DIVISION OF INFECTION AND IMMUNITY

UCL

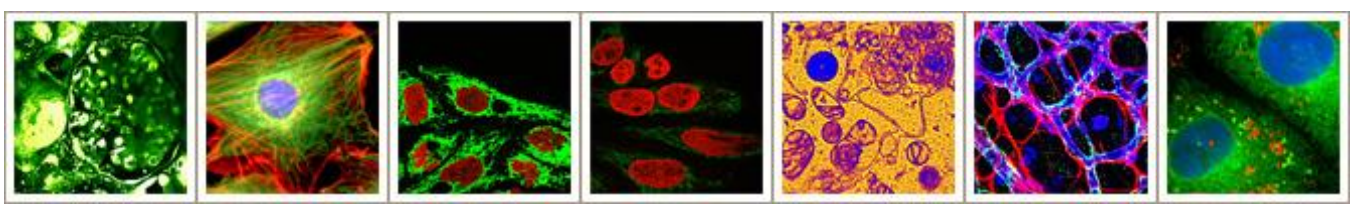
PhD

in

Infection, Immunity

&

Transplantation



PhD in Infection, Immunity & Transplantation

Welcome from the Director of Postgraduate Studies (Research), Ariberto Fassati MD PhD

"The future of medical research depends on the training of the best scientists and clinician scientists who will become leaders in their field. Maintaining the pool of excellence is a challenge that requires long-term vision and commitment. Our PhD programme is a critical part of this vision. We welcome applications from the best graduates who are committed to strive for excellence in science. With us, they will receive outstanding training, guidance and support to prepare them becoming leaders in their field"

Overview

UCL was founded in 1826 and was the first University to admit women and men on equal grounds without any discrimination based on religion. Since then, it has been hugely successful and consistently ranks among the top 20 Universities worldwide and it ranks within the top three in the UK with Cambridge and Oxford. UCL is the 10th most cited University overall (*Essential Science Indicators 2020* from Clarivate Analytics) and is the top-rated UK university for research strength (Research Excellence Framework 2014). UCL receives one of the largest shares of funding in the UK from the Medical Research Council, the Wellcome Trust and the European Research Council. There are 29 Nobel prize-winners amongst UCL alumni, current and former staff, including the latest UCL Nobel prize winner Prof. John O'Keefe (Medicine and Physiology 2014). 56 Fellows of the Royal Society are current or emeritus UCL Faculty.

The UCL Division of Infection & Immunity is part of the Faculty of Medical Sciences. In the last Research Assessment Exercise (RAE 2014), the Infection and Immunology panel graded 80% of outputs from the Division as 4* (world leading) or 3* (internationally excellent). The Division has state of the art facilities, including three level 3 containment laboratories and multi-parameter flow cytometry and has access to high content imaging, high throughput screening and next generation sequencing.

The Division comprises the **Department of Infection and the Department of Immunology** and two **Institutes**:

- **The UCL Institute of Immunity and Transplantation**: https://www.ucl.ac.uk/immunity-transplantation
- **The UCL Africa Health Research Institute**: https://www.ahri.org/about/

The Department of Infection focuses on pathogen biology (HIV-1, Herpesviruses, hepatitis viruses mycobacterium tuberculosis, pneumococcus, SARS-CoV-2, transmissible cancers) pathogens evolution, immune regulation by pathogens and translational medicine.

The Institute of Immunity and Transplantation (IIT) is based at the Royal Free campus in London and it is hosted in the new Pears building. The IIT focuses its research on transplantation and tissue

engineering, vaccination, cell and gene therapy, chronic infection, autoimmunity, immunological therapy for cancer and inherited immunological diseases.

The UCL African Health Research Institute (AHRI), based in Durban, South Africa, is funded by the Wellcome Trust and focuses its research on global health problems such as HIV-1 and Tuberculosis, drug resistance, SARS-CoV-2, population surveillance, viral reservoirs and co-infections.

The Division of Infection and Immunity has strong links to UCL hospitals, which include University College Hospital (UCH), The Royal Free Hospital, Great Ormond Street Hospital for Children (GOSH), The National Hospital for Neurology and Neurosurgery, the Hospital for Tropical Diseases, the Moorfields Eye Hospital and other members of UCL Partners. Furthermore, the Division has a global reach through the AHRI and collaborative research programmes in Malawi.

The Cruciform building seen from the main UCL quad

The new Pears building at the Royal Free campus

We aim to:

- Teach our PhD students how to perform world-leading research into Infection & Immunity (basic or translational).
- Prepare them to become independent researchers.
- Foster interdisciplinary research.

We have selected primary supervisors intending to host a student on the basis of excellence of their research, quality of the projects and track record in supervising students.
The Division of Infection & Immunity has been very successful in training PhD students. Over 60% of our students carry on with their career in academia at world leading Institutions, and another 22% enter the academic medical profession.

Structure of the PhD

Each student will have a primary supervisor and a thesis committee, which will include a secondary supervisor (acting as thesis committee chair) and one or two faculty members who can provide guidance and insight over the duration of the project. The thesis committee will have an advisory role and will meet at regular intervals during the PhD. The thesis committee will foster intellectual exchange and collaborations between the student and faculty members as well as among faculty members based at the different Institutes.

Students will have access to lectures and courses organized by the Division. Currently there are 21 courses covering Bacteriology, Virology, Parasitology, Mycology, Epidemiology, Immunology, Allergy and Immunodeficiency. Students will transfer (upgrade) from MPhil to PhD one and a half years after registration. Upgrade is conditional on satisfactory progress and the student will be required to present his/her research at a Divisional seminar, write a report and pass a viva examination.

Funding

Please note that we are currently unable to offer studentships, however we welcome applications from individuals who have secured their own studentship or intend to apply for a studentship. Information on scholarships can be found here: http://www.ucl.ac.uk/prospective-students/scholarships

UK nationals, EU citizens with settled status and overseas students may apply to the Birkbeck-UCL MRC Doctoral training programme within the themes of “Fundamental mechanism of Disease” or “Experimental and Personalised Medicine”. Successful applicants will be able to take a PhD in the Division of Infection & Immunity. The Wellcome Trust PhD programme in Optical Biology (https://opticalbiology.org/) also has a number of supervisors based in the Division of Infection and Immunity.

Overseas students can apply to the MRC DTP programme and the Wellcome Trust Optical biology programme, which have a few overseas studentships available. Alternatively, they must obtain independent funding that covers tuition fees £26,160 (FT fee in 2021) per year for 3 years subject to yearly increments plus living expenses. Funds to cover consumables for research are desirable but may not be necessary, depending on the supervisor.

Admission criteria and process

Admission is competitive. Students must have obtained a First class degree or equivalent from a good Institution. Candidates with an Upper Second class (2.1) degree or equivalent can also apply but in this case the standing of the Institution awarding the degree will have more weigh, along with A-levels (or equivalent) results. Overseas students should look here for guidance on academic degree equivalence: http://www.ucl.ac.uk/prospective-students/international/countries
Previous research experience will be considered.

Overseas students must also demonstrate English language proficiency (for guidance please visit: http://www.ucl.ac.uk/prospective-students/graduate/apply/english-language)

Candidates who meet these criteria will be shortlisted for formal interview (in person or remotely). To apply for a PhD in the Division of Infection and Immunity, students must use the online Portico system: https://www.ucl.ac.uk/prospective-students/graduate/research-degrees/infection-immunity-mphil-phd.

***Before you apply, it advisable that you look carefully at the projects available below and at the profiles of the Principal Investigators in the Division. You should provide a statement letter explaining which lab or labs you would like to join and why*. Please try to be specific**

Direct your queries to: Frances Collins (f.collins@ucl.ac.uk) or by telephone: +44 (0) 20 3987 2443.

Seminars and events

Attending seminars and presentations is an important aspect of the PhD. UCL offers a large selection of seminars and events with invited speakers from top Institutions worldwide. Students are encouraged to attend such seminars that are relevant to their studies and their scientific interests.

The Division organizes weekly external and internal seminars in the fields of Infection (Virology, Parasitology, Bacteriology) and Immunology and students are expected to attend the external seminars and present their work at the internal seminars.

Every year a PhD Colloquium is held where all the PhD students in the Division present their research. Prizes for the two best presentations are awarded on the day. A prominent scientist is invited to address the students at the end of the day with a talk covering his/her scientific discoveries and career.

A Postgraduate/Postdoc Club is organized by students and postdoctoral fellows with the support of the programme Committee. The Club invites external speakers in different areas (science, politics, media, industry, finance). Each talk is followed by a reception where the students can talk informally with the speaker.

Career development

Career development advice will be provided throughout the PhD by supervisors and thesis committees.
The Postgraduate Club will host meetings with senior faculty members who will provide advice on career progression (postdoc, fellowships, independent PI, how to set up your own lab). In addition, the Club will host informal talks and meetings with senior people working in Industry, Biotech, Scientific Writing and Entrepreneurs.

UCL has a dedicated Career office that offers advice on various aspects of the career progression, including preparation for job interviews and self-promotion http://www.ucl.ac.uk/careers

UCL, through its Professional Development Programme, offers a vast choice of targeted courses for skills training, including communication skills, writing grant proposals, assertiveness, ethics etc. http://www.ucl.ac.uk/hr/od/pdp/theme.php

The Division of Infection & Immunity has been awarded a Silver Athena Swan Award (http://www.ucl.ac.uk/infection-immunity/wom_ath) and is committed to supporting women in science.

In addition to the social events organized by the Division of Infection & Immunity, UCL offers a wide choice of leisure and social activities, including many clubs and societies and sporting facilities: http://www.ucl.ac.uk/prospective-students/study-abroad-guide/life-at-ucl/leisure-social

Projects and Supervisors

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Epithelial Stem Cell biology and Regenerative Medicine Lab

Our group research aims at understanding how epithelial organs such as thymus, oesophagus and pancreas develop, change with aging, and become susceptible to diseases. The lab is currently based at the Francis Crick Institute and projects are carried out accessing facilities at both UCL and Crick institutes.

The thymus controls the development of immune competence and tolerance, and its functional dissection and subsequent reconstruction with desired cell populations might provide powerful tools applicable to many medical conditions, including primary or acquired immune deficiencies.

Our work brings a multidisciplinary approach by combining stem cell biology, bioengineering technologies for organ reconstruction, microfluidics, next generation sequencing and molecular analysis of T cell development. The outcome of this work will set the basis for novel clinical protocols for organ transplantation and immunodeficiency disorders.

Potential PhD projects are interdisciplinary and address fundamental questions related to human thymus biology and T cell development, tolerance and development of translational approaches for congenital and acquired immune disorders.

Relevant publications

1.Campinoti, Gjinovci, Ragazzini et al. Reconstitution of a functional human thymus by postnatal progenitor cells and natural whole organ scaffolds. Nature Communications 2020, Dec 11:632 doi.org/10.1038/s41467-020-20082-7 - PMID: 33311516
2.Claudinot et al. Beyond Lineage Restriction: Tp63-Expressing Adult Epithelial Stem Cells Have Latent Hairy Skin Competence. Nature Communications 2020 Nov 6;11(1):5645. doi.org.10.1038/s41467-020-19485-3 - PMID: 33159086
3.Park et al. A cell atlas of human thymic development defines T cell repertoire formation. Science 2020 Feb 21;367(6480).
4.Piccinini E and Bonfanti P. Disassembling and Reaggregating the Thymus: The Pros and Cons of Current Assays. Methods in Molecular Biology 2019;1899:129-142
5.Giobbe et al. Extracellular matrix hydrogel derived from decellularized tissues enables endoderm organoids culture. Nature Communications 2019 Dec 11;10(1):5658.
6. Loukogeorgakis et al. In utero transplantation of in vitro expanded autologous amniotic fluid stem cells results in efficient long-term hematopoietic engraftment. Stem Cells 2019 doi:10.1002/stem.3039
7.Bonfanti et al. “Hearts and Bones”: The Ups and Downs of “Plasticity” in Stem Cell Biology. EMBO Molecular Medicine. 2012 May;4(5):353-61. Review
8. Bonfanti et al. Microenvironmental Reprogramming of Thymic Epithelial Cells to Skin Multipotent Stem Cells. Nature. 2010 Aug 19;466(7309):978-82

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Reading and understanding the T cell repertoire

The adaptive immune system is based on a unique molecular system which generates an enormous diversity of receptors on T and B lymphocytes, each with the potential to recognise a different molecular pattern, and hence stimulate a specific immune response to a particular pathogen. The size of the receptor diversity in every individual is estimated to be in the order of 109 – 1010 different receptors. With the advent of massively parallel high throughput sequencing it has now become possible to analyse this repertoire directly, and we have developed a new quantitative pipeline exploiting this technology for T cell receptor repertoire studies. This data has the potential to shed light on basic immunological paradigms, providing quantitative data on clone size, clone diversity and kinetics during immune responses which will be a key step in our long term objective of building multi-level mathematical models of immune system function. The data also has enormous potential in more applied applications, such as diagnosis of infectious disease, cancer and autoimmunity.

Potential PhD projects combine wet lab and computational training opportunities. The experimental data use high throughput sequencing to analyse repertoires from a range of clinical sample collections, which include samples from individuals with infectious disease (tuberculosis, HIV and COVID-19), autoimmunity, immunodeficiency, transplantation or cancer. Computational analysis focuses on developing ways to interrogate this data to understand the underlying biology. Specifically we develop methods to compare different TCR sequences, and cluster them in ways which reflect their functional antigen specificity. The goal is to be able to predict the peptide specificity of a T cell receptor from its sequence alone. We are collaborating with Prof. John Shawe-Taylor to apply recent advances in machine learning to protein sequence analysis.

The projects will provide training in immunology, molecular biology and computational biology. The projects will therefore be positioned at the intersection between machine learning and high throughput genomic technologies, which is one of the fastest moving and most exciting areas of the biomedical sciences.

Website

Benny Chain https://www.ucl.ac.uk/infection-immunity/people/professor-benny-chain
John Shawe-Taylor http://www0.cs.ucl.ac.uk/staff/J.Shawe-Taylor/

1. Joshi K et al Spatial heterogeneity of the T cell receptor repertoire reflects the mutational landscape in lung cancer. Nat Med. 2019 Oct;25(10):1549-1559. PMID: 32494063.
2. Peacock T, Heather JM, Ronel T, Chain B. Decombinator V4 - an improved AIRR-compliant software package for T cell receptor sequence annotation. Bioinformatics. 2020 Aug 27:btaa758. doi: 10.1093/bioinformatics/btaa758. Epub ahead of print. PMID: 32853330.
3. Sampson D, Yager TD, Fox B, Shallcross L, McHugh L, Seldon T, Rapisarda A, Hendriks RA, Brandon RB, Navalkar K, Simpson N, Stafford S, Gil E, Venturini C, Tsaliki E, Roe J, Chain B, Noursadeghi M. Blood transcriptomic discrimination of bacterial and viral infections in the emergency department: a multi-cohort observational validation study. BMC Med. 2020 Jul 21;18(1):185. doi: 10.1186/s12916-020-01653-3.

Prof Ariberto Fassati MD PhD

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Project areas: Transmissible cancers and HIV-1 latency.
We study two pathogens that have a remarkable ability to evade the immune system, namely HIV-1 and the canine transmissible venereal tumour (CTVT). Both of these pathogens can persist in a latent form. Curing HIV-1 infection will require eliminating the latent viral reservoir either by purging infected cells or by inducing a state of super-latency that mimics the repression of endogenous retroviruses in our genome. We have combined chemical biology and "omics" approaches to understand the mechanisms controlling HIV-1 latency and how drugs may regulate it. We found that Hsp90 is a druggable master regulator of HIV-1 latency and are currently elucidating the mechanisms. We discovered that the hormone receptor RORC2 is critical for HIV-1 reactivation from latency ex vivo. We are now studying how RORC2 influences HIV-1 gene expression and if selective RORC2 inhibitors work in humanized mice infected with HIV-1. Also, we are exploring how the 3D organization of chromatin within which HIV-1 integrates influences viral entry into or exit from latency. This is important to develop more targeted strategies that leverage specific epigenetic pathways that regulate latency.

Some years ago, we demonstrated that CTVT is a cancer that transmits as a cellular parasite. CTVT escapes allorecognition when it transmits, irrespective of the dog's leukocyte antigen type, yet it can be rejected by the immune system when the drug vincristine is administered. Such an extreme bi-modal phenotype is most interesting because it may suggest ways to prevent transplant rejection, and ways to trigger rejection of human cancers. We have recently shown that vincristine triggers CTVT rejection by activating the innate immune system and are investigating the epigenetic mechanisms controlling CTVT's bi-modal phenotype. To understand how a cancer may become transmissible, we are serially passaging a primary mouse melanoma in progressively immune-discordant mice to study its evolution by "omics" approaches.

Tomas Raul Wiche Salinas, Yuwei Zhang, Daniele Sarnello, Alexander Zhyvoloup, Laurence Raymond Marchand, Delphine Planas, Manivel Lodha, Debashree Chatterjee, Kasia Karwacz, Sally Oxenford, Jean-Pierre Routy, Heather Amrine-Madsen, Petronela Ancuta and **Ariberto Fassati**. Th17 cell master transcription factor RORC2 regulates HIV-1 gene expression and viral outgrowth. bioRxiv 2021.03.27.435072 (in press, ***Proc Natl Acad Sci U S A***)

Anderson I, Low JS, Weston S, Weinberger M, Zhyvoloup A, Labokha AA, Corazza G, Kitson RA, Moody CJ, Marcello A, **Fassati A**. Heat shock protein 90 controls HIV-1 reactivation from latency. ***Proc Natl Acad Sci U S A***. 2014 Ap 15;111(15):E1528-37

Murgia C, Pritchard JK, Kim SY, Fassati A, Weiss RA. Clonal origin and evolution of a transmissible cancer. ***Cell***. 2006;126(3):477-87.

Frampton D, Schwenzer H, Marino G, Butcher LM, Pollara G, Kriston-Vizi J,..and Fassati, A. Molecular Signatures of Regression of the Canine Transmissible Venereal Tumor. ***Cancer Cell.*** 2018;33(4):620-33 e6.

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Decoding the evolutionary record: What advanced models of sequence change can reveal about DNA, genes, and gene products

Nature has been performing ultra-high throughput in vivo site-directed mutagenesis studies for the past few billion years. The resulting evolutionary record contains a wealth of information about proteins, their structure, function, and physiological context, and how proteins adapt to changing circumstances. Unfortunately, standard phenomenological models used to analyse sequence change generally assume the effects we are most interested in - the variations of selection between different locations and at different times - do not exist. By constructing more mechanistic models that explicitly consider the process of mutation and selection we can decipher the resulting patterns of sequence variation and conservation, providing us access to Nature's lab notebook. We use these models to represent the nature of the selective constraints acting on protein sequences, to examine how protein sequences in influenza adapt to changes of host, and to characterize the effect of mutations on proteins - what proportions are deleterious, neutral, advantageous - an important distribution for modelling of population genetics.

Project: The analysis of selection on non-coding regions

Our entire genome, as well as that of all pathogens, is shaped by the process of molecular evolution. In particular, the nucleotide bases and amino acids found in different locations are sculpted by the constraints at those locations, constraints that arise from the function, structure, physiological role, and context at that site. Some important locations must preserve some important property such as size, charge, or hydrogen bonding location. Other locations need to change as the constraints on that site change due to, for instance, a change in function or a change in host. Still other locations in pathogen genomes or immune system genes need to change rapidly so as to avoid causing an effective immune response, or to respond to the changing pathogens. A number of standard approaches have been developed to analysing the strength and nature of the selection (and changes in the selection) in protein-coding genes - one of the most common is to compare the rate of nucleotide substitutions that do or do not result in amino acid changes. These and other methods do not work well in non-coding regions, where there is no amino acid to change. Yet much of the interesting evolutionary dynamics involves changes in non-coding regions such as promoters. There has been increased interest in other non-coding regions as well, including where various RNA molecules are transcribed but not translated into proteins. There is also much interest in the non-coding regions of 'selfish elements' in the genomes such as endogenous retroviruses and other transposable elements. This project would involve developing computational approaches to analyse selection acting on non-coding parts of the genome, including adapting these methods to the study of transposable elements in the genome, and how they are regulated by the host in which they reside.

Relevant papers:

Benjamin P. Blackburne, Alan J. Hay, and Richard A. Goldstein (2008), Changing patterns of selective pressure in Human Influenza H3, PLoS Pathogens, 4, e1000058, PMID: 18451985.

Mario dos Reis, Alan J. Hay, and Richard A. Goldstein (2009), Using Non-Homogeneous Models of Nucleotide Substitution to Identify Host Shift Events: Application to the Origin of the 1918 'Spanish' Influenza Pandemic Virus, J Mol Evol., 69 ,333-345, PMID: 19787384.

Asif U. Tamuri, Mario dos Reis, Alan J. Hay, Richard A. Goldstein (2009). Identifying changes in selective constraints: Host shifts in influenza. PLoS Comput Biol., 5, e1000564, PMID: 19911053.

Mario dos Reis, Asif U. Tamuri, Alan J. Hay, Richard A. Goldstein (2011). Charting the host adaptation of influenza viruses. Mol Biol Evol 28:1755-1767, PMID: 21109586.

Asif U. Tamuri, Mario dos Reis, Richard A. Goldstein (2012). Estimating the distribution of selection coefficients from phylogenetic data using sitewise mutation-selection models, Genetics, 190:1101-1115, PMID: 22209901.

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Microbial and immunological basis of infection by mucosal bacteria and viruses

The man focus of my work is the microbial and immunological basis of severe infection caused by bacterial and viral mucosal pathogens in the UK and Africa, and their prevention through vaccination. We have developed innovative human experimental infection approaches to understanding the early interactions between pathogens and their human host in pneumococcal, Group B streptococcus and COVID19 infection models. In particular, we have shown that contrary to current thinking, during commensal carriage, *Streptococcus pneumoniae* invades the human mucosa triggering inflammation without disease which may facilitate transmission. Our population-based studies of vaccine-preventable disease in Africa have led to national vaccine implementation, vaccine evaluation and large-scale studies of modified vaccine schedules.

Potential PhD project areas include:

1) The cellular and molecular basis of bacterial colonisation and transmission at the mucosal surface
2) Shifts in the genomic and antimicrobial resistance profiles of *Streptococcus pneumoniae* following the introduction of conjugate-polysaccharide vaccine and large-scale antibiotic use.
3) The impact of vaccination on the immune control of SARS COV-2 in experimental human infection

Projects will exploit state-of-the-art immunological, imaging and genome analysis and new evolutionary mathematical modelling approaches. Studentship will provide training in cell biology, immunology, bacterial genome analysis, infectious disease epidemiology and fundamental population genetics and phylogenetics. There will be an emphasis on ensuring that analyses undertaken are linked to relevant functional biological questions to improve the mechanistic understanding of pathogenesis and are of public health importance.

Selected references:

1) Weight CM, Venturini C, Pojar S, Jochems SP, Reine J, Nikolaou E, Solorzano C, Noursadeghi M, Brown JS, Ferreira DM, **Heyderman RS**. Microinvasion by *Streptococcus pneumoniae* induces epithelial innate immunity during colonisation at the human mucosal surface. **Nat Commun**. 2019;10:3060
2) Gori A, Harrison OB, Mlia E, Nishihara Y, Chan JM, Msefula J, Mallewa M, Dube Q, Swarthout TD, Nobbs AH, Maiden MCJ, French N, **Heyderman RS**. Pan-GWAS of *Streptococcus agalactiae* Highlights Lineage-Specific Genes Associated with Virulence and Niche Adaptation. **mBio**. 2020;11:e00728-20.
3) Kalizang'oma A, Chaguza C, Gori A, Davison C, Beleza S, Antonio M, Beall B, Goldblatt D, Kwambana-Adams B, Bentley SD, **Heyderman RS**. *Streptococcus pneumoniae* serotypes that frequently colonise the human nasopharynx are common recipients of penicillin-binding protein gene fragments from *Streptococcus mitis*. Microb Genom. 2021 In press
4) Bar-Zeev N, Swarthout TD, Everett DB, Alaerts M, Msefula J, Brown C, Bilima S, Mallewa J, King C, von Gottberg A, Verani JR, Whitney CG, Mwansambo C, Gordon SB, Cunliffe NA, French N, **Heyderman RS**, VacSurv Consortium. Impact and effectiveness of 13-valent pneumococcal conjugate vaccine on population incidence of vaccine and non-vaccine serotype invasive pneumococcal disease in Blantyre, Malawi, 2006-18: prospective observational time-series and case-control studies. **Lancet Glob Health**. 2021 Jul;9:e989-e98.
5) Swarthout TD, Fronterre C, Lourenco J, Obolski U, Gori A, Bar-Zeev N, Everett D, Kamng'ona AW, Mwalukomo TS, Mataya AA, Mwansambo C, Banda M, Gupta S, Diggle P, French N, **Heyderman RS**. High residual carriage of vaccine-serotype *Streptococcus pneumoniae* after introduction of pneumococcal conjugate vaccine in Malawi. **Nat Commun**. 2020;11:2222.

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My lab studies the interaction between HIV and CD4+ T cells. We seek to understand how HIV manipulates T cells to support viral replication and spread, and the consequences of this for the virus and the host. We are also applying our expertise in viral cell biology to dissect mechanisms of SARS-CoV-2 replication and spread between cells, and adaptation of SARS-CoV-2 to host focussing on innate immunity.

Cell-to-cell spread is the dominant mode of HIV dissemination and takes place at immune cell contacts called virological synapses (VS). This confers a many of advantages for the virus including rapid infection of target cells, evasion of components of the innate and adaptive immunity and increased resistance to some antiretrovirals. Therefore cell-cell spread poses a considerable barrier to eradicating HIV from infected individuals. We seek to understand how this process works at the molecular level and to exploit cell-cell spread to uncover new biology about HIV. For example, we have recently discovered that cell-cell spread at the VS drives CD4+ T cells to become permissive to HIV infection. This is exciting as it provides a new paradigm for why cell-cell spread is so efficient – the virus changes T cells to make them better able to support replication. We are now asking how cell-cell spread triggers T cell permissivity, how this influences antiviral defences (e.g innate immune sensing) and what viral and cellular determinants regulate these processes. We have also shown that cell-cell spread of HIV reprograms CD4 T cells in a unique way that means these cells are more likely to hide in tissues and we are now working to understand mechanism and implications for pathogenesis.

The overall goal of our research is understand the interaction between viruses and their hosts. To do this we use range of experimental techniques and approaches including (but not limited to) tissue culture, virological and immunological assays, molecular biology, mutagenesis and genetic manipulation of viruses and cells, advanced imaging approaches and multicolour flow cytometry.

PhD projects are available to work on any aspect of the above areas of research on HIV and SARS-CoV-2. My lab currently consists of 3 post-doctoral scientists and 1 PhD student and funded by the Wellcome Trust. We regularly host MSc and iBSc project students and are an interactive lab that collaborates with many other groups around UCL and beyond.

Selected recent publication:

1 Reuschl A-K. et al., HIV-1 Vpr drives a tissue residency-like phenotype during selective infection of resting memory T cells. (2021) *BioRxiv* https://doi.org/10.1101/2021.01.25.428084
2 Mesner D. et al., (2020) Loss of Nef-mediated CD3 down-regulation in the HIV-1 lineage increases viral infectivity and spread, *Proc Natl Acad Sci USA* 117: 7382-7391.
3 Haider T. et al., HIV envelope truncation confers resistance to SERINC5 restriction (2021). *Proceeding of the National Academy of Sciences USA* 118: e2101450118.
4 Len AC. Et al., (2017) HIV-1 activates signaling independently of antigen to drive viral spread. *Cell Reports* 18: 1062-1074.
5 Thorne LG, Bouhaddou M, Reuschl AK, Zuliani-Alvarez L, et al., Evolution of enhanced innate immune evasion by the SARS-CoV-2 B.1.1.7 UK variant. (2021) *bioRxiv*. Jun 7:2021.06.06.446826. doi: 10.1101/2021.06.06.446826. Preprint.
6 Thorne L.G., Reuschl A-K., Zuiliani-Alvarez L. et al. SARS-CoV-2 sensing by RIG-I and MDA5 links epithelial infection to macrophage inflammation. (2021) EMBO J *40 (15):* e107826

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We study immune responses in the liver, an organ that has evolved a uniquely tolerant immunological environment to deal with the onslaught of antigens it receives from the gut. Defining the characteristics of hepatic immunity is critical to understanding how three of the most prevalent and devastating human pathogens, HBV, HCV and malaria, take advantage of this niche in which to replicate and/or persist. Our group focuses on immune responses to hepatitis B in order to inform the development of novel immunotherapeutic strategies for this and other highly prevalent liver diseases. We are internationally recognized as being at the forefront of advances in this fast-moving area.

Liver disease is the only cause of mortality currently on the increase in the UK, due to the increase in alcoholic and fatty liver disease in addition to viral hepatitis. Liver inflammation and fibrosis leading to cirrhosis and liver cancer are unifying end-points in these diseases. To this end we are also now starting to dissect immune mechanisms in liver fibrosis and liver cancer.

Our lab is an enthusiastic, sociable and committed group of basic and clinical scientists.
Find out more about us and our work on our website: http://www.ucl.ac.uk/maini-group

We are highly interactive, working closely with staff in a number of clinics to obtain the patient samples so vital to our work, as well as with scientific collaborators here at UCL and internationally (see collaborators link in above website).

We have a great track record, with our PhD and BSc students having very successful and enjoyable attachments to our group. Our students are renowned for publishing high impact papers that are highly cited and for having their work recognized with local and international prizes.

If you join our lab you will have your own project on a topical aspect of hepatitis immunity that will interlink with those of the other team members for maximum productivity. We have traditionally concentrated on antiviral T cell responses but are increasingly also studying NK cells, myeloid cells and specialized liver-resident cells (e.g. stellate cells).

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We are a very dynamic and culturally diverse group, whom research focuses on delineating the cellular and molecular mechanisms controlling immune-regulation in health and how these pathways are dysregulated in autoimmune disease. We have pioneered the discovery of a novel subset of B-cells, known as regulatory B-cells (Bregs), which possess powerful immune-suppressive capacity. Our studies have overturned the pre-existing paradigm of B-cells being exclusively pathogenic in autoimmunity. In mice and humans, we have demonstrated that Bregs can directly suppress pro-inflammatory cytokine production by, and proliferation of, naïve, memory, and auto-reactive T-cells, whilst supporting the differentiation of regulatory T-cells via the release of IL-10. In autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) and, Bregs have lost their capacity to suppress pro-inflammatory T-cell responses and fail to control inflammation. By studying Breg function in healthy versus disease, we discovered for the first time that B-cells and Bregs present lipid-antigen to iNKT-cells via CD1d, that in healthy individuals iNKT-cells are converted into immunoregulatory iNKT-cells in response to Breg lipid presentation, but that in SLE defects in B-cell CD1d recirculation lead to altered lipid presentation, and reduced number and suppressive capacity of iNKT-cells. More recently, our research has uncovered the signals that drive and regulate Breg development and activation and has unravelled an important role for gut microbiota in the differentiation of Bregs and plasma cells producing antibody and identified novel gut-derived metabolites that alter systemic inflammatory processes.

The projects available will aim to investigate 1) the effect that diet and/or dietary components have on the metabolism of B cells 2) how changes in the gut-microbiota can be harness for the cure of rheumatoid arthritis.

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T cell repertoire as a complex ecosystem

The evolution of diverse clonal populations underlies the development of cancers, antibiotic resistance, and protective immune responses. Predicting outcomes of the dynamical processes shaping clonal evolution is of considerable practical importance, but the current theory breaks down when analysing highly diverse populations where there are many distinct clones. An important example of such a system is the adaptive immune system, where the highly diverse antigen receptors act as natural genetic 'barcodes' for identifying clonal lineages, which can be read out by sequencing at scale. In this PhD project, we will develop computational and mathematical techniques to understand the dynamic processes, which regulate the extremely diverse population of T cells, and their response to antigen.

As a PhD student, you will have access to unique longitudinal sequencing data on T cell receptor repertoires in the context of BCG vaccination, tuberculosis infection and treatment of COVID-19 infection. The project will address key questions such as the longevity of the immune response, and how this relates to the the dynamics of individual T cell clones. For example, we have recently shown that early exposures in infancy leave an outsized, life-long imprint on the T cell clonal hierarchy (Gaimann et al. eLife 2020). On the theory side, you will become an expert in mathematical models of stochastic processes and in Bayesian statistics, both key skills that will only grow in importance across the multitude of fields becoming increasingly data-rich.

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We investigate host-pathogen interactions in order to increase our mechanistic understanding of protective and pathogenic immune responses in infectious diseases, and inform the development of novel therapies or approaches for patient stratification. We particularly focus on innate immunity by modelling host-pathogen interactions in human macrophages. Although macrophages are important sentinels of the immune system, which can sense and respond to danger, restrict pathogens by intracellular killing pathways and regulate wide-ranging immune responses, they also host a number of important human pathogens such as HIV-1 and *Mycobacterium tuberculosis*. Hence we are interested in the mechanisms by which these pathogens can either evade host defence mechanisms in macrophages or stimulate harmful immune responses. Our work extends from in vitro laboratory models to challenge experiments in humans and sampling of tissues at the site of disease in order to understand host-pathogen interactions in vivo. In view of the multivariate complexity of the immune response in infectious diseases, we extensively use genome-wide transcriptional profiling strategies in order to obtain as systems level view together with detailed molecular resolution. Within the Division of Infection & Immunity at UCL, we work closely with Professor Benny Chain's group who focus on developing computational approaches to interrogate high dimensional data in immunology, and Professor Greg Tower's group who focus on innate immunity to retroviruses.

Existing projects in the group include:

- HIV-1 & *Mycobacterium tuberculosis* co-infection in macrophages
- Defining protective immunity to human tuberculosis
- Augmentation and regulation of immune responses to tuberculosis by vitamin D
- Innate immune governance of the fate of inflammatory monocytes in tuberculosis
- Targeting neutrophil recruitment in pneumococcal meningitis

Selected references:

Tomlinson G, Chimalapati S, Pollard T, Lapp T, Cohen J, Camberlein E, Stafford S, Periselneris J, Aldridge C, Vollmer W, Picard C, Casanova J-L, Noursadeghi M, Brown J*. TLR-mediated inflammatory responses to *Streptococcus pneumoniae* are highly dependent on surface expression of bacterial lipoproteins. **J Immunology 2014 (doi:10.4049/jimmunol.1401413)**.

Towers G and Noursadeghi M. Interactions between HIV-1 and the Cell-Autonomous Innate Immune System. 2014. **Cell Host & Microbe 2014 (doi: 10.1016/j.chom.2014.06.009).**

Mlcochova P, Watters S, Towers GJ, Noursadeghi M, Gupta RK. Vpx complementation of 'non-macrophage tropic' R5 viruses reveals robust entry of infectious HIV-1 cores into macrophages. **Retrovirology. 2014 (doi: 10.1186/1742-4690-11-25)**.

Kundu R, Chain BM, Coussens AK, Khoo B, Noursadeghi M. Regulation of CYP27B1 and CYP24A1 hydroxylases limits cell-autonomous activation of vitamin D in dendritic cells. **Eur J Immunol. 2014 (doi: 10.1002/eji.201344157).**

Tomlinson GS, Bell LCK, Walker NF, Tsang J, Brown JS, Breen R, Lipman M, Katz DR, Miller RF, Chain BM, Elkington PTG, Noursadeghi M. HIV-1 infection of macrophages dysregulates innate immune responses to *Mycobacterium tuberculosis* by inhibition of interleukin 10. **J Infectious Diseases. 2013 (doi: 10.1093/infdis/jit621).**

Rasaiyaah J, Tan CP, Fletcher AJ, Price AJ, Blondeau C, Hilditch L, Jacques DA, Selwood DL, James LC, Noursadeghi M, Towers GJ*. HIV-1 evades innate immune recognition through specific co-factor recruitment. **Nature. 2013. (doi:10.1038/nature12675).**

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Unravelling cellular crosstalk between tissue-resident T cells and stromal cells driving liver fibrosis

The Pallett lab studies the cellular interactions and communication between local immune cells and their underlying stroma in the human liver. We have previously highlighted the importance of a highly specialised population of memory T cells, named tissue-resident T cells (or T_{RM}) that reside permanently within the liver, unable to recirculate round the body. These 'frontline immune sentinels' mediate rapid responses against invading pathogens and cancer, which has led to great interest in harnessing T_{RM} as targets for novel vaccination strategies and immunotherapy. However, it is emerging that T_{RM} may also have a dark-side, playing a role in tissue-specific damage, and promoting the development and progression of tissue fibrosis/cirrhosis – this unorthodox role is what we will delve into.

Why do we care? In 2018 cirrhosis (and associated liver disease) was named the leading cause of mortality in individuals aged 35-49 in the UK. Worldwide cirrhosis, and its complications cause >1.32 million deaths each year, with many considered preventable due to the growing contribution of obesity and alcohol misuse to this burden. But as it stands there are no direct anti-fibrotic treatments available, so there is an urgent unmet clinical need to understand immunological mechanisms of fibrosis/cirrhosis to uncover potential new avenues for therapeutic intervention.

The Pallett lab therefore specifically seeks to explore the cellular "conversation" that cross-regulates the cellular localisation, survival, function and fibrogenic potential of liver-resident T_{RM} and the hepatic stromal cells, considered the master mediators of fibrosis. The project will involve working closely with our clinical colleagues to obtain high-quality tissue samples, and exciting state-of-the-art technologies, such as multiplex imaging (T_{RM} location in collaboration with the Francis Crick Institute), CyTOF (to determine the cellular conversation in collaboration with the Tape lab; Cancer Insitute; UCL) and the generation of novel 3D cell-culture systems (to mimic the fibrotic liver *in vitro*). Finally, the project will be co-supervised by myself and Prof. Mala Maini so you would become part of a highly productive multi-disciplinary team with a great track record.

Selected relevant publications:

1. Pallett L.J. *et al* **JEM** (2017) "IL-2^{high} tissue-resident T cells in the human liver: Sentinels for hepatotropic infection"
2. Gill U.S. & Pallett L.J. *et al* **Gut** (2019) "Fine needle aspirates comprehensively sample intrahepatic immunity"
3. Pallett L.J. & Burton A.R. *et al* **JEM** (2020) "Longevity and replenishment of human liver-resident memory T cells and mononuclear phagocyte"
4. Ichikawa T. *et al* **Nat Immunol** (2019) "$CD103^{hi}$ T_{reg} cells constrain lung fibrosis induced by $CD103^{lo}$ tissue-resident pathogenic CD4 T cells"

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The Peppa lab has an interest in chronic viral diseases (HBV, HIV) and emerging viral infections (SARS-CoV-2) of global health significance with a strong focus on translational research. Our research work benefits from unprecedented access to one of the largest and well characterised clinical cohorts of people living with HIV and viral hepatitis patients; these groups of patients suffer detrimental health care outcomes associated with immune dysfunction, ongoing inflammation, accelerated ageing and increased vulnerability to emerging infections. Our aim is to increase our understanding of the role of key immune cell components, in particular Natural Killer cells, during viral disease that can be harnessed to improve the lives of our patients.

Available projects include:

- Identification of novel therapeutic targets and/or predictive biomarkers: This project involves integration of 'omic technologies' to infer regulatory networks and drivers of immunity and ongoing inflammation in distinct anatomical compartments in patients with HIV and CMV coinfection. This high-resolution strategy will enable patient monitoring and stratification for therapeutic interventions to prevent comorbidities associated with premature ageing.
- Development of NK based cellular therapeutics: Develop a scalable platform for the expansion of adaptive NK cells with enhanced functionality and predictable selectivity. Genetic engineer human NK cells with features that improve their capacity to recognise and kill HIV- and HBV-infected target cells (in collaboration with Waggoner Lab, USA). This approach could circumvent many of the limitations inherent to the current immunotherapeutic approaches as a novel therapeutic avenue for viral disease.
- HIV related immunosuppression and responses to SARS-CoV-2: There is currently little information on vaccine efficacy/correlates of protection in this vulnerable population group. This work will examine the development of specialised NK cell populations exhibiting memory-like features in response to natural infection and vaccination with implications for the development of new vaccine targets.

Training opportunities

The Institute of Immunity and Transplantation, Pears Building, provides world-class laboratory facilities for virology, immunology, and clinical research. Outstanding research amenities at include equipment and services for cellular immunology (state of the art flow cytometry facilities), immunometabolism (Seahorse technology), molecular and experimental medicine, human genomics, vaccine development, cellular imaging, genetic engineering, and bioinformatics.

Key Publications

1. Touizer E, Alrubayyi A, Rees-Spear C, Fisher-Pearson N, Griffith S, Muir L, Pellegrino P, Waters L, Burns F, Kinloch S, Rowland-Jones S, Gupta K R, Gilosn R, Peppa D, McCoy L. Failure to seroconvert after two doses of BNT162b2 SARS-CoV-2 vaccine in uncontrolled HIV infection. **Lancet HIV** May 2021.
2. Aljawharah Alrubayyi, Ester Gea-Mallorquí, Emma Touizer, Dan Hameiri-Bowen, Jakub Kopycinski, Bethany Charlton, Natasha Fisher-Pearson, Luke Muir, Annachiara Rosa, Chloe Roustan, Christopher Earl, Peter Cherepanov, Pierre Pellegrino, Laura Waters, Fiona Burns, Sabine Kinloch, Tao Dong, Lucy Dorrell, Sarah Rowland-Jones, Laura E. McCoy, Dimitra Peppa. Characterization of humoral and SARS-CoV-2 specific T cell responses in

people living with HIV. **Nat Commun** 12**,** 5839 (2021). https://doi.org/10.1038/s41467-021-26137-7

3. Gupta RK, Abdul-Jawad S, McCoy LE, Mok HP, Peppa D, Salgado M, Martinez-Picado J, Nijhuis M, Wensing AMJ, Lee H *et al*. HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation. **Nature** 2019 10.1038/s41586-019-1027-4.
4. Maini MK and Peppa D. Shared immunotherapeutic approaches in HIV and HBV: Combine and Conquer. ***Current Opinion in HIV and AIDS***. 2020
5. Bradley T, Peppa D, Pedroza-Pacheco I, Li D, Cain DW, Henao R, Venkat V, Hora B, Chen Y, Vandergrift NA, Overman RG, Edwards RW, Woods CW, Tomaras GD, Ferrari G, Ginsburg GS, Connors M, Cohen MS, Moody MA, Borrow P, Haynes BF. RAB11FIP5 expression and altered natural killer cell function are associated with induction of HIV broadly neutralizing antibody responses, **Cell** 2018 Oct 4;175(2):387-399e17.
6. Peppa D, Pedroza-Pacheco I, Pellegrino P, Williams I, Maini MK, Borrow P. Adaptive Reconfiguration of Natural Killer Cells in HIV-1 Infection. **Front Immunol.** 2018 Mar 16;9:474.
7. Peppa D, Gill US, Reynolds G, Easom NJ, Pallett LJ, Schurich A, Micco L, Nebbia G, Singh HD, Adams DH, Kennedy PT, Maini MK. Up-regulation of a death receptor renders antiviral T cells susceptible to NK cell-mediated deletion. **J Exp Med**. 2013 Jan 14;210(1):99-114.

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Immune regulation via co-stimulatory, co-inhibitory receptors and regulatory T cells in health and autoimmunity

CD4+ Regulatory T cells (Tregs) are crucial to maintain tolerance, balancing effector T cell responses to harmful agents and suppressing unwanted responses. However, too little control may lead to autoimmunity (e.g. juvenile idiopathic arthritis or type 1 diabetes), while too much control may contribute to the development of cancers. Co-stimulatory and co-inhibitory receptors are crucial to determine functional outcomes upon activation. We are focussing on the relatively novel co-receptor family of CD96, CD226 and TIGIT, receptors highly expressed on Tregs but with little understanding of their function, and who share the ligand CD155. The pathway has been implicated in autoimmunity and cancer. We aim to elucidate the CD226, TIGIT and CD96 signalling, receptor-receptor and receptor-ligand interactions and study their role in primary human Treg function in health and disease.

Moreover, we currently lack Treg-specific markers and functional experiments are complex and may not represent in vivo activity. Therefore, we have established a clinically-applicable Treg gene signature that reflects Treg "fitness" as a possible biomarker assay and to help us understand how Tregs are dysfunctional at the site of inflammation. A full PhD project with the studies being extended and would likely focus on the mechanistic basis behind altered Treg fitness in disease

The Pesenacker lab is using cellular and molecular immunology techniques, including the cutting-edge gene-editing system CRISPR-Cas9, cloning, cell culture, primary Treg expansion and editing, advanced flow cytometry, confocal microscopy and nanoString analysis, including biomarker discovery pipeline.

Details of potential Projects

CD96, CD226 and TIGIT co-receptor family as immune regulators
- *-> functional differences between CD96 variants*
- *-> receptor-receptor-ligand interaction*
- *-> co-receptor intracellular receptor trafficking/signalling upon ligation*
- *-> role of co-receptors in Treg function*

Treg gene signature as measure of Treg fitness
- *-> utilizing the Treg gene signature as biomarker for disease activity*
- *-> understanding how the Treg signature genes define Treg fitness functionally*
- *-> can Treg-targeted therapeutic approaches re-set the Treg gene signature?*

Notably, any project will directly contribute to ongoing work in the Pesenacker lab and therefore holds the potential for co-authorship of any resulting publication. For more information, do not hesitate to contact Anne.

Key publications:

- Pesenacker AM, et al. (2021) Using crispr-cas9 to elucidate the role of TNF-receptors in Treg function. In preparation.
- Hoeppli RE, and Pesenacker AM. Targeting Tregs in Juvenile Idiopathic Arthritis and Juvenile Dermatomyositis-Insights From Other Diseases. *Front Immunol.* 2019;10:46.
- Pesenacker AM, et al. Treg gene signatures predict and measure type 1 diabetes trajectory. *JCI insight.* 2019;4(6).
- Pesenacker AM, et al. A Regulatory T-Cell Gene Signature Is a Specific and Sensitive Biomarker to Identify Children With New-Onset Type 1 Diabetes. *Diabetes.* 2016;65(4):1031-9.
- Lam, AJ et al. Optimized CRISPR-mediated gene knockin reveals FOXP3-independent maintenance of human Treg identity. Cell reports 36, 109494 (2021).

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Molecular basis of human cytomegalovirus pathogenesis

Our research concentrates on the mechanisms human cytomegalovirus (HCMV) employs to promote, sustain and reactivate lifelong latent infections of the host. As obligate parasites, viruses must usurp, disable or re-prioritise key cellular processes for their own replication and survival and thus we investigate the molecular details of the interaction of HCMV with the host cell. In addition, we are interested how the interaction of HCMV with the cell impacts on immune surveillance. Thus we take a mechanistic approach to generate an understanding of HCMV persistence and pathogenesis in vivo and, consequently, the development of strategies to target it therapeutically.

Our current areas of interest include:

Defining the contribution of cellular signalling pathways to HCMV infection. Viral reactivation is dependent on host cell signaling on host cell identity. We are interested in defining the importance of these pathways for HCMV reactivation and, additionally, why dendritic cells are important for this process. The overall aim is to foster a deeper understanding of cellular signalling pathways, how they impact on HCMV biology and, ultimately, how the manipulation of these pathways could be a therapeutic strategy to inhibit viral replication.

The contribution of cellular factors to the establishment of latency. We have recently identified a discrete set of cellular encoded miRNAs that are differentially regulated in the very early stages of HCMV latent infection. It is clear from our previous work that, in order to establish a latent infection, HCMV successfully counters a hostile cellular environment via manipulation of host cell signalling. Thus future projects will seek to determine the contribution miRNAs – which represent highly sensitive regulatory rheostats within the cell - make to this process and, by extension, their biological role in the host cell.

The immune response to HCMV and vaccination. HCMV dedicates over 40% of its 230kb genome to immune evasion strategies – enabling it to counter a prodigious host immune response. We are interested in the aspects of that response which are potently anti-viral to learn more about the control of chronic infections in vivo and help guide our ongoing efforts to develop an urgently needed vaccine against HCMV. More about the lab can be found at www.reevescmvlab.com

Recent publications from students in the lab

Mason R et al (2020) *J. Gen. Virol.* **101(6):**635-44
Murray M.J. et al (2020) *J. Virol.* **94 (7):**e02012-19
Baraniak, I. et al (2019) *Lancet EBioMedicine* **50:**45-54
Dupont L. et al (2019) *J. Biol. Chem.* **294(35):**12901-1291
Baraniak I. et al (2019) *J. Inf. Dis.* **220(2)**:228-232
Poole E.L. et al (2018) *Cell Reports* **24(3)**:594-606
Baraniak I et al (2018) *PNAS* 115(24):6273-6278

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Understanding the CD28/CTLA-4 pathway in the control of T cell responses

The adaptive immune response (T cells and B cells) provides long lasting specific protection against constantly evolving pathogens. This requires a vast array of receptors (TCR and BCR) to be generated to cover all possible pathogens and is achieved by randomly generating millions of highly diverse receptors. The downside to this process is that receptors can be generated that are capable of recognizing our own tissues resulting in autoimmune diseases. The CD28/ CTLA-4 pathway is involved in preventing this from happening and loss of CTLA-4 in mice and humans results in profound and often fatal autoimmune disease.

The Sansom Lab works on understanding the molecular and cellular mechanisms of CD28/ CTLA-4 function and the impact of their mutation in disease. The CD28/ CTLA-4 pathway consists of a stimulatory receptor (CD28) and an inhibitory receptor (CTLA-4), which bind to two shared ligands with varying affinities. My lab discovered a new biological process (transendocytosis) whereby CTLA-4 effectively captures and destroys the ligands, which stimulate CD28. This mechanism is used by regulatory T cells to suppress T cell activation. My lab uses a variety of approaches involving molecular biology- cloning and expression of genes, study of clinical mutations, cell biology and *in vitro* immunology approaches to understand the fundamental properties of this system. The work utilizes extensive cell culture, immune cell function, flow cytometry, confocal microscopy, and mathematical modeling approaches to address these questions.

Potential PhD project areas include:
1). Studying the impact of patient-derived mutations in CTLA-4, CD80 and CD86 pathways.
2). Investigating the differential functions of CD80 and CD86 in immune responses.
3). Understanding the molecular mechanism of Transendocytosis.

References

- Qureshi, O.S., *et al.* (2011). Trans-endocytosis of CD80 and CD86: a molecular basis for the cell-extrinsic function of CTLA-4. Science *332*, 600-603.
- Schubert, D.*, et al.* (2014). Autosomal dominant immune dysregulation syndrome in humans with CTLA4 mutations. Nature Medicine *20*, 1410-1416.
- Soskic, B., et.al., (2014). A Transendocytosis Perspective on the CD28/CTLA-4 Pathway. Adv Immunol *124*, 95-136.
- Walker, L.S., and Sansom, D.M. (2015). Confusing signals: Recent progress in CTLA-4 biology. Trends in immunology *36*, 63-70.
- Hou, T.Z. et.al.,(2015). A Transendocytosis model of CTLA-4 function predicts its suppressive behaviour on regulatory T cells. J Immunol *194*, 2148-2159.
- Sansom, D.M. (2015). Moving CTLA-4 from the trash to recycling. Science *349*, 377-378.

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Defining the cellular and molecular mechanisms controlling T cell immunity

The immune system has evolved specific homeostatic mechanisms to ensure that both the numbers and antigen-recognition receptor diversity of T cells are maintained at relatively constant levels for much of our lifetimes. There are many disease conditions, however, ranging from acquired or genetic immunodeficiencies, to autoimmune diseases and ageing, in which T cell homeostasis is disrupted. This can lead to lymphopenia, shifts in TCR repertoires, reduced responsiveness to vaccines, and increased susceptibility to infection. Under normal conditions, T cells exist in multiple sub-compartments with overlapping requirements for survival, and form a huge 'ecosystem' of competing or co-existing 'species' defined by their TCR specificity, age and experience of past infections. A systems understanding of the complex dynamics underlying T cell homeostasis will allow us to target interventions for these immune disorders and re-establish normal T lymphocyte immunity. The aim of the Seddon lab is to better understand the cellular and molecular mechanisms controlling homeostasis of the T cell compartments and how these mechanisms help maintain immunity throughout life.

Specific areas of interest include:

- Characterising the role of NF-kB signaling in the functional maturation of newly generated T cells (J Exp Med 2016: 213:1399-1407, Immunity 2019. 50, 348–361.e344)
- Defining the cellular behavior that underlies homeostasis of the naïve T cell compartments (PNAS 2015, 112:E6917-6926, PLoS Biol 2018. 16(4):e2003949)
- Identifying the mechanisms of self renewal required for long term T cell memory (eLife 2017. 8:716–23, eLife 2019, 6:596).

The PhD project will augment ongoing studies and provide training in molecular, cellular and/or computational immunology.

The Seddon laboratory is located in the newly opened Institute of Immunity and Transplantation at the Royal Free Hospital, that offers state of the art facilities and training environment. The Seddon laboratory has an excellent track record of PhD student training; all students finish with one or more papers and previous students have three times been runners up and on one occasion, the winner, of the British Society of Immunology Bright Sparks award.

Example Papers from past PhD students (in bold)

Verheijen, M., Rane, S., Pearson, P., Yates, A.J., and B. Seddon. 2020. Cell Reports, in press.
Webb, L.V., Barbarulo, A., Huysentruyt, J., Vanden Berghe, T., Takahashi, N., Ley, S., Vandenabeele, P., and Seddon, B. (2019). Immunity 50, 348–361.e344
Webb, L.V., S.C. Ley, and B. Seddon. (2016). *J Exp Med* 213:1399-1407.
Schim van der Loeff, I., L.Y. Hsu, **M. Saini,** A. Weiss, and B. Seddon. (2014). *J Immunol* 193:2873-2880.
Marshall, D., C. Sinclair, S. Tung, and B. Seddon. (2014). *J Immunol* 193:5525-5533.
Sinclair, C., Bains, I., Yates, A. and B. Seddon (2013). *PNAS*. 110 (31), E2905-E2914
Sinclair, C., Saini, M., van der Loeff, I.S., Sakaguchi, S., and Seddon, B. (2011). *Sci Signal 4*, ra77.

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The main focus of our research is the analysis of antigen-specific T lymphocyte responses to tumours and the development of immunotherapy approaches for the treatment of cancer and chronic infection. In order to generate therapeutic T cells of desired specificity we use retroviral vectors to transfer the genes encoding antigen-specific T cell receptors (TCR) and chimeric antigen receptors (CAR) into primary T cells. We have developed strategies to improve the expression and function of therapeutic TCR, and we use animal models to test the efficacy of tumour protection in vivo. We perform molecular and cellular studies with gene engineered human T cells and with murine T cells. At present we are recruiting patients into two clinical trials testing the concept of TCR gene therapy in humans.

We also employ genetic engineering to regulate the metabolic activity of gene modified T cells, with the goal to either enhance effector T cell differentiation or memory formation in vivo. The CRISPR technology is used to perform targeted gene editing, which allows us to disrupt genes encoding proteins that are involved in triggering the exhaustion of therapeutic T cells. Finally, we have used the transfer of TCR and CAR into regulatory T cells to achieve antigen-specific immune suppression in vivo as potential treatment for autoimmune conditions.

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Emerging Virus Preparedness: Use of Gene Therapy Vectors
The current COVID-19 pandemic highlights importance of preparedness against emerging infectious diseases. While it is difficult to predict what pathogens will cause future pandemics, influenza viruses remain major suspects with high potential to cause pandemics. Furthermore, there are several regionally emerging viruses prioritised in the World Health Organisation (WHO) R&D Blueprint [1], including viruses like Zika virus (ZIKV) which in 2016 was declared a Public Health Emergency of International Concern. Many such viruses are currently the cause of tropical diseases with the potential to spread to temperate regions due to climate change. Here I would like to propose two possible PhD projects with the theme of emerging virus preparedness, both in collaboration with National Institute for Biological Standards and Control (NIBSC), as I am also working in Advanced Therapies Division at NIBSC.

Universal immunoprophylaxis against influenza viruses by gene-delivered nanobodies (in collaboration with Dr Simon Hufton, Biotherapeutics, NIBSC)**:** We have been developing alpaca-derived, cross-subtype neutralizing single domain antibodies (nanobodies) against influenza and their delivery using gene therapy vectors [2]. This gene-mediated immunoprophylaxis approach may allow us to protect the high-risk population with poor vaccine response (e.g. immunocompromised patients, elderly etc) from a wide range of influenza strains including those new to humans with high pandemic potential. Further development includes broadening target strains, 'humanisation' of the nanobody constructs and optimization of nanobody effector function. The student will study biochemistry and structural biology of nanobody-pathogen interaction, immunology focusing on nanobody-host immune system interaction and gene therapy technology.

Development of pseudotypes of viruses with global epidemic potential (in collaboration with Dr Giada Mattiuzzo, Virology, NIBSC)**:** The Emerging Virus Group at NIBSC has been contributing to a rapid response to emergencies caused by enveloped viruses by developing standards and assays for diagnostics and serology. These activities heavily rely on pseudotype virus (PV) technology based on gene therapy vector systems [3] which enables us to study dangerous viruses more safely and outside special containment like BSL3/4. While it has been relatively easy to make PVs for viruses that bud at the cell surface, e.g. Ebola virus, MERS [4] and SARS CoV-2 coronaviruses, we recognise our shortcomings in making PVs for viruses that bud intracellularly, e.g. flaviviruses (dengue, zika etc). This project will explore and compare current and new PV systems in order to increase our capability in PV making and assay development for a wider range of viruses including those yet unknown.

[1] https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts
[2] https://www.frontiersin.org/articles/10.3389/fimmu.2020.00627/full
[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6118154/?report=classic
[4] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6759245/

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B cell signalling and antigen presentation in immune protection and pathology

We are interested in the fundamental mechanisms by which B lymphocytes detect and respond to invading pathogens. We have pioneered the idea that the B cell antigen receptor uses mechano-sensitivity to discriminate the binding to antigens in the B cell immune synapse. We would like to understand the molecular pathways leading from the B cell receptor to B cell activation and antigen presentation and how they promote the selection of protective B cell clones during antibody responses. Conversely, we are investigating why the same pathways sometimes contribute to immune pathology caused by abnormal B cell activation, such as in autoimmunity, allergy and in B cell lymphoma.

We are a dynamic group of researchers using a variety of disciplines including immunology, genetics, biophysics, bioinformatics and live-cell imaging to answer these questions. We have had fantastically creative PhD students in the past who have gone on to very successful research careers. Examples of possible PhD projects areas in the lab include:

1. Regulation of B cell germinal centre reactions by antigen retention on follicular dendritic cells
2. Identification of novel genes controlling IgG and IgE B cell responses associated with human disease using whole-genome CRISPR screens
3. Mapping of pathways promoting the pathogenesis and transformation of B cell lymphomas

Selected publications:

Newman, R. and Tolar, P. (2021) Chronic calcium signaling in IgE^+ B cells limits plasma cell differentiation and survival, Immunity, *in press*.

Malinova, D., Wasim, L., Engels, N. and Tolar, P. (2021) Endophilin A2 regulates B cell protein trafficking and humoral responses. EMBO Rep, e51328.

Roper, S. I., Wasim, L., Malinova, D., Way, M., Cox, S., Tolar, P. (2019) B cells extract antigens at Arp2/3-generated actin foci interspersed with linear filaments. eLife 8. doi:10.7554/eLife.48093.

Spillane, K. M., Tolar, P. (2017) B cell antigen extraction is regulated by the physical properties of antigen presenting cells. J. Cell Biol. *216*, 217–230.

Nowosad, C. R., Spillane, K. M., and Tolar, P. (2016) Germinal center B cells recognize antigen through a specialized immune synapse architecture. Nat Immunol *17*, 870-77.

Natkanski, E., Lee, W.-Y., Mistry, B., Casal, A., Molloy, J.E., and Tolar, P. (2013) B cells use mechanical energy to discriminate antigen affinities. Science *340*, 15

Prof Greg Towers

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Host-Virus Interactions and evasion of innate immune sensing by HIV

Our lab studies the interaction between viruses and their hosts with a focus on HIV-1. We investigate the molecular details of host-virus interactions to help us understand mammalian cell biology, virology and evolution and to develop novel therapeutic approaches for viral infection and inflammation. Research is focused on how viruses evade the intracellular innate immune system that typically protects us from infection. We have shown that HIV-1 uses host-derived cofactors such as cyclophilin A and CPSF6 to cloak its nucleic acid and evade cytoplasmic DNA sensors. We are now asking how DNA sensing works and how HIV-1 proteins specifically antagonize innate immune defensive mechanisms. We take a multi-disciplinary approach to considering our research questions. We genetically manipulate cells and viruses, and use protein biochemistry and fluorescence microscope based techniques. We collaborate to access structural techniques including Nuclear Magnetic Resonance and X Ray crystallography as well as electron microscopy. We believe that no host-virus biology makes sense unless viewed from the perspective of antagonistic evolution as described by the Red Queen hypothesis and we use computational and phylogenetic approaches to understand the evolutionary relationships between virus and host.

We are funded by a Wellcome Trust Senior Fellowship, a European Research Council Advanced Grant, the Medical Research Council and the NIHR UCL/UCLH Biomedical Research Centre. We employ 8 post-doctoral scientists, including an industry trained chemist, 2 PhD students and a clinical PhD fellow.

Current questions include

1. What is the nature of the innate immune response that is unleashed when HIV is revealed to innate sensors?
2. How does cytoplasmic DNA sensing work and how do viruses evade or antagonize it?
3. Can we develop novel, broad specificity, antiviral inhibitors that trigger an innate immune response to protect against, or treat, viral infection?

See website for further details of projects: www.ucl.ac.uk/towers-lab

Recent Publications

- Fletcher, A. J., D. E. Christensen, C. Nelson, C. P. Tan, T. Schaller, P. J. Lehner, W. I. Sundquist, and G. J. Towers. 2015. TRIM5alpha requires Ube2W to anchor Lys63-linked ubiquitin chains and restrict reverse transcription. EMBO J 34:2078-2095.
- Rasaiyaah, J., C. P. Tan, A. J. Fletcher, A. J. Price, C. Blondeau, L. Hilditch, D. A. Jacques, D. L. Selwood, L. C. James, M. Noursadeghi and G. J. Towers. 2013. HIV-1 evades innate immune recognition through specific co-factor recruitment. Nature. 503:402-405.
- Price, A. J., A. J. Fletcher, T. Schaller, T. Elliot, K. Lee, V. N. Kewalramani, J. Chin, G. J. Towers, and L. C. James. 2012. CPSF6 defines a conserved capsid interface that modulates HIV-1 replication. PLoS Pathogens 8:e1002896.

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Immune Regulation and Type 1 Diabetes

The Walker lab is interested in understanding how the immune system is regulated such that responses to infectious agents can be mounted yet tolerance to self-tissues is maintained. Failure of such regulation can lead to the development of autoimmune diseases like Type 1 Diabetes, Rheumatoid Arthritis and Multiple Sclerosis.

The group typically comprises around 6-7 researchers, with a broad mix of postdocs, students and technical support. There are currently 2 postdocs, 4 PhD students and 1 research assistant. We hold fortnightly lab meetings and there are also opportunities to present data in larger forums through regular joint lab meetings with other groups within the Institute of Immunity & Transplantation.

The broad areas of interest in the lab are:

- Pathogenesis and regulation of autoimmune diabetes in animal models and Type 1 Diabetes patients
- Regulatory T cell homeostasis and function in vivo
- The role of costimulatory molecules (CD28, CTLA-4) in immune activation and immune regulation
- The development and function of follicular helper T cells

The lab is funded by an MRC Programme Grant and additional project grant support from Diabetes UK, the European Union, the Rosetrees Trust and MedImmune.

Find out more about the Walker Lab via our website:

http://www.lucywalkerlab.com/index.html