriptomic data (scRNA-seq) from healthy donors across age groups responding to different vaccines. The student will learn and perform: 1. Cell-type annotation using machine-learning models (CellAssign, CellTypist, scVI). 2. Gene set enrichment analysis (AUCell and fgsea). 3. Mapping key transcripts onto pathways (LIANA, OmniPath) and protein-protein networks. The Fraternali lab has curated a Unified Protein-Protein Interaction Network (UniPPIN) from public datasets and has expertise in network analysis (information-theoretic tools, community detection, etc.). These methods have been applied in the lab on other systems, and the student will be guided to automate (Python/R) these in silico protocols.

Relevant publications 1

1. Ng JCF,…Mauri C.,… Fraternali F. sciCSR infers B cell state transition and predicts class-switch recombination dynamics using single-cell transcriptomic data. Nat Methods 21, 823–834 (2024). https://doi.org/10.1038/s41592-023-02060-1

Relevant publications 2

2. Margreitter C, …, Fraternali F. BRepertoire: a user-friendly web server for analysing antibody repertoire data. Nucleic Acids Res. 46(W1):W264-W270. (2018).

Professor Simon Gaisford

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Theme: Experimental and Translational Medicine

Research overview

Understanding the impact of infection in disease and healthcare, and in particular the use of live probiotic supplements to improve overall gut health

Rotation project **(including a brief outline of how this will develop into a PHD project)**

In this rotation project we will build a new instrument designed for studying the real-time growth of biofilms in central venous catheters (CVCs). 15% of patients with an in-dwelling CVC will get an infection and this often leads to sepsis, so the infection must be cleared. This is time consuming (48h) and costly (£10k per infection), so developing new analytical tools that allow (i) methods of biofilm eradication and (ii) development of a new generation of catheters is very important. The technique we will develop is called isothermal flow microcalorimetry and it is an entirely novel approach for biofilm research, with huge untapped potential. We will design (in CAD software) a calorimeter vessel optimised for holding a section of catheter tubing and will print it with metal laser-sintering 3D printing (this in itself will be a world-first for calorimeter design). We will then construct the calorimeter and test it to make sure bacterial suspensions can be flowed through it. Finally, we will see if the new calorimeter is sensitive enough to detect the formation of biofilms. The group at UCL is the largest in the world for medical calorimetry and you will get experience of instrument design, assay development, basic microbiology and general research skills. The project is in partnership with the UCL Centre for Clinical Microbiology (based at the Royal Free hospital), so you will also get clinical exposure.

Relevant publications 1

Said J et al (2015) Development of a flow system for studying biofilm formation on medical devices with microcalorimetry. Methods, 76, 35.

Relevant publications 2

Austin P et al (2024) The potential for isothermal microcalorimetry to detect venous catheter infection isolates and establish antibiograms. Nutrition, 119, 112319

Dr Pierre Gélat

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Theme: Experimental and Translational Medicine

Research overview

Endometriosis is a condition in which the endometrium, the layer of tissue that normally covers the inside of the uterus, grows outside of it. Endometriosis is a chronic disease affecting one woman in 10 as is associated with severe, life-impacting pain for which novel clinical solutions are desperately required.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Optimised focused ultrasound therapy for the treatment of endometriosis using a computational modelling approach High-intensity focused ultrasound (HIFU) is a non-invasive non-ionising modality in which an ultrasonic field focuses on a localised region delivering sufficient energy to ablate tissue. HIFU is transforming the treatment of many medical conditions, with a growing number of clinical applications at various stages of research, development and commercialisation. FDA and NICE approval have been obtained for the treatment of uterine fibroids, prostate cancer and essential tremor. A recent systematic review states that HIFU therapy shows promise as a non-invasive approach for managing abdominal wall endometriosis and rectosigmoid deep infiltrating endometriosis. While efficacy outcomes are encouraging, safety considerations warrant attention. In particular, the study recommends the optimisation of treatment protocols [1]. This rotation project involves using the open-source Python library OptimUS (https://github.com/optimuslib/optimus) [2] to simulate the propagation of ultrasonic waves in anatomical media, investigating a clinical scenario relating to the treatment of endometriotic lesions. Image segmentation on anonymised patient data will be carried out to identify key anatomical groups and simulations will be deployed onto the UCL Myriad cluster to map ultrasonic fields inside the body. This project will serve as preliminary work for a PhD where the successful applicant will function within a cross-disciplinary team comprising engineers, mathematicians and consultant gynaecologists to investigate a range of clinical scenarios for which optimal treatment planning strategies for endometriosis will be devised. The outcomes of these simulations will then be used to design tailored ultrasound endometriosis treatment probes.

Relevant publications 1

[1] Ali, M.M., Awad Elderiny, H., Shaaban Abdelgalil, M. and Mohamed Othman, A., 2024, May. Is high-intensity focused ultrasound a magical solution to endometriosis? A systematic review. In Baylor University Medical Center Proceedings (pp. 1-13). Taylor & Francis.

Relevant publications 2

[2] van't Wout, E., Haqshenas, R. and Gélat, P., 2024, May. Simulating Focused Ultrasound with the Boundary Element Method. In 2024 IEEE UFFC Latin America Ultrasonics Symposium (LAUS) (pp. 1-4). IEEE.

Dr Mattia Gerli

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Theme: Experimental and Translational Medicine

Research overview

This project aims to create a single-cell atlas of human amniotic fluid (AF) in Congenital Diaphragmatic Hernia (CDH) and generate CDH lung AF organoids as an advanced disease model and drug testing tool to enhance understanding, diagnosis, and treatment of CDH.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Congenital Diaphragmatic Hernia (CDH) is a severe congenital disorder with a high mortality rate. Predicting long-term lung function is challenging due to unreliable prenatal parameters. Amniotic fluid (AF) surrounds and supports the fetus and is rich in cells. Recently, we published a single-cell map of human AF, demonstrating that AF epithelial cells can form three-dimensional organoids (AFOs) resembling fetal lung tissue. We have successfully generated CDH organoids from AF and tracheal fluid, which exhibit disease features, confirming their value for in vitro disease modelling. The rotation project will involve the isolation of AF cells from CDH pregnancies and the generation of CDH and non-CDH AFOs and performing single-cell RNA sequencing on these samples. Preliminary data will undergo bioinformatics analysis to identify key cellular differences. Building on these findings, the PhD project will expand the organoid library and implement other advanced single-cell techniques for comprehensive multiomic analysis of CDH AF cells and CDH AFOs. Detailed characterisation of cellular identities in CDH versus non-CDH organoids, including studies on proximal and distal lung differentiation, will enhance understanding of disease mechanisms. Furthermore, correlating organoid data with clinical CDH samples and patient outcomes will validate the feasibility of this model in prenatal medicine.

Relevant publications 1

https://www.nature.com/articles/s41591-024-02807-z

Relevant publications 2

https://www.frontiersin.org/journals/bioengineering-and-biotechnology/articles/10.3389/fbioe.2023.1058970/full

Professor Maria Hawkins

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Theme: Experimental and Translational Medicine

Research overview

Radiation is used to curatively treat> 50% of cancers. We study the role of radiation (X-ray and proton) in cancers of the gastrointestinal tract. We are using organoids and precision cut tumour and liver slices to study the effect of radiation we are expanding to use other technologies such as organ-on-a-chip.

Rotation project (including a brief outline of how this will develop into a PHD project)

During the rotation project the student will learn how to undertake and plan a radiation experiment using Xray and or protons and commence initial measurements of DNA damage in normal tissue and cancer . 2 separate experiments: i) organs on a chip with normal vasculature/cancer/and bood brain barrier and ii) patient-derived precision-cut liver slices (PCLS), colorectal cancer (CRC) metastasis slices in a 3D printed liver phantom. Our organ phantom houses the liver slices at specific points in the radiation pathway (as would be delivered to a person with liver cancer), and then compare the DNA damaging effects of the radiation directly to the dose delivered to the tissue specimen. Early quantification of the radiation-induced DNA damage will measured through the creation of γH2AX foci in cell nuclei. γH2AX is a phosphorylated protein that is recruited to the site of the most lethal form of DNA damage, a double strand break. The induction and repair of DNA damage can be measured by a change in the γH2AX signal at early and late times points post-irradiation (30 min and 24 h). Late quantification of the radiation effects will be taken at 6-8 days to understand how the cell respond to radiation- for example vessels and blood brain barrier and whether these changes facilitate better drug delivery and /or spread of cancer due to damage of the vessels. We are collaborating with biologists and physicists.

Relevant publications 1

Emergent mechanical control of vascular morphogenesis Whisler et al., Sci. Adv. 9, eadg9781 (2023) 11 August 2023

Relevant publications 2

Jagatia, R.E. Palma (2023). "Patient-derived precision cut tissue slices from primary liver cancer as a potential platform for preclinical drug testing." eBioMedicine 97: 104826

Dr Mariya Hristova

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Theme: Experimental and Translational Medicine

Research overview

Neonatal hypoxic-ischaemic (HI) brain injury is a major cause of mortality and morbidity. Our multidisciplinary research utilises the knowledge about the molecular mechanisms of HI brain damage and aims to develop clinical treatment for it through repurposing of drugs and combining nanotechnology, cell culturing and in vivo HI-modelling (EGA-IfWH and SoP, UCL).

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Oxidative stress, inflammation and mitochondrial dysfunction substantially contribute to HI brain damage. Mitochondria are major sources of reactive oxygen species (ROS) and critical targets of ROS-induced cellular damage. One of the limitations of clinical application of antioxidants is related to side effects associated with violation of redox balance in cells. Numerous cellular signalling pathways participate in redox regulation, and can be blocked by antioxidants, yielding unwanted deleterious effects. Targeted antioxidants' delivery to mitochondria can be an effective therapeutic approach to treat HI. Signal transducer and activator of transcription 3 (STAT3) is strongly upregulated post-HI. STAT3 inhibition in rodent HI models is neuroprotective. However, clinical application of STAT3 inhibitors is not feasible due to limited aqueous solubility. We aim to develop clinically applicable nanoparticle formulations combining STAT3 inhibition, mitochondria-targeting antioxidants and mitochondria-protecting compounds (already in clinical practice and trials for non-HI conditions) to provide neuroprotection in HI. The rotation project involves: • Comparison of the drugs: each drug separately and the combinations in non-nanoparticle formulations – cell viability essay (toxicity) • Formulation optimisation – encapsulated individually – rotary evaporation, assessment of drug loading and encapsulation efficiency, laser diffraction analysis, transmission electron microscopy, cell viability essay (toxicity) • Formulation optimisation – co-encapsulation. The full PhD project will test the viable combinations of drugs in vivo (in non-nanoparticle and in nanoparticle form) in a mouse model of neonatal HI: to develop a dose response curve through short term assessment of brain damage, and then test the most promising combination for long term damage, as well as different routes of administration. http://dx.doi.org/10.1111/jnc.13490 https://doi.org/10.3389/fphys.2019.01351 http://dx.doi.org/10.3389/fimmu.2019.02610 https://doi.org/10.1038/s41598-020-60858-x https://doi.org/10.3389/fphys.2019.00282

Relevant publications 1

Hristova M*, Rocha-Ferreira E, Fontana X, Thei L, Buckle R, Christou M, Hompoonsup S, Gostelow N, Raivich G, Peebles D. Inhibition of Signal Transducer and Activator of Transcription 3 reduces neonatal hypoxic-ischemic brain damage. J Neurochem 2015, doi: 10.1111/jnc.13490

Relevant publications 2

Rocha-Ferreira E#, Sisa C#, Bright S, Fautz T, Harris M, Contreras Riquelme I, Agwu C, Kurulday T, Hill D, Lange S, Hristova M, Curcumin: novel treatment in neonatal hypoxic-ischaemic brain injury, Front Physiol. 2019, https://doi.org/10.3389/fphys.2019.01351

Dr Joseph Jacob

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Research overview

Chronic lung disease are a global health priority as they cause huge morbidity and mortality. Chronic obstructive pulmonary disease, a disease related to smoke inhalation will be the third highest cause of death worldwide by 2025. Our project will guide students in the use of medical image analysis to measure disease on computed tomography scans of the lungs in our large imaging datasets.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

There is an urgent need for new imaging biomarkers to improve the lives of millions living with chronic lung disease. This project, and a resulting PhD representing a partnership between imaging scientists and clinicians, delivers that by building on our past success. Over the course of two prior PhDs at CMIC, UCL, we have developed a quantification tool called AirQuant that measures airway damage on lung computed tomography imaging. AirQuant metrics of airway narrowing and curvature were shown to strongly associate with patient survival in patients with lung fibrosis demonstrating the potential of AirQuant for generating imaging biomarkers. The next step is to improve evaluation of other measures of airway abnormality such as filling of the airways with sticky mucus, a sign of lung disease. By quantifying mucus within airways AirQuant will be able to analyse damage in a disease called Chronic Obstructive Pulmoanry Disease which will be the third biggest cause of death worldwide by 2025. The student will learn the basics of image analysis in a way that is directly clinically relevant through direct clinical co-supervision in an established supervisory partnership. The project placement will focus on understanding the background literature in the field and becoming familiar with the existing capabilities of AirQuant. A project in this year will involve labelling datasets (using an efficient in-house labelling technique) for mucus plugging and fine tuning an existing segmentation algorithm to distinguish unblocked airways from airways blocked with mucus.

Relevant publications 1

https://www.atsjournals.org/doi/10.1164/rccm.201908-1600OC

Relevant publications 2

https://link.springer.com/article/10.1007/s00330-023-09914-4

Dr Majella Lane

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Research overview

Plaque psoriasis is a chronic skin disease that affects approximately 2% of the UK population and is characterised by sustained inflammation of the skin and itchy, inflamed, scaly lesions. We propose the development of an effective, new topical formulation of an anti-inflammatory drug that targets the sphingosine-1-phophate (S1P) pathway.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Plaque psoriasis is a chronic skin disease that affects approximately 2% of the UK population and is characterised by sustained inflammation of the skin and the development of inflamed, scaly lesions. We propose the development of an effective, new topical formulation of an anti-inflammatory drug that targets the sphingosine-1-phophate (S1P) pathway. In recent years, the S1P pathway has emerged as an exciting new target in psoriasis. Fingolimod (FIN), which is approved for the treatment of multiple sclerosis, is an analogue of S1P that binds to sphingosine-1-phosphate (S1P) receptors on lymphocytes and was shown to reduce skin inflammation after administration by injection. The drug properties of FIN are conducive to skin permeation but no skin permeation data has been reported for the molecule. To establish baseline skin permeability parameters, a systematic study of FIN permeation across full thickness (epidermis + dermis) skin will be determined using Franz cells apparatus with porcine ear skin as an established model for human skin. This will form the rotational project for the student. With an established baseline permeability dataset for FIN, in the PhD programme we shall develop optimal formulations that control FIN delivery to the desired skin target. Studies will be extended to cover evaluation of skin permeation in psoriatic skin samples. We will also perform a pharmacodynamic validation of the topical delivery approach using CHO cells overexpressing S1P1 (CHO-S1P1) and monitor the key biological responses needed for efficacy in vivo: cAMP levels, S1P1 receptor internalisation in CHO cells and S1P1 receptor signalling.

Relevant publications 1

Okura, I., et al., Fingolimod ameliorates imiquimod-induced psoriasiform dermatitis by sequestrating interleukin-17-producing gamma delta T cells in secondary lymph nodesJ Dermatol Sci, 2021. 102(2): p. 116-25.

Relevant publications 2

Barbero, A.M. and H.F. Frasch, Pig and guinea pig skin as surrogates for human in vitro penetration studies: a quantitative review.Toxicol In Vitro, 2009. 23(1): p. 1-13.

Professor Nick Lane

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Research overview

My research is on how energy flow, specifically membrane bioenergetics, structures evolution from the origin of life and the eukaryotic cell to human health, ageing and even consciousness

Rotation project **(including a brief outline of how this will develop into a PHD project)**

This rotation project and full PhD is grounded in the recent discovery that volatile general anaesthetics appear to disrupt chiral-induced spin polarization in complex I of the respiratory chain. Our own preliminary work using high resolution tissue fluorespirometry in fruit flies confirms that isoflurane and sevoflurane inhibit respiration at complex I, with concerted downstream effects including reversal of the ATP synthase, and allied increases in membrane potential and reactive oxygen species flux. The rotation project will measure the effects of anaesthetics on a series of Drosophila lines with mutations in complex I and other respiratory complexes to establish whether they produce effects on anaesthetic sensitivity, as predicted, relative to WT flies. This project will involve developing a new method of measuring recovery times from anaesthetics based on image analysis of pixel change every 1/50 second. The main PhD project will develop this work to use high-resolution tissue fluorespirometry (O2k) in the most interesting fly lines identified in the rotation project, and link these changes with other respiratory parameters including NADH fluorescence, quinone reduction state, and super-resolution microscopy or cryoelectron tomography of cristae structure in control versus anaesthetized mitochondria. Finally there will be scope to collaborate with Luca Turin to measure electron spin resonance and possibly mitochondrial magnetic fields in fly mitochondria.

Relevant publications 1

Rodriguez E, Peng B, Lane N. Anaesthetics disrupt complex I-linked respiration and reverse the ATP synthase. Biochimica et Biophysica Acta Bioenergetics. In press (2024). MS available on request.

Relevant publications 2

Camus MF, Rodriguez E, Kotiadis V, Carter H, Lane N. Redox stress shortens lifespan through suppression of respiratory complex I in flies with mitonuclear incompatibilities. Experimenal Gerontology 175: 112158 (2023).

Professor Alex Leff

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Research overview

People with acquired or degenerative brain injury can make significant gains in their language function by using apps that provide specific, guided practice. We have developed several of these. They adapt to patients' abilities using basic algorithms, but would be much more efficient with a machine learning/AI approach.

Rotation project (including a brief outline of how this will develop into a PHD project)

The student will be working on data collected in the backend of one or more of our therapy apps iReadMore (reading), ListenIn (auditory comprehension), and iTalkBetter (speech production). As patients work their way through thousands of therapy trials, they get better at the items they practice. Each trial is recorded with data including correct/incorrect, error type, reaction-time etc. For example, iReadMore has ~50 users and has generated more than 600,000 rows of data (each = one therapy trial). The challenge is to use these data to drive the therapy algorithms both within and across patients. In the rotational project the student will work on data already collected from published phase II randomised controlled trials of the app(s). The first aim will be to see if there is structure in the data that can be used to generate rules regarding therapy flow; e.g. what is the optimum number of times an item needs to be presented? What is the optimal time period to re-present learned items to aid consolidation? The research will lead to a PhD project whereby the student will move onto data being collected prospectively from real-world users. Once an optimised algorithm has been developed, this will be tested using AB methodology (users are randomly allocated to the current or new therapy algorithm to test algorithm superiority). Further projects could include making predictions (in terms of time required and projected improvements made) for new patients based on data taken from matched past and present users.

Relevant publications 1

1. Upton, E., Doogan, C., Fleming, V., Leyton, P. Q., Barbera, D., Zeidman, P., ... & Leff, A. (2024). Efficacy of a gamified digital therapy for speech production in people with chronic aphasia (iTalkBetter): behavioural and imaging outcomes of a phase II item-randomised clinical trial. Eclinicalmedicine, 70.

Relevant publications 2

3. Fleming, V., Brownsett, S., Krason, A., Maegli, M. A., Coley-Fisher, H., Ong, Y. H., ... & Leff, A. P. (2021). Efficacy of spoken word comprehension therapy in patients with chronic aphasia: a cross-over randomised controlled trial with structural imaging. Journal of Neurology, Neurosurgery & Psychiatry, 92(4), 418-424.

Professor Chaozong Liu

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Research overview

Chaozong Liu's research is directed toward biomedical devices processing for enhancing the treatment of musculoskeletal disorders. Include (1) early detection and early treatment of musculoskeletal disorders. (2) biomedical device surface processing for regulate protein adsorption and cells attachment. (3) biomaterials and additive manufacturing innovation for orthopaedic application.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Osteosarcoma is a type of bone cancer. It is more common in teenagers and young adults but also occurs in adult patients. Surgery is an important part of treatment and is used to remove the tumour and some of the healthy tissue around it. The sarcoma resections often result in large, complex tissue defects which require a complex reconstruction in order to allow the patient the best possible postoperative long-term functional outcome. Bone tissue engineering and regenerative medicine is an emerging approach for bone regeneration. It uses a porous scaffold as a template to guide cell attachment, differentiation, proliferation and tissue regeneration. In addition, scaffolds have been exploited for delivery of targeted therapies to bone in order to supply molecules like growth factors or drugs locally to treat the bone disorders. The applicants have developed an additive manufacturing integrated PEEK-collagen hybrid composite scaffold that can be tailored to the patients' bone defects to provide an appropriate physiological environment for bone defect reconstruction. Early study has indicated that the bone targeting drug (in this case alendronate) can be loaded into the designed scaffold. Incorporation of this targeted system into the scaffold will have substantial benefits for the management of postoperative infection and reduce the occurrence of complications. This project will combine training and skill development to develop a bone-targeted drug integrated patient-specific PEEK-collagen hybrid scaffold for bone defect reconstruction after resection of bone sarcomas.

Relevant publications 1

3. Farnaz Ghorbani , Minjoo Kim , Behafarid Ghalandari , Mingjing Zhang , Swastina Nath Varma , Lisa Schobel , Chaozong Liu , Aldo R. Boccaccini. Architecture of β-Lactoglobulin Coating Modulates Bioinspired Alginate DialdehydeGelatine/ Polydopamine Scaffolds for Subchondral Bone Regeneration, Acta Biomaterialia (2024), doi: https://doi.org/10.1016/j.actbio.2024.04.028

Relevant publications 2

8. S. Bao, D. Yu, Z. Tang, H. Wu, H. Zhang, N. Wang, Y. Liu, H. Huang, C. Liu, X. Li, Z. Guo, Conformationally regulated "nanozyme-like" cerium oxide with multiple free radical scavenging activities for osteoimmunology modulation and vascularized osseointegration, Bioactive Materials 34 (2024) 64-79. https://doi.org/10.1016/j.bioactmat.2023.12.006

Professor Omar Mahroo

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Theme:	Experimental and Translational Medicine

Research overview

Neurons in the retina detect light, generating electrical signals, which are processed and sent to the brain allowing us to see. The electrical response of the human retina can be recorded non-invasively as the electroretinogram. This can yield insight into normal retina function and also mechanisms of dysfunction in disease.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

In this project, retinal electrophysiological recordings will be made and analysed to generate new discoveries relating to human retinal function in health and disease. The retina is one of the most interesting parts of the nervous system and retinal diseases are important causes of blindness. The student will be based at the UCL Institute of Ophthalmology and at Moorfields Eye Hospital. This joint site is one of the most productive combined clinical and vision research institutes in the world. Electroretinograms (ERGs) will be recorded in healthy volunteers and novel analyses will be applied to generate insights into how the retina works and adapts across a range of light intensities. Also, ERGs recorded in patients with rare genetic retinal diseases will be analysed. Novel experimental testing protocols will be used as well as new methods of analysis to shed insight both into normal retinal function and into precise mechanisms of disease. This will help us better understand these diseases, yield new, clinically useful diagnostic tests, and also open avenues for future research into new treatments. The project can be extended into a PhD with a programme of experiments and analyses that can be applied to healthy participants and patient cohorts. Previous PhD students have made impactful discoveries, presented work internationally, won prizes and authored papers in internationally renowned journals. The project will also make use of a newly furbished lab with state-of-the-art retinal electrophysiology equipment as well as portable devices that can be used in clinics.

Relevant publications 1

Mahroo OA. Visual electrophysiology and "the potential of the potentials". Eye (Lond). 2023 Aug;37(12):2399-2408. doi: 10.1038/s41433-023-02491-2. Epub 2023 Mar 16. PMID: 36928229; PMCID: PMC10397240.

Relevant publications 2

Jiang X, Xu Z, Soorma T, Tariq A, Bhatti T, Baneke AJ, Pontikos N, Leo SM, Webster AR, Williams KM, Hammond CJ, Hysi PG, Mahroo OA. Electrical responses from human retinal cone pathways associate with a common genetic polymorphism implicated in myopia. Proc Natl Acad Sci U S A. 2022 May 24;119(21):e2119675119. doi: 10.1073/pnas.2119675119. Epub 2022 May 20. PMID: 35594404; PMCID: PMC9173800.

Professor Juan Pedro Martinez-Barbera

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Theme: Experimental and Translational Medicine

Research overview

This project is focused on paediatric diffused midline glioma (DMG), an extremely devastating paediatric brain cancer that is usually diagnosed in children 5-7 years old. The prognosis is abysmal with an 95% mortality at 2 years after diagnosis. The only effective treatment is radiotherapy, but this is palliative and the vast majority of tumours relapse 3-6 months post-RT with fatal consequences. We hypothesise that senescent cells present in the tumour and tumour microenvironment (TME), as the consequence of oncogene-induced senescence and/or radiation-induced senescence fuel tumour growth and relapse.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The overarching goal of this project is to reveal the molecular and cellular mechanisms underlying the tumour-promoting activity of senescent cells in tumour development and relapse in DMG. Senescence is a response to cellular stressors such as oncogenic signalling, replicative exhaustion and genotoxic agents. Upon senescence induction, cells enter a stable cell cycle arrest. Senescent cells can elicit cell non-autonomous activities through the senescence-associated secretory phenotype (SASP), a complex secretory programme composed of a cytokines, growth factors, and other active chemicals. Our preliminary data show the presence of senescent cells in DMG murine models and human samples during tumour development and after RT, both in cells within the tumour and in the tumour microenvironment (TME). Building on these findings, the PhD student will: (Aim 1) Reveal the cell types that become senescence, both within the tumour lineage and TME in developing and post-RT relapsed tumours. These cell populations will be molecularly characterised (e.g. scRNA-seq) in mouse tumours. We have the genetic tools to address this question (see reference). (Aim 2) Uncover the molecular and cellular mechanisms underlying the tumour-promoting activities of senescent cells. The student will ablate senescent cells in the developing tumours to characterise the consequences of senescent cell ablation on the cellular composition of the TME. (Aim 3) Evaluate preclinically the efficacy of combination therapies of radiotherapy and senolytic treatments. Optimisation of these combination therapies will involve mathematical modelling, which will be carried out in collaboration with Dr Jamie Dean (UCL Faculty of Engineering Sciences).

Relevant publications 1

3. Haston, S, Gonzalez-Gualda, E, Morsli, S, Reen, V, Calderwood, A, Moutsopoulos, I, Panousopoulos, L, Carreno, G, Guiho, R, Manshaei, S, Gonzalez-Meljem, JM, Lim, HY, Simpson, DJ, Birch, J, Pallikonda, HA, Chandra, T, Macias, D, Doherty, GJ, Rassl, DM, Rintoul, RC, Signore, M, Mohorianu, I, Gil, J, Muñoz-Espín, D and Martinez-Barbera, JP. Clearance of senescent macrophages ameliorates tumorigenesis in KRAS-driven lung cancer. Cancer Cell 2023 Jul 10;41(7):1242-1260.e6.

Relevant publications 2

4. McHugh, D, Sun, B, Hernández-González, F, Mellone, M, Guiho, R, Pombo, Pietrocola, JF, Birch, J, Kallemeijn, W, Khadayate, S, Dharmalingam, G, Vernia, S, Tate, EW, Martínez-Barbera, JP, Withers, DJ, Thomas, GJ, Serrano, M, and Gil, J. COPI vesicle formation and N-myristoylation are targetable vulnerabilities of senescent cells. Nat. Cell Biol. 2023 Nov 27. doi: 10.1038/s41556-023-01287-6.

Dr David Michod

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Research overview

My research group studies the role of key epigenetic regulators in the context of paediatric diffuse midline glioma (pDMG), the most devastating paediatric malignancies. We combine cell biology, innovative epigenomic mapping strategy, next generation sequencing and in vivo experiments to identify new targets and evaluate the therapeutic potential.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The goals of this project are to unravel the role of the protein mixed lineage leukaemia (MLL) in the context of paediatric diffuse midline glioma and to evaluate preclinically the therapeutic potential of targeting the MLL complex against pDMG. pDMG has a dismal prognosis, with no curative treatments, making it one of the most devastating paediatric malignancies. pDMG is characterized by a specific mutation, H3K27M, resulting in the expression of a mutant histone 3 protein. H3K27M functions as a dominant negative mutation that severely alter the chromatin state of pDMG cells which result in the transcriptional activation of the oncogenic programme leading to pDMG development. The objectives of this proposal are: 1. To identify the MLL-chromatin interactions in pDMG cells. We will use Cut&Tag and Cut&Run assays to reveal the specific chromatin interactions of MLL, its cofactors and the associated histone modifications using a range of well characterised patient-derived pDMG cell lines. 2. To reveal the effects of MLL ablation in pDMG cells. We will combine siRNA knockdown and protein degradation approaches to reveal the function of all components of the MLL complex and the associated histone modifications in the specific context of H3K27M expression. 3. To assess the therapeutic efficacy of targeting MLL in vitro and in vivo. We will test the efficacy of a range of inhibitors, some clinically approved, against pDMG in cultured cells and, in both immunosuppressed and immunocompetent murine models to provide data to support a clinical trial. Additional supervisor: Professor JP Martinez-Barbera.

Relevant publications 1

Alcohol-abuse drug disulfiram targets pediatric glioma via MLL degradation. Meier S, Cantilena S, Chirou MVN, Anderson J, Hargrave D, Salomoni P, et al. Cell Death Dis. 2021;12(8).

Relevant publications 2

New Developments in the Pathogenesis, Therapeutic Targeting, and Treatment of H3K27M-Mutant Diffuse Midline Glioma. Argersinger DP, Rivas SR, Shah AH, Jackson S, Heiss JD. Cancers (Basel). 2021 Oct 21;13(21):5280.

Dr Chris Morris

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Research overview

In autophagy, a protein called LC3 targets intracellular material that has been ear-marked for degradation and promotes fusion with lysosomes. A closely related process called LC3-associated phagocytosis (LAP), targets extracellular proteins or bodies that have been internalised into the cell – these might include pathogens or therapeutics such as mRNA nanoparticles.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The rotational and full PhD project will build upon our recent paper describing the skin phenotype of the LAP deficient "delta WD" mouse model that harbours a mutation in the Atg16l1 gene. Rotational Project Aim: To characterise the role played by LAP in the uptake and trafficking of mRNA-loaded therapeutic lipid nanoparticles (LNPs) in the skin. Objective 1: isolation and culture of keratinocytes from wild-type and delta WD mice. Cells will be characterised by Western Blot and qPCR analysis. Objective 2: perform high content live cell imaging of LNP uptake by skin keratinocytes at the LMCB and employ AI-powered analytics to deconvolute the datasets (co-supervised by Dr Kate Ricketts, UCL Division of Surgery and Interventional Science). Cells will be labelled/transfected with reporters of key endocytic compartments such as early/late endosomes & lysosomes (e.g. EEA-1/LAMP1) as well as proteins involved in LAP (LC3-GFP). Results from this rotational project will underpin further studies into (1) the molecular pathways implicated in LNP trafficking, (2) electron microscopy analysis of LNP uptake, and (3) the deployment of 3D organotypic skin cultures to examine the delivery of therapeutic mRNAs to inflamed skin models that recapitulate the inflammatory skin disease, psoriasis. This project is ideal for students wishing to undertake a multidisciplinary project which aims to identify and understand the biological barriers to the development of effective therapeutic platforms. The student will be well supported in their training by existing team members in the Morris lab as well as those in the Ricketts lab.

Relevant publications 1

10.1016/J.XJIDI.2024.100283

Relevant publications 2

10.1038/S41416-022-01783-W

Professor Reza Motallebzadeh

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Research overview

The aim of the proposed study is to develop, characterize, and validate a novel in vitro 3D human kidney organoid culture system ultimately aimed at screening for compounds capable of modulating the tubulointerstitial microenvironment crosstalk that perpetuates development of fibrosis in chronic kidney disease (CKD). Kidney organoids will be developed using adult human renal cells combined with hydrogels derived from decellularized adult human kidney extracellular matrix (ECM). Although current synthetic and xenogenic ECM (eg. Matrigel) hydrogels offer robust mechanical support for in vitro cell culture, they lack the necessary organ-specific biochemical and mechanical cues to promote endogenous cell function. Our hypothesis is that scaffolds composed of native kidney ECM will support more optimal organoid development by providing an organ-specific 3D human renal microenvironment.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The purpose of the project is to develop a human kidney organoid model of the kidney tubulointerstitium to better understand the role of heterotypic cell interactions and pathogenesis of fibrosis and to provide a model system in which to test candidate therapies. To achieve this, the student will carry out the following: - Create a 3D culture model of the renal tubulointersititium by combining primary cultures of human proximal tubular epithelial cells (PTEC) and interstitial fibroblasts (IFs), derived from normal and fibrotic kidneys, and characterise organoid ultrastructure. This will take forward our current work that has used kidney-ECM hydrogels seeded with a tubular epithelial cell line (HK2). - Use the culture system to model fibrosis e.g. response to TGF-b. - Use the culture system to test candidate anti-fibrotic compounds and as a platform for screening for novel candidates. The project milestones for a PhD candidate would be as follows - Milestone 1 (Year 1): Optimise conditions for reproducible kidney-ECM hydrogels from normal and fibrotic kidneys, in particular improving gelation techniques. Rheological assessment. Milestone 2 (Year 2): Develop and optimise human kidney organoids. Primary cells will be isolated from normal and fibrotic human kidneys and applied to human kidney-ECM hydrogels derived from healthy and fibrotic kidneys, respectively. Immunofluorescence based-imaging and electron microscopy will be used to delineate the structure, differentiation and functional characteristics of the organoids. Milestone 3 (Year 3): Modelling renal fibrosis in organoids and testing anti-fibrotic compounds. Analysis of cell injury by immunofluorescence and RT-qPCR for renal tubular injury markers and pro-inflammatory cytokines. The project will benefit from working with industry partners (including UCB Pharma and UCL spin-out Engitix), which will provide valuable experience of industry processes.

Relevant publications 1

Identification of an altered matrix signature in kidney ageing and disease. J Am Soc Nephrol 2021 Jul;32(7):1713-1732. doi: 10.1681/ASN.2020101442. Epub 2021 May 28.

Relevant publications 2

Norman JT, Clark IM, Garcia PL. Hypoxia promotes fibrogenesis in human renal fibroblasts. Kidney Int. 2000;58:2351-2366

Professor Hirak Patra

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Research overview

Macrophages play a crucial role in various diseases, including cancer, atherosclerosis, cardiovascular, immune-related diseases etc. Specific targeting of these immune cells using smart nanosystems can enhance drug delivery and imaging capabilities. In this MRC project, we will develop a macrophage-targeting nano toolbox for improved disease management and personalised solution.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The rotation project will develop and test novel NP-based approaches for re-educating tumour-associated macrophages (TAMs) by modifying their tumour-promoting phenotype into a tumoricidal state. Human macrophage cell lines or primary macrophages will be co-cultured with various human cancer cell lines or tumour organoids to induce TAMs (methodologies are already established in the collaborator's lab at KCL). TAMs selectively overexpress certain receptors on their surface which will be targeted. Designer NPs specifically targeting these receptors through their unique surface functionalisation will be loaded with macrophage-activating cytokines, drugs or nucleic acid cargo and delivered to the co-cultured TAMs or normal macrophages (Month 1-2). We will evaluate i) the selective delivery of these NPs into TAMs but not in normal macrophages, ii) the repolarisation of TAMs from an anti-inflammatory phenotype to a proinflammatory phenotype, and iii) the ability of re-educated TAMs to kill or restrict tumour growth in co-culture models (Month 2-4). These in vitro experiments will provide proof of concept data to develop the nano toolbox in therapeutic macrophage targeting and pave the way for subsequent in vivo animal experiments for preclinical testing and clinical development and first in human challenge studies. Supervision: Prof Patra, an expert in nanomedicine will provide overall guidance, project direction, and expertise in developing nano toolbox. Dr Mukhopadhyay from KCL is an expert in macrophage biology and immunology. Both the labs have state-of-the-art facilities in nanomedicine and cell and molecular biology. Both supervisors will Assist with experimental design, data analysis, and thesis and manuscript preparation.

Relevant publications 1

Onyishi CU, Desanti GE, Wilkinson AL, Lara-Reyna S, Frickel EM, Fejer G, Christophe OD, Bryant CE, Mukhopadhyay S, Gordon S, May RC. Toll-like receptor 4 and macrophage scavenger receptor 1 crosstalk regulates phagocytosis of a fungal pathogen. Nat Commun. 2023 Aug 14;14(1):4895. doi: 10.1038/s41467-023-40635-w. PMID: 37580395; PMCID: PMC10425417.

Relevant publications 2

Zhu GH, Azharuddin M, Pramanik B, Roberg K, Biswas SK, D'arcy P, Lu M, Kaur A, Chen A, Dhara AK, Chivu A, Zhuang Y, Baker A, Liu X, Fairen-Jimenez D, Mazumder B, Chen R, Kaminski CF, Kaminski Schierle GS, Hinkula J, Slater NKH, Patra HK. Feasibility of Coacervate-Like Nanostructure for Instant Drug Nanoformulation. ACS Appl Mater Interfaces. 2023 Apr 12;15(14):17485-17494. doi: 10.1021/acsami.2c21586. Epub 2023 Mar 28. PMID: 36976817; PMCID: PMC10103128.

Dr Dimitra Peppa

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Theme: Experimental and Translational Medicine

Research overview

A specific subset of NK cells with memory traits shows enhanced longevity and superior anti-tumour responses compared to conventional NK cells. Interestingly, a group of CD8 T cells also exhibit NK-like qualities, exerting effective responses against leukemia cells without PD1 induction. These subsets may become preferred choices for genetic modification.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The proposed PhD project aims to evaluate the efficacy of CD19 CAR engineered memory NK cells (mNK) and innate-like CD8 T cells in combating tumours in vitro. The research will provide a promising strategy for treating patients with refractory CD19+ B cell malignancies. In the first year, starting with established CD19-targeting CAR constructs, innate-like CAR T and CAR-mNK cells will be produced. The focus will be on transduction efficiency and potential changes in cell phenotype, function, and proliferative capacity. Tumor-killing efficacy of these engineered populations will be assessed using cell lines and a reiterative stimulation model, comparing outcomes with conventional CAR cells. In the second year, CAR-mNK or innate-like CAR T cells will be subjected to culture conditions mimicking nutrient and oxygen deprivation to evaluate their resilience in such environments. Metabolic profiling and assays will be conducted to understand cellular responses under stress. The third year will involve further targeted manipulation of cells to enhance their performance. This research will benefit from collaboration between Dr. Peppa, an expert in NK cells, and Dr. Schurich, an expert in CAR T cell metabolism. The student will gain research experience and opportunities to contribute to two dynamic research teams, facilitating an interdisciplinary approach to this project.

Relevant publications 1

Arellano-Ballestero H, Zubiak A, Dally C, Orchard K, Alrubayyi A, Charalambous X, Michael M, Torrance R, Eales T, Das K, Tran MGB, Sabry M, Peppa D, Lowdell MW. Proteomic and phenotypic characteristics of memory-like natural killer cells for cancer immunotherapy. J Immunother Cancer. 2024 Jul 20;12(7):e008717. doi: 10.1136/jitc-2023-008717. PMID: 39032940; PMCID: PMC11261707.

Relevant publications 2

Muliaditan T, Halim L, Whilding LM, Draper B, Achkova DY, Kausar F, Glover M, Bechman N, Arulappu A, Sanchez J, Flaherty KR, Obajdin J, Grigoriadis K, Antoine P, Larcombe-Young D, Hull CM, Buus R, Gordon P, Grigoriadis A, Davies DM, Schurich A, Maher J. Synergistic T cell signaling by 41BB and CD28 is optimally achieved by membrane proximal positioning within parallel chimeric antigen receptors. Cell Rep Med. 2021 Dec 21;2(12):100457. doi: 10.1016/j.xcrm.2021.100457. PMID: 35028604; PMCID: PMC8714859.

Dr Nikolas Pontikos

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Theme: Experimental and Translational Medicine

Research overview

Our lab is a team of computer scientists, geneticists and clinicians, working on the joint analysis of genetics, medical imaging and text data to develop decision support systems for diagnosis, prognosis and treatment of rare eye diseases. We combine a deep understanding of ophthalmology with computational expertise and big datasets.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Inherited retinal diseases (IRDs) are a leading cause of blindness in children and working age adults. These conditions are caused by mutations in one of 270 genes. It is currently very challenging to detect these conditions before irreversible sight loss has occurred. Genetic testing is the gold standard for diagnosis but population wide screening is not cost-effective nor achievable. On the other hand recent technological advances in multimodal retinal imaging has made the technology cheap, non-invasive and widely available. The Eye2Gene project aims to utilise some of the largest population level datasets available of retinal scans to improve the detection and differential diagnosis of IRDs by applying AI to retinal imaging in order to improve the early detection rate of these conditions. The rotation project will focus on developing a proof of concept image screening AI tool in a completely novel retinal imaging technology that uses ultra widefield during which the student will learn about convolutional neural networks. The project will develop into a revolutionary PhD on next generation phenotyping using AI in the field of rare diseases. The student will have the opportunity to work at the cutting edge of AI on classification, segmentation and generative tasks, working within a highly motivated and engaged team of computer scientists, geneticists, clinicians and IRD patients. The student will have the opportunity to address many technical challenges including class imbalance, phenotype-genotype heterogeneity, out of distribution recalibration, historical biases and privacy-preserving computation that will require novel methodology to be developed.

Relevant publications 1

https://doi.org/10.21203/rs.3.rs-2110140/v1

Relevant publications 2

https://doi.org/10.1136/bmjopen-2022-071043

Professor Sergio Quezada

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Research overview

Adoptive cell therapy (ACT) with tumour-infiltrating lymphocytes (TIL) is a successful form of cancer immunotherapy where a patient's TILs are expanded ex vivo and re-infused promoting potent tumour control. This project will investigate the impact of the expansion process on T cell reactivity and function to inform next-generation TIL therapy.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The phenotype of tumour-specific TILs within a treatment product (e.g. CD4+:CD8+ ratio) appears to impact responses to TIL-ACT in melanoma1,2. We are studying how these phenotypic qualities are shaped by the expansion process, and how adaptations to expansion can improve the TIL product. The persistence and phenotype of tumour-reactive TILs will be tracked throughout the TIL expansion process. These data will then be used to identify potential ways to improve TIL production. During the rotation, the student will develop wet lab expertise in current standard approaches for TIL expansion from tumours, gain exposure to tumour-reactivity validation techniques, and generate a preliminary single-cell RNA sequencing dataset of TILs from fresh tumour and the subsequent expansion. The student will also learn the basics of the computational analyses. The full PhD project will continue these works across multiple patient samples. This includes validation of tumour-reactive TILs in vitro, lineage tracing of validated tumour-reactive TILs throughout the expansion process, and analysis of the multi-omic data to short-list potential process manipulations. It is expected that the student will play a key role in the computational analyses required for the PhD project. Potential manipulations (e.g. CRISPR knockouts or cytokine cocktails) will be tested in TIL expansions and experimentally evaluated for their effects on key parameters, including tumour clearance potential in in vitro culture systems and murine ACT models. There is room for flexibility depending on the findings, allowing creativity and exposure to different techniques.

Relevant publications 1

Krishna, S., … Rosenberg, S.A. Stem-like CD8 T cells mediate response of adoptive cell immunotherapy against human cancer. Science. 2016.

Relevant publications 2

Fernandez, V.A., … Svane, I.M. Biomarkers for response to TIL therapy: a comprehensive review. J Immunother Cancer. 2024.

Professor Ahad Rahim

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Theme: Experimental and Translational Medicine

Research overview

The Rahim and Tuschl groups work closely to develop cutting-edge genetic therapies for debilitating neurometabolic disorders of childhood. Using cell, mouse and zebrafish models of these disorders, the aim of their work is to provide proof-of-concept data for novel treatments that can be translated into clinical practice.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Manganese is an essential trace metal and critical for brain physiology. At the same time, manganese overload is neurotoxic and causes a disabling movement disorder seen in children with mutations in the manganese transporters SLC30A10 and SLC39A14. Current treatment is limited to intravenous chelation therapy with EDTA which is burdensome and associated with adverse effects. Therefore, there is an overwhelming need to develop new treatments that will improve the quality of life of affected children. This project aims to develop cutting-edge and life-changing gene therapy that builds on proof-of-concept data confirming that hepatic expression of wild-type SLC30A10 can rescue manganese neurotoxicity in SLC30A10 knockout mice. During the rotation project, the student will clone a novel human liver tropic gene therapy viral vector expressing the transporter gene SLC30A10 that is expected to have a more favourable safety profile during clinical translation. SLC30A10 expression and functionality will be assessed in liver Hep3B cells that are deficient in SLC30A10 using qPCR, Western blot and ICP-MS. This will then lead onto the full PhD project during which the student will conduct a pre-clinical study to manufacture the viral vector and determine efficacy of functional rescue in CRISPR/Cas9 edited liver cells, organoid systems and in the knockout mouse model. The student will join an enthusiastic and supportive team of translational neuroscientists and clinical experts, take an active role in project design and execution, and develop a broad multidisciplinary, methodological and transferrable skill set required to develop into an independent scientist.

Relevant publications 1

Massaro G, Geard AF, Nelvagal HR, Gore K, Clemo NE, Waddington SN, Rahim AA. Compairson of different promotors to improve AAV vector-mediated gene therapy for neuronopathic Gaucher disease. Hum Mol Genet. 2024 May 16:ddae081. doi: 10.1093/hmg/ddae081

Relevant publications 2

Anagianni S, Tuschl K. Genetic disorders of manganese metabolism. Curr Neurol Neurosci Rep. 2019. 19:33.

Dr Christopher Serpell

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Theme: Experimental and Translational Medicine

Research overview

Sequence defined synthetic macromolecules (phosphoestamers) that block protein-protein interactions (PPIs) could address mechanisms of oncogenesis and create a new path towards therapeutics. This project aims to advance phosphoestamers which block the interactions of mutant RAS proteins (which drive 30% of cancers) through lipid nanoparticle formulation and biological studies.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Dr Serpell has identified sequence-defined macromolecules (phosphoestamers) which selectively block the interaction between oncogenic mutant KRAS, and RAF1 (a major oncological target) in protein assays with IC50 values down to 25 nM. Phosphoestamers could become a new class of drug against cancer, and could also address protein-protein interactions in diseases from neurodegeneration to viral infection. The next step is cellular studies. Phosphoestamers are physicochemically similar to nucleic acids, so may require similar delivery strategies, such as lipid or polymer nanoparticles (Dr Gurnani's expertise) for engaging with intracellular targets (KRAS). In the rotation project, the student will initiate cell studies. Firstly, they will quantify inhibition of KRAS's interactions with its other partners (PI3K, SOS, and RASGAP) by a phosphoestamer through grating-coupled interferometry. Biostability will be quantified by incubating the phosphoestamer with serum proteins, with degradation measured by gel electrophoresis. Cellular uptake (with and without lipid/polymer nanoparticle formulation) will be studied using a fluorophore-tagged phosphoestamer quantitatively using flow cytometry and spatially using live cell fluorescence microscopy. The outcome of the rotation will be the first data on phosphoestamer activity in cells. These findings will lead into a full PhD project which will include a wider range of phosphoestamers, examine phenotypic and mechanistic effects in mutant and wild-type cells, optimisation of phosphoestamer chemistry, cell-specific targeting of nanoparticles, and EndoPore delivery systems. Prof Michelle Garrett (University of Kent, cancer drug discovery biology) and Dr Vineeta Tripathi (Vitarka Therapeutics, EndoPore) will contribute to the project, giving the student insights into the entire therapeutics pipeline.

Relevant publications 1

B. R. Claringbold, S. Vance, A. R. Paul, M. D. Garrett, C. J. Serpell, Sequence-defined oligophosphoesters for selective inhibition of the KRAS G12D/RAF1 interaction, BioRxiv, 2024, DOI: 10.1101/2024.03.12.584553

Relevant publications 2

N. K. Dastgerdi, N. Gumus, H. Bayraktutan, D. Jackson, K. Polra, P. F. McKay, F. Atyabi, R. Dinarvand, R. J. Shattock, L. Martinez-Pomares, P. Gurnani, C. Alexander, Charge neutralized poly(β-amino ester) polyplex nanoparticles for delivery of self-amplifying RNA, Nanoscale Adv., 2024,6, 1409-1422

Professor Joe Standing

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Theme: Experimental and Translational Medicine

Research overview

Combination antimicrobials to combat antimicrobial resistance

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Antimicrobial combinations are essential to combat complex, antimicrobial resistant (AMR) infections. To date, antibiotic combination treatments have been derived empirically and are often suboptimal. Defining the optimal drug combination of antimicrobials and the associated dosing schedules to maximise efficacy and minimise the risk for AMR selection is complex and requires extensive preclinical development. We have invested in state-of-the-art laboratory facilities including automated plate readers and the hollow fibre infection model (mimicking antimicrobial pharmacokinetics in plastic rather than mice) and coupled with advanced mathematical and statistical modelling, are now in a position to answer pressing questions including: What is the optimum choice and dose of antibiotic combination to treat AMR Gram negative bacteria or Candida auris? Which combination and dose produce the highest barrier to further resistance development? This project will screen large clinical isolate banks that have already been phenotypically and phenotypically characterised against combinations of therapeutics to answer the above. The 3-month placement will begin by looking at meropenem-amikacin combinations against a 200-isolate bank of Gram negatives where you will learn the basic microbiology techniques and R coding to mathematically determine optimal combination effects and resistance suppression.

Relevant publications 1

https://pubmed.ncbi.nlm.nih.gov/32769975/

Relevant publications 2

https://pubmed.ncbi.nlm.nih.gov/37283195/

Professor Richard Stratton

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Research overview

Analysing of the effects of Immunoglobulin G (IgG) autoantibodies from systemic sclerosis patients' plasma samples on human skin cells maintained in tissue culture will lead to improved understanding of the molecular pathways driving this disease and allow for better treatments designed to block the damaging effects of IgG.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Systemic sclerosis (also called scleroderma, SSc), is a severe autoimmune disease in which dysregulated immunity leads to damaging cellular activation in the skin and internal organs. In the rotation project under Aim 1, the student will purify IgG autoantibodies from SSc patients' plasma samples and test their effects on cultured human keratinocytes. Normal human keratinocytes will be maintained in media only, or else stimulated by addition of early stage SSc IgG autoantibodies, or with healthy control IgG and then profiled for changes in gene expression by RNAseq. Differentially expressed genes will be identified using R programming followed by Pathway Analysis. Furthermore, the conditioned media from these experiments will be profiled using Multiplex protein assays to identify the full range of cytokines released by the SSc IgG treatment. Under Aim 2, key mechanistic events underlying the effects of SSc IgG will be explored. Small molecule drug inhibitors targeting selected signalling pathways identified under Objective 1, and monoclonals targeting key cytokines, will be evaluated for the capacity to block the activating effects of SSc IgG. Finally, under Aim 3, keratinocytes will be maintained with fibroblasts in a human 3-D skin model (organotypic culture) with and without addition of the SSc IgGs. The effects of the IgG on keratinocyte-fibroblast cross talk leading to scleroderma-like fibrosis will be evaluated and potential therapeutic inhibitors, as identified under aim 2, explored further in this model system. Hence the student will acquire a wide range of research skills whilst developing new therapeutic approaches to a serious disease.

Relevant publications 1

Moezinia C, Wong V, Watson J, Nagib L, Lopez Garces S, Zhang S, Ahmed Abdi B, Newton F, Abraham D, Stratton R. Autoantibodies Which Bind to and Activate Keratinocytes in Systemic Sclerosis. Cells. 2023 Oct 20;12(20):2490. doi: 10.3390/cells12202490. PMID: 37887334; PMCID: PMC10605821.

Relevant publications 2

Abraham D, Lescoat A, Stratton R. Emerging diagnostic and therapeutic challenges for skin fibrosis in systemic sclerosis. Mol Aspects Med. 2024 Apr;96:101252. doi: 10.1016/j.mam.2024.101252. Epub 2024 Feb 6. PMID: 38325132.

Dr Yasuhiro Takeuchi

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Research overview

The project aims to develop molecularly imprinted polymer nanoparticles (MIP NPs) as cost-effective, scalable, and robust synthetic antibodies against common cold coronaviruses and respiratory syncytial virus, integrating antiviral moieties to enhance efficacy and improve patient care outcomes.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The envisaged project focusses on investigating the potential of molecularly imprinted polymer nanoparticles (MIP NPs, aka synthetic antibodies) as therapeutic agents against common cold coronaviruses (HCoV) and respiratory syncytial virus (RSV). Synthetic antibodies are created through molecular imprinting, offering advantages such as scalability, cost-effectiveness, and robustness. The project involves identifying suitable viral antigens/epitopes, developing MIP NPs targeting these, and integrating antiviral drugs/moieties for enhanced efficacy. The research plan includes rational design of MIPs, synthesis of MIP NPs, and physicochemical and biological characterisation. This latter will be assessed for cellular toxicity and antiviral efficacy in vitro. The potential impact of this research on patient care is significant, as it could lead to the development of novel, cost-efficient antiviral therapies not just for respiratory viral infections but also with broader applicability and improved patient outcomes, ultimately reducing the burden on healthcare systems and offering hope for combating outbreaks like COVID-19.

Relevant publications 1

https://journals.asm.org/doi/full/10.1128/jvi.00685-21?rfr_dat=cr_pub++0pubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org

Relevant publications 2

https://www.nature.com/articles/nprot.2016.030

Professor Greg Towers

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Research overview

We study how intracellular innate immunity protects us from infection and how nonetheless, viruses can escape our defences to infect and cause disease. We use comparative virology to understand what makes pandemic viruses special focussing on HIV, Flaviviruses and Coronaviruses including SARS-CoV-2 and Middle Eastern Respiratory Syndrome virus (MERS).

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Our approach is to compare host responses to infection between viruses with different transmission rates or behaviours. For example, previous work demonstrated how pandemic HIV has a uniquely adapted its capsid to escape sensing by capsid sensor TRIM5 and DNA sensor cGAS. In other studies, we showed how SARS-CoV-2 variants of concern have adapted to improve transmission by upregulating expression of specific innate immune antagonists, particularly Orf9b, Orf6 and Nucleocapsid. We are also comparing human- and camel-tropic MERS isolates to understand what prevents MERS becoming pandemic. We use molecular virology, structural biology, and computational approaches to address our research questions. Typically, we infect cells and then measure host responses and viral replication by PCR and then immunofluorescence microscopy, RNAseq and mass spectrometry. We then manipulate cells (RNA interference or CRISPR/Cas), or make virus mutants, and measure what changes in terms of viral replication and host response. If replication is reduced, we measure whether this is due to enhanced interferon production using JAK/STAT inhibitor ruxolitinib. Comparison of different viruses is key to understanding the mechanisms of pandemic potential. Viral relationships are studied using phylogenetics and evolutionary approaches. We also study the role of innate immunity in cancer. Rotation projects are based on our coolest observations at the time you arrive and are developed in collaboration with the student and supervising post-doc, dependent on experience and interests. Our lab is around twelve people, funded by Wellcome, UKRI, NIH, MRC, Rosetrees Foundation, the National Institute of Health Research and the Evolution Education Trust.

Relevant publications 1

Zuliani-Alvarez et al. (2022) Evasion of cGAS and TRIM5 defines pandemic HIV. Nat Microbiol.7:1762-1776

Relevant publications 2

Thorne et al. (2022) Evolution of enhanced innate immune evasion by SARS-CoV-2. Nature 602:487-495

Dr Geoff Wells

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Research overview

Our group focusses on the design, synthesis and evaluation of small molecules that interact with biological target molecules. We use a combination of computational modelling, synthetic medicinal chemistry, and biophysical assays to develop inhibitors of transcription factors and antimicrobial drug targets, including coronavirus and bacterial cell division proteins.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The pandemic caused by the SARS-CoV-2 coronavirus continues to have repercussions on societies across the world, particularly sub-populations with pre-existing health conditions and/or low vaccine coverage. It is important to develop new antiviral agents to tackle future coronavirus outbreaks. During this project we will develop a series of small molecule inhibitors of selected coronavirus non-structural proteins (NSPs) including nsp10, a small adaptor protein that forms heterodimers with the exonuclease protein nsp14 and the RNA methyltransferase nsp16. Inhibiting the activity of nsp10 should impact on the enzymatic activities of nsp14 and nsp16 and inhibit viral replication. This mode of action should result in antiviral compounds that, either alone or in combination with other antivirals, protect populations from SARS-CoV-2 and new emergent coronaviruses. We have identified promising small molecule fragment hits that bind to nsp10 that can be developed into high affinity small molecule leads for this target. In collaboration with Frank Kozielski (crystallography and biophysical assays) and Shozeb Haider (molecular modelling) we will synthesise and test potential nsp10 inhibitors during this project. The project will provide cross-disciplinary training in current medicinal chemistry techniques and biophysical assays within our labs at UCL School of Pharmacy. There is considerable scope to continue with the project during a PhD by pursuing additional small molecule development approaches and working on other parts of our antiviral and antibacterial drug development portfolio.

Relevant publications 1

1. Kozielski F. et al. Identification of fragments binding to SARS-CoV-2 nsp10 reveals ligand-binding sites in conserved interfaces between nsp10 and nsp14/nsp16. RSC Chem. Biol., 2022,3, 44-55.

Relevant publications 2

2. Rogstam A. et al. Crystal Structure of Non-Structural Protein 10 from Severe Acute Respiratory Syndrome Coronavirus-2. Int. J. Mol. Sci. 2020, 21, 7375.

Associate Professor Haiyan Zhou

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Research overview

Nucleic acid therapeutics (NAT) represents a cutting-edge and rapidly advancing field of genetic therapies, and revolutionizes rare disease treatment and personalized medicine. The Zhou lab pioneers preclinical development and clinical translation, advancing personalized nucleic acid therapies for patients with debilitating and incurable rare genetic conditions.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The objective of this project is to develop a strategic framework and guidelines to assess and prioritise pathogenic genetic variants amenable to nucleic acid therapy and promote the development of personalised medicine for rare diseases. The project will leverage health data in genomics to identify children with rare diseases who might benefit from the advanced RNA-targeted therapy. This project will be part of the MRC/NIHR Rare Disease Node on establishing a UK Platform of Nucleic Acid Therapy for rare diseases (UPNAT, https://rd-research.org.uk/node/upnat/), a national translational programme in key partnership with NIHR BRCs, University of Cambridge, University of Oxford and Genomics England. The student will be involved in the UPNAT framework, on genomic and health data collected from various databases, e.g. Genomics England, DECIPHER, the National Congenital Anomalies and Rare Disease Registration Service (NCARDRS). The student will work on the data analysis in collaboration with researchers bioinformaticians from UPNAT. The student will continue NAT design, for example splice-switching antisense oligonucleotides (ASOs), and follow the preclinical development process of ASOs for one selected target. The appointed student will benefit from being embedded within the international collaborative network of UpNAT on RNA therapy in rare disease. They will receive supervision and mentoring from UpNAT Node PIs with diverse and complementary cross disciplinary expertise in the preclinical and clinical translation of NAT in rare genetic disorders.

Relevant publications 1

2. Aguti S, Cheng S, Ala P, Briggs S, Muntoni F and Zhou H. Strategies to improve the design of gapmer antisense oligonucleotide on allele-specific silencing. Molecular Therapy Nucleic Acids. June 04, 2024 https://doi.org/10.1016/j.omtn.2024.102237

Relevant publications 2

1. Zhou H, Arechavala-Gomeza V, Garanto A. Experimental Model Systems Used in the Preclinical Development of Nucleic Acid Therapeutics. Nucleic Acid Ther. 2023 May 5.