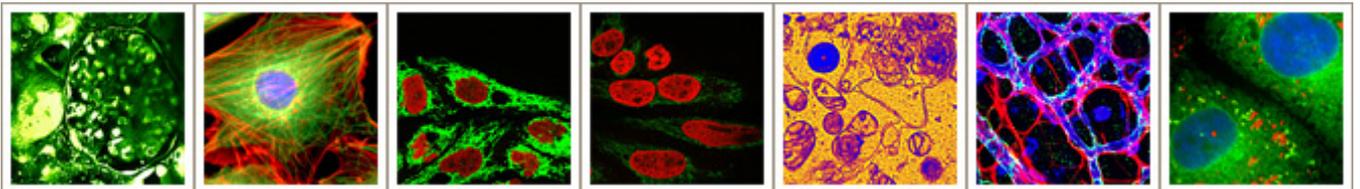




**PhD**  
**in**  
**Infection, Immunity**  
**&**  
**Transplantation**



# 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 two level 3 containment laboratories, high through put screening facilities and has access to high content imaging, multi-parameter flow cytometry, 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 focuses its research on transplantation and tissue engineering, vaccination, cell and gene

therapy, chronic infection, autoimmunity, immunological therapy for cancer and inherited immunological diseases. In the spring 2021, the IIT will be located in the new Pears building with state-of-the-art facilities and lab space.

**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, 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.



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 and EU citizens with settled status 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 (non-EEA nationals) must obtain independent funding that covers tuition fees £25,900 (FT fee in 2020), per year for 3 years subject to yearly increments and living expenses. Funds to cover consumables for research are desirable but may not be necessary.

## **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 weight, 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 is 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 Jackson (f.jackson@ucl.ac.uk) or by telephone: +44 (0)203 108 2118.

### **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 Club is organized by students 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](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

**Dr Paola Bonfanti**

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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. In press
- 2.Claudinot et al. Beyond Lineage Restriction: Tp63-Expressing Adult Epithelial Stem Cells Have Latent Hairy Skin Competence. In press
- 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  $10^9 - 10^{10}$  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.

Since we demonstrated that a mammalian cancer cell can evolve into a transmissible “parasite”, I have maintained a keen interest in transmissible cancers. The canine transmissible venereal tumour (CTVT) is part of a small family that includes two clonally transmissible cancers in the Tasmanian devil and another one that affects clams. The extraordinary feature of CTVT is that it escapes allorecognition when it transmits, irrespective of the dog’s leukocyte antigen type, yet it can be completely rejected by the immune system when the drug vincristine is administered to affected dogs. *Such an extreme behaviour is most interesting because it may suggest ways to make tissues bypass allorecognition to prevent rejection after transplantation, and make cancer cells detectable by the immune system to improve current immune check point therapies in human cancers.* We have recently discovered that vincristine triggers activation of the innate immune system and secretion of two chemokines that attract immune cells at the tumour site, initiating a cascade of events that lead to tumour rejection. ***Potential PhD project:*** we are interested in the epigenetic mechanisms that make CTVT switch from being invisible to the immune system to being rejected.

Latency is a key aspect of HIV-1 biology that causes persistent viral infection and prevents a cure. However, we have limited understanding of how latency is established and how it is reversed. In the last few years, we have employed high through put screening, transcriptomics and HIV-1 integration site analysis to advance our understanding of HIV-1 latency. In particular, our recent data suggest that HIV-1 evolved to integrate its genome in to active chromatin regions containing clusters of co-regulated genes important for T-cell activation and metabolism. These active chromatin regions are known to be plastic and to change their spatial organization, becoming repressed, when CD4 T cells switch from activated to quiescent. The HIV-1 genome may be more frequently integrated in to these dynamic chromatin compartments, and changes in their spatial organization in response to external stimuli may have a profound influence on viral entry into latency. ***Potential PhD project:*** we are interested in investigating the connections between 3D chromatin organization, T-cell differentiation, HIV-1 integration and latency. Illuminating the relationship between dynamic changes in 3D chromatin organization, HIV-1 latency and the biology of T-cells not only will provide a new perspective on HIV latency, but it may also reveal new insights to modulate it for therapeutic purposes.

### Relevant publications:

- Fassati A. What a dog transmissible tumor can teach us about cancer regression. *Mol Cell Oncol.* 2018 Aug 6;5(4):e1472059
- Frampton D, Schwenger H, Marino G, Butcher LM, Pollara G, Kriston-Vizi J, Venturini C, Austin R, de Castro KF, Ketteler R, Chain B, Goldstein RA, Weiss RA, Beck S, and Fassati A. Molecular Signatures of Regression of the Canine Transmissible Venereal Tumor. *Cancer Cell.* 2018 Apr 9;33(4):620-633
- Murgia C, Pritchard JK, Kim SY, Fassati A, Weiss RA. Clonal origin and evolution of a transmissible cancer. *Cell.* 2006 Aug 11;126(3):477-87
- Zhyvoloup A, Melamed A, Anderson I, Planas D, Lee CH, Kriston-Vizi J, Ketteler R, Merritt A, Routy JP, Ancuta P, Bangham CRM, and Fassati A. Digoxin reveals a functional connection between HIV-1 integration preference and T-cell activation. *PLoS Pathog.* 2017 Jul 20;13(7):e1006460
- Satou Y, Katsuya H, Fukuda A, Misawa N, Ito J, Uchiyama Y, Miyazato P, Islam S, Fassati A, Melamed A, Bangham CRM, Koyanagi Y, Sato K. Dynamics and mechanisms of clonal expansion of HIV-1-infected cells in a humanized mouse model. *Sci Rep.* 2017 Jul 31;7(1):6913

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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...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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### **Virus vs. Antibody: Characterising viral immune evasion by conformational masking.**

**Overview:** For a virus to maintain infection it must evade or disable the host immune response. Dr. Joe Grove is using a combination of basic virology techniques and cutting edge super-resolution microscopy to study the fundamental mechanisms of viral immune evasion, with a particular focus on antibody evasion by hepatitis C virus (HCV) and human immunodeficiency virus (HIV). Joe is establishing his group having just been awarded a prestigious Sir Henry Dale Fellowship. The student will work closely with him on an exciting multidisciplinary program of research.

**Rotation Project:** To initiate infection of a new target cell, viruses interact with receptors at the plasma membrane to gain entry to the cell interior<sup>1</sup>. Our immune system produces antibodies that bind to virus particles and prevent entry; however, viruses have evolved strategies to evade antibodies, allowing them to prevail despite our immune response. The Grove lab is investigating conformational masking, an antibody evasion strategy that essentially cloaks viruses from recognition by antibodies.

Antibody evasion strategies, such as conformational masking, can render virus entry less efficient. Therefore, when grown in the absence of antibodies some viruses will adapt towards more efficient entry by losing their antibody evasion mechanisms. Characterising these adapted viruses allows us to study the fundamental mechanisms of virus entry and immune evasion. Current experiments in the Grove lab have identified adaptations to HCV that alter virus entry and immune evasion; however, the extent of these alterations remains unknown. The student will use retroviral pseudotypes bearing recombinant HCV glycoproteins to evaluate the entry and antibody sensitivity of these adapted viruses.

The student will gain experience in a variety of important laboratory techniques including cloning, cell culture, transfection, virus handling and flow cytometry. Joe is also applying cutting edge super-resolution microscopy to quantify the interaction of viruses with antibodies<sup>2</sup>. The student will be introduced to the principles of super-resolution microscopy and gain practical experience of virus imaging. The rotation would provide the basis for a full PhD project with the studies being extended to live virus work and patient samples; the full project would also include comprehensive training in advanced imaging and corroborative experiments with HIV. Notably, this rotation project will directly contribute to ongoing work in the Grove lab and therefore holds the potential for co-authorship of any resulting publication.

For more information, do not hesitate to contact Joe.

1. Grove, J. & Marsh, M. Host-pathogen interactions: The cell biology of receptor-mediated virus entry. *J Cell Biol* 195, 1071–1082 (2011).
2. Grove, J. Super-resolution microscopy: a virus' eye view of the cell. *Viruses* 6, 1365–1378 (2014).

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**Microbial and immunological basis of infection by mucosal pathogens.**

**Regulation of host inflammation**

**Bacterial genomics and Molecular Epidemiology**

My Group is based in the UK and Africa and addresses the microbial and immunological basis of severe infection caused by mucosal pathogens and their prevention through vaccination; the regulation of inflammation; bacterial genomics and molecular epidemiology applied to vaccine evaluation. Our mucosal pathogens of interest include *Neisseria meningitidis*, *Streptococcus pneumoniae*, Group B streptococcus (GBS) and respiratory viruses such as influenza and SARS COV-2. Recently we have used human experimental infection to show that contrary to current thinking, *Streptococcus pneumoniae* invades human mucosa triggering inflammation without disease. We are now exploring the vulnerability of older people to pneumococcal disease and why vaccine protection is sub-optimal. We have used advance bacterial genomic analysis to study the population effects of pneumococcal vaccine introduction and the emergence of antimicrobial resistance. study. We have used large-scale GBS genomic analysis to explain why some GBS strains are carried harmlessly by humans or animals, while others cause meningitis/sepsis in newborns.



**Potential PhD project areas include:** The control of pathogen colonisation and transmission at the mucosal epithelial surface; shifts in genomic profiles of *Streptococcus pneumoniae* following the introduction of conjugate-polysaccharide vaccine and the emergence of antimicrobial resistance; and understanding the impact of GBS virulence factor glycosylation on disease potential. Our highly interdisciplinary and friendly group currently consists of 5 post-doctoral scientists, an epidemiologist and 3 PhD students funded by the MRC, NIHR, Wellcome Trust and Bill & Melinda Gates Foundation. We have with strong links with other groups at UCL, throughout the UK and Africa. Projects will exploit state-of-the-art immunological, imaging and genome analysis, human challenge models 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:**

Gori A....Heyderman RS. Pan-GWAS of *Streptococcus agalactiae* Highlights Lineage-Specific Genes Associated with Virulence and Niche Adaptation. *mBio*. 2020;11:e00728-20.

Swarthout TD....Heyderman RS. High residual carriage of vaccine-serotype *Streptococcus pneumoniae* after introduction of pneumococcal conjugate vaccine in Malawi. *Nat Commun*. 2020;11:2222.

Weight C....Heyderman RS. Epithelial micro-invasion by *Streptococcus pneumoniae* induces epithelial-derived innate immunity during colonisation at the human mucosal surface. *Nature Communications* 2019; 10:3060

Jochems SP et al. Innate and adaptive nasal mucosal immune responses following experimental human pneumococcal colonization. *J Clin Invest*. 2019; 130: 4523-4538

Lourenco J....Heyderman RS. Determinants of high residual post-PCV13 pneumococcal vaccine-type carriage in Blantyre, Malawi: a modelling study. *BMC Med*. 2019 Dec 5;17:219

## Dr Clare Jolly

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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.

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. We also have a long-standing interest in the cell biology of HIV assembly in T cells and have recently begun applying our expertise in viral cell biology to study SARS-CoV-2.

The overall goal of our research is understand the interaction between viruses and their hosts and to use viruses a tool to understand how cells function in health and disease. 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, immunofluorescence microscopy and multicolour flow cytometry.

My lab currently consists of 2 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 relevant papers:

- 1 Mesner D., Hotter D., Kirchhoff F., and Jolly C. (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.
- 2 Titanji BK., Pillay D., and Jolly C. (2017). Combination antiretroviral therapy and cell-cell spread of wild-type and drug-resistant human immunodeficiency virus-1. *J Gen Virol* 98: 821-834.
- 3 Len AC., Starling S., Shivkumar M. and Jolly C. (2017) HIV-1 activates signaling independently of antigen to drive viral spread. *Cell Reports* 18: 1062-1074.
- 4 Starling S., and Jolly C. (2016) LFA-1 engagement triggers T cell polarization at the virological synapse. *J Virol* 90: 9841-9854.
- 5 Gropelli E., Starling S. and Jolly C (2015) Contact-induced mitochondria polarization supports HIV-1 virological synapse formation. *J Virol.* 89: 14-24.
- 6 Gropelli E., Len A., Granger L., and Jolly C. (2014) Retromer regulates HIV-1 envelope glycoprotein trafficking and incorporation into virions. *PLoS Pathog* 10:e1004518
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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).

**Prof. Claudia Mauri**

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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.**

## Professor Emma Morris

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I am a clinician scientist working in the field of allogeneic haematopoietic stem cell transplantation, cell and gene therapy for patients with haematological malignancies and inherited (primary) immunodeficiencies (PIDs). I work closely with Professor Siobhan Burns and we run a joint research group. Our research spans the entire translational pathway from understanding disease pathogenesis (using animal models, in vitro functional assays, experimental immunology and molecular biology), validation of diagnostic assays and the development of novel therapeutic approaches such as stem cell transplantation, gene therapy and gene editing. We are particularly focussed on developing novel therapeutic gene editing approaches.

We are part of the UCL Centre for Immunodeficiency which includes Great Ormond Street Hospital, UCL Institute of Child Health, Royal Free London Hospital, University College London Hospital and the UCL Institute of Immunity & Transplantation. We collaborate closely with Dr Claire Booth and Professor Adrian Thrasher at UCL ICH and global leaders in PID gene therapy. This allows us access to the largest cohort of PID patients in Europe.

The primary immunodeficiencies (PIDs) are a rare group of inherited diseases characterized by severe dysfunction of adaptive and/or innate immunity, typically arising from genetic mutations in haematopoietic stem cells. Uncorrected PID can lead to recurrent, progressive, or life-threatening infections, autoimmunity, autoinflammatory manifestations, and malignant disease (typically lymphoma or epithelial neoplasias). Nearly 400 distinct immunodeficiencies have now been described, with approximately 20 accounting for over 90% of cases. Excluding common variable immunodeficiency (CVID), 3 of the most common are severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome, and chronic granulomatous disease (CGD). I also participate in clinical translational research in stem cell transplantation and remain interested in T cell engineering and cellular immunotherapies.

### Current research projects in the group:

1. Gene editing for CTLA4 Haploinsufficiency.
2. Towards Gene Editing for Inherited Immunodeficiencies: Functional modelling & correction of novel disease-causing STAT1 variants.
3. Gene editing for APDS1 – a novel gene therapy approach for gain of function (GOF) mutations.
4. Understanding T cell immunity in anti-NMDAR encephalitis: Developing therapeutic tools for neurological autoimmunity.
5. Understanding the pathogenesis of recently identified genetic variants in key immune signalling pathways such as STAT1, STAT3, NFKB1, NFKB2 and LRBA.

### Recent (selected) publications:

- HSCT for CGD? Yes, and the sooner the better. Emma C Morris. *Blood*. 2020; *In Press*.
- Engineered T cells Flt around their targets. Emma C Morris. *Nat Immunol*. 2020; *In Press*.
- Extended clinical and immunological phenotype and transplant outcome in CD27 and CD70 deficiency. Sujal Ghosh, et al. *Blood*. 2020; *In Press*.
- RNA-deleterious synonymous mutations are a novel and common cause of GATA2 deficiency. Emilia J Kozyra, et al. *Leukemia*. 2020; **34(10):2673-2687**.
- Effective Lentiviral Gene Therapy for X-linked Chronic Granulomatous Disease. Donald B Kohn, Claire Booth, et al. *Nature Medicine*. 2020; **26(2):200-206**.

- Framework engineering to produce dominant T cell receptors with enhanced antigen-specific function. Sharyn Thomas, et al. **Nat Commun.** 2019; 10(1):4451.
- Predictors of recovery following allogeneic CD34<sup>+</sup>-selected cell infusion without conditioning to correct poor graft function. Cuadrado M, et al. **Haematologica.** 2019; Nov 21:haematol.2019.226340.
- Comparative Analysis of Melphalan versus Busulphan T-Cell Deplete Conditioning using Alemtuzumab in Unrelated Donor Stem Cell Transplantation for Acute Myeloid Leukaemia. Rob S. Sellar<sup>§</sup>, Varun Mehra<sup>§</sup>, et al. **Br J Haematol.** 2019; Oct;187(1):e20-e24.
- Successful outcome following allogeneic haematopoietic stem cell transplantation in adult patients with inherited primary immunodeficiency. T Fox, et al. **Blood.** 2018; 131(8):917-931.
- Editing gene engineering to enhance function. Morris EC. **Blood.** 2018; 131(3):272-273.
- Gene therapy for Wiskott-Aldrich syndrome in a severely affected adult. Morris EC, et al. **Blood.** 2017; 130(11):1327-1335.

**Professor Mahdad Noursadeghi**

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10 million new cases of tuberculosis lead to 1.5 million deaths per year, making *Mycobacterium tuberculosis* the most common microbial cause of death world-wide. These numbers represent the tip of the iceberg of infection, since most people who become infected never develop disease. We aim to understand the determinants of different outcomes of infection. We hypothesise that differences in immune responses lead either to bacterial control (protective immunity), or to a cascade that drives the pathogenesis of disease. We investigate this hypothesis in vitro using laboratory models of microbial interactions with macrophages and T cells, an in vivo by studying immune responses in people with latent infection and active TB. We evaluate immune responses at the level of individual molecules and immune systems by genome-wide transcriptomic analysis of blood samples and of tissue from the site of disease, or from the site of standardised antigenic challenges. We apply our findings to discovery and validation of biomarkers predict the risk of TB, for identification of novel targets for host-directed therapies, and identification of the correlates of protective immunity to inform novel vaccine design. We further extend these approaches to study immune responses to other acute viral and bacterial infections, and models of co-infection

#### **Selected publications:**

1. Sampson D.... [Noursadeghi M](#). Blood transcriptomic discrimination of bacterial and viral infections in the emergency department: a multi-cohort observational validation study. *BMC Med*. 2020;18(1):185. doi:10.1186/s12916-020-01653-3.
2. Turner CT...[Noursadeghi M](#). Blood transcriptional biomarkers for active pulmonary tuberculosis in a high-burden setting: a prospective, observational, diagnostic accuracy study. *Lancet Respir Med*. 2020;8(4):407-419. doi:10.1016/S2213-2600(19)30469-2.
3. Gupta RK...[Noursadeghi M](#). Concise whole blood transcriptional signatures for incipient tuberculosis: A systematic review and patient-level pooled meta-analysis. *Lancet Respir Med*. 2020. doi.org/10.1016/S2213-2600(19)30282-6.
4. Periselneris...[Noursadeghi M](#), Brown JS. Relative Contributions of Extracellular and Internalized Bacteria to Early Macrophage Proinflammatory Responses to Streptococcus pneumoniae. *mBio*. 2019;10(5). doi:10.1128/mBio.02144-19.
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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.

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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 potentially 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](http://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- $\kappa$ B 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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A main focus of our research is the analysis of antigen-specific T lymphocyte responses and the development of immunotherapy for the treatment of cancer. In order to generate therapeutic T cells of desired specificity our group has been amongst the pioneering labs developing TCR gene therapy for the treatment of cancer. In this project, we will define in detail the immune responses in patients with renal cancer, and address the question whether immunity prevents the progression of sub-clinical small renal tumours to clinically manifest cancer. This project involves the detailed analysis of tissue and blood samples from patients using cutting edge technologies to define immunological, genetic and biological parameters associated with kidney cancer development. Ultimately, this project will provide insights for developing novel immunotherapies for the management of kidney cancer.

#### **RECENT PUBLICATIONS:**

Dertschnig S, Evans P, Santos E Sousa P, Manzo T, Ferrer IR, Stauss HJ, Bennett CL, Chakraverty R. Graft-versus-host disease reduces lymph node display of tissue-restricted self-antigens and promotes autoimmunity. **J Clin Invest.** 2020 Apr 1;130(4):1896-1911

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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>

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[4] <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6759245/>

## Prof Pavel Tolar

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### Regulation of antibody responses by B cell receptor mechanics, signalling and antigen uptake

The Tolar lab investigates molecular mechanism of B cell activation in antibody responses. A regulated B cell response is critical for host protection, vaccine efficacy and for avoiding antibody-mediated pathology. The decision of B cells to mount antibody production is controlled by the B cell antigen receptor (BCR), which binds antigens and initiates two essential functions: intracellular signalling for B cell activation and endocytosis of antigen for presentation to helper T cells. We have discovered that antigen binding to the BCR provides not just a biochemical trigger of these functions but also a mechanical input, which helps to grade the B cell response according to the strength of antigen binding. We would like to understand the molecular mechanisms underlying this mechano-sensitivity and its role in selection affinity maturation in germinal centres. We are also interested in the regulation of B cell interactions with antigens in vivo and in the wiring logic of the downstream BCR signalling and endocytic pathways that decide whether and how B cells respond to antigen and why they sometimes promote B cell pathology. We are using a combination of a variety of approaches including imaging, biophysical methods, nanotechnology, high-throughput genomics and in vivo models.

#### Potential projects in the lab include:

1. Studies of vaccine capture, retention and presentation to B cells by lymph node immune and stromal cells.
2. Identification of BCR endocytic pathways in regulation of antigen presentation
3. Investigation of signalling pathways encoding differences in activation of IgM, IgG and IgE B cells
4. Studies of BCR mutations involved in B cell lymphomas

#### Selected publications:

1. 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, 1587–1590. PMID: 23686338.
2. 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. PMID: 27183103.
3. Tolar, P. (2018). Great stretches for your antibody workout. *Nat. Nanotech.* 14, 101-2. PMID: 30643272.
4. 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. PMID: 31815664.

## 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](http://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.

## Prof Lucy Walker

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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. Failed regulation can lead to the development of autoimmune diseases like Type 1 Diabetes, Rheumatoid Arthritis and Multiple Sclerosis.

The group typically comprises around 6-8 researchers, with a broad mix of postdocs, students and technical support. There are currently 4 postdocs, 2 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 a Wellcome Trust Investigator Award with additional project grant support from charity and industry funders.

### Recent Publications

- Targeting co-stimulatory molecules in autoimmune disease. Edner NM, Carlesso G, Rush JS, Walker LSK. Nature Reviews Drug Discovery. 2020 Online ahead of print.
- Follicular helper T cell profiles predict response to costimulation blockade in type 1 diabetes. Edner NM, Heuts F, Thomas N, Wang CJ, Petersone L, Kenefeck R, Kogimtzis A, Ovcinnikovs V, Ross EM, Ntavli E, Elfaki Y, Eichmann M, Baptista R, Ambery P, Jermutus L, Peakman M, Rosenthal M, Walker LSK. Nature Immunology. 2020 Oct;21(10):1244-1255
- CTLA-4-mediated transendocytosis of costimulatory molecules primarily targets migratory dendritic cells. Ovcinnikovs V, Ross EM, Petersone L, Edner NM, Heuts F, Ntavli E, Kogimtzis A, Kennedy A, Wang CJ, Bennett CL, Sansom DM, Walker LSK. Science Immunology. 2019 May 31;4(35).

Find out more about the Walker Lab via our website and twitter account:

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

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