Cambridge Institute for Therapeutic Immunology & Infectious Disease

Institute Directory
The Cambridge Institute for Therapeutic Immunology and Infectious Disease (CITIID) was established by the Department of Medicine to support both fundamental and translational research on human disease.

CITIID houses up to 250 scientists working in research groups focussed on understanding the pathogenesis and improving the management of immune-related disorders, as well as transforming our understanding of how infectious agents interact with humans. Later in this directory you’ll find out more about these studies.

There is also a strong focus on health issues of global importance, and on antimicrobial resistance. In particular, we work closely with key overseas partners including universities, agencies and industry to ensure that we can increase our global impact in a coordinated programme.

CITIID brings together geographically dispersed groups working on immunity and infection across the Cambridge Biomedical Campus, the largest Biomedical campus in Europe. By encouraging research at the clinical interface, for example in the Cambridge Clinical Research Centre and with industry, CITIID also facilitates the translation of scientific discoveries into clinical benefits.

Its location on the Cambridge Biomedical Campus places CITIID at the centre of the Cambridge Cluster where it benefits from the closeness of several other major health-related organisations such as the Royal Papworth Hospital, MRC-Laboratory of Molecular Biology, CRUK Cambridge Institute and Astra Zeneca’s global research and development headquarters.

CITIID transforms immunity and infection research in Cambridge by providing researchers with advanced facilities that enable them to optimise their work on understanding human immune, inflammatory and infectious diseases. By bringing together its clinical capabilities and key industry partners, CITIID is also well-placed to drive therapeutic breakthroughs, improve patient outcomes and advance population health both in the UK and abroad.
Designed to Lead Developments in Autoimmunity

CITIID is already driving therapeutic breakthroughs in immune-related diseases such as inflammatory bowel disease, type-1 diabetes, vasculitis and systemic lupus erythematosus. The incidence of such disease is rising worldwide at a truly alarming rate and collectively they represent a major global public health issue. We study what drives these diseases – how they develop and evolve, and how they cause harm to humans – and use this understanding to develop new therapeutic strategies that can be translated quickly and safely to patients worldwide.

A key strength of CITIID is that immune-mediated disease is studied alongside infectious disease. The human immune system has evolved to defend us against the dangerous microorganisms that cause disease; autoimmunity and inflammatory diseases are caused when this defence mechanism malfunctions. Crucially, a dysfunctional immune system uses the same molecular pathways and mechanisms as a healthy immune system uses to fight infection, which means vital insights emerge from tackling infectious disease and autoimmunity together.

Over the last four years scientists at CITIID have established a whole genome sequencing-based programme to investigate undiagnosed primary immunodeficiency. This has provided over three hundred diagnostic reports, uncovered many genes associated with primary immunodeficiency, and allowed the genetic variation in the development of these diseases to be explored.
Designed to Combat Multi-Drug Resistance

Antimicrobial resistance is one of the biggest threats to global health and international food security. Scientists at CITIID develop novel approaches to overcome this challenge.

Considering how human genetics responds to infection is a key component in understanding the role of the microbiome in health and disease. By using cutting-edge scientific methods to monitor the spread of antimicrobial resistance, our scientists can even use historical data to understand the spread of multi-drug resistance long after an outbreak. Such studies have an enormous impact on our ability to manage the continued spread of a disease and allow us to anticipate future threats.

A Centre for Global Answers

Infectious disease, antimicrobial resistance and autoimmunity are three of humanity’s deadliest foes and are major global challenges. Cambridge is one of the world’s leading research universities, working across disciplines with international partners to find solutions to manage and eradicate these threats.

CITIID is at the centre of efforts to understand the spread of disease. We have researchers working in countries across the globe, meaning we have a very real understanding of the impact diseases have on patients. Many of our projects are in third world countries where socio-economic factors make the impacts of these diseases even greater.
CITIID
Leading Discovery and Innovation

CITIID is primarily located in the newly constructed and purpose-built Jeffrey Cheah Biomedical Centre, where we share state of the art research laboratories with the Cambridge Stem Cell Institute and the Milner Therapeutics Institute. CITIID also has a footprint in Addenbrookes’s Hospital to facilitate clinical translation, as well as the Molecular Immunology Unit that is embedded within the MRC Laboratory of Molecular Biology.
The Jeffrey Cheah Biomedical Centre
A New Site of Research Excellence

The Jeffrey Cheah Biomedical Centre was established in 2016 with funding from the
Higher Education Funding Council for England (HEFCE) UK Research Partnership
Infrastructure Fund (UKRPIF), the University of Cambridge Capital Fund, and
philanthropic donations. The majority of our researchers are located in this state-of-the-
art facility on the Cambridge Biomedical Campus.
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<td>Works on functional genetic and proteomic technologies to identify novel genes and therapeutic approaches in virus:host interaction.</td>
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Florian Marks
Operates a network of field sites capable of conducting multi-center epidemiological field studies for basic research and clinical trials.

Nick Matheson
Studies host-virus interactions to provide insights into viral pathogenesis, cell biology, and novel therapeutic approaches.

Eoin McKinney
Studies aberrant immune response to indicate novel tests and/or interventions that can help clinicians treating immune pathology.

Yorgo Modis
Our overarching goal is to gain a mechanistic understanding at the molecular level of how the cell detects cytosolic viral RNA and how it silences viral gene expression.

Ankur Mutreja
Uses advanced bacterial genomics and metagenomics to better understand the evolution and spread of pathogens.

James Nathan
Gains novel insights into oxygen and metabolite sensing pathways, providing potential new therapeutic targets for inflammatory disease and cancers.

Virginia Pedicord
Seeks mechanistic insights into the influence of commensal microbes on local and systemic immune responses.

Lalita Ramakrishnan
Researches the pathogenesis of tuberculosis, and tries to understand both host and pathogen strategies that can interact to result in clearance or disease.

John Sinclair
Studies the molecular basis of viral latency and reactivation and how the host immune response combats viral disease.

Ken Smith
Combines genomics, immunology and clinical medicine to analyse the regulatory mechanisms underpinning immune-mediated disease and develop diagnostic tools.

Alex Taylor
Is evolving and engineering synthetic genetic polymers, xeno nucleic acids (XNA), as novel tools for reprogramming biology and precision medicine.

Chris Wallace
Develops statistical methods and uses integrative statistical analysis of genomic data to improve diagnosis and treatment of immune mediated diseases.

Mark Wills
Is interested in the immunobiology of HCMV in lytic and during latent infection, and how the pathogen persists for the lifetime of its human host.
Much of the research undertaken in CITIID has a focus on real-life challenges. As such, it has a significant positive impact on the people’s lives.

The stories below describe some examples of the impact that our research has on a daily basis.

**From genetic analysis to personalised medicine in inflammatory bowel disease.**
Our research found a transcriptional signature that is detectable within peripheral blood and correlates with long term clinical outcome in IBD.

**New treatments for Tuberculosis.**
Our researchers revealed that the actively-growing bacteria induce bacterial efflux pumps that could be therapeutic targets using existing drugs.

**The immunity of inflammatory bowel disease is exposed.**
Our researchers developed experimental methods for examining the environmental stresses and microbes that could be responsible for triggering IBD.

**Improving sanitation in rural Africa.**
Our researchers are providing evidence that simple behavioural changes can improve the health of rural communities in the third world.

**Cholera: a global challenge.**
Our researchers are using information locked within the genomes of historic cholera samples to predict the spread of past cholera pandemics throughout Africa.
CITIID offers a range of core facilities to its researchers and the wider scientific community. Some of these are listed below, and our facility contacts are more than happy to discuss your specific needs.

**NIHR Cambridge BRC Phenotyping Hub**
Equipped with state-of-the-art equipment including high speed cell sorters, bench top analysers, microscopes and high content/high throughput equipment.

**Imaging**
Offering a variety of instruments and analysis techniques.

**Computing**
High-performance computing (HPC) cluster and 200TB network storage that is configured similar to the University of Cambridge HPC.

**Immuno-metabolism**
Offering cutting-edge, high-resolution liquid chromatography mass spectrometry (LC-MS).

**Bio-Safety Level 3**
CL-3 containment facilities for working with non-attenuated clinical organisms.
We focus on how specific bacteria that cause infectious disease in humans in low-middle income countries evolve and spread with a specific focus on typhoid fever, bacillary dysentery (Shigella), as well as other diarrhoeal diseases such as cholera and rotavirus. Our areas of research over the next 5 years include our continued work on the phylogeography of enteric bacteria, looking closely at evolutionary adaptation and clonal replacement of gastrointestinal pathogens in endemic settings through cohort studies and hospital surveillance. More broadly our key areas of focus are the impact of antimicrobial access and treatment on the gut microbiota and the generation of drug resistant pathogens. This work will maintain an international focus and will lead into developing new interventions for treating and preventing infections cause by antimicrobials resistant pathogens.

Previously our lab was located at the Wellcome Africa-Asia programme in Vietnam where we ran an internationally recognised programme of research on enteric infections. This work was closely linked to the University of Cambridge and the Sanger Institute.

**PUBLICATIONS**

The phylogeography and incidence of multi-drug resistant typhoid fever in sub-Saharan Africa. Park SE, Pham DT… Baker S; *Nature Communications* 2018 DOI: 10.1038/s41467-018-07370-z

The Role of Maternally Acquired Antibody in Providing Protective Immunity Against Nontyphoidal Salmonella in Urban Vietnamese Infants: A Birth Cohort Study.

de Alwis R, Tu LTP … Baker S; *Journal of Infectious Disease* 2018; DOI: 10.1093/infdis/jiy501

New Variant of Multidrug-Resistant Salmonella enterica Serovar Typhimurium Associated with Invasive Disease in Immunocompromised Patients in Vietnam.

Mather AE, Phuong TLT … Baker S; MBio 2018; DOI: 10.1128/mBio.01056-18

Typhoid conjugate vaccines: a new tool in the fight against antimicrobial resistance.


Quantifying antimicrobial access and usage for paediatric diarrhoeal disease in an urban community setting in Asia.

Thi Quynh Nhi L, de Alwis R … Baker S; *Journal Antimicrobial Chemotherapy* 2018; DOI: 10.1093/jac/dky231

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We are strongly focused on using genetic manipulation to discover the genes involved in various biological systems, using somatic mutagenesis in mice to discover cancer genes and genetic screens in ES cells in culture.

Allan is also a serial entrepreneur and has established several biotechnology companies. While in the USA he founded Lexicon Pharmaceuticals Inc. that is publicly traded, and Spectral Genomics Inc. that was later acquired. In the UK he founded Kymab Ltd. in 2010, and Petmedix Ltd. in 2017.

PUBLICATIONS

Revealing hidden complexities of genomic rearrangements generated with Cas9.
Boroviak K, Fu B ... Bradley A; Scientific Reports 2017; DOI: 10.1038/s41598-017-12740-6

Comprehensive annotation and evolutionary insights into the canine (Canis lupus familiaris) antigen receptor loci.
Martin J, Ponstingl H ... Bradley A; Immunogenetics 2018; DOI: 10.1007/s00251-017-1028-0

Molecular synergy underlies the co-occurrence patterns and phenotype of NPM1-mutant acute myeloid leukemia.
Dovey OM, Bradley A ... Vassiliou GS; Blood 2017; DOI: 10.1182/blood-2017-01-760595

Enhancing the genome editing toolbox: genome wide CRISPR arrayed libraries.
Metzakopian E, Strong A ... Bradley A; Scientific Reports 2017; DOI: 10.1038/s41598-017-01766-5
Gene mutations or environmental factors such as infection or drugs can have genome-wide effects on gene expression levels across many different pathways. However, it is not always clear which of these perturbations can be buffered by the system and which lead to detrimental outcomes as reflected in morphological changes or reduced health.

We investigate in vivo gene regulatory responses to challenges such as genetic mutations, chromatin disruption and infection. Specifically, we use our zebrafish mutant archive of ~43,000 alleles covering 60% of protein-coding genes, CRISPR/Cas9 mutagenesis and genome-wide sequencing approaches to understand the relationship of chromatin structure, transcriptional changes and phenotypic outcomes. For example, partial loss of gene function can have substantial effects on genome-wide gene expression levels without gross morphological defects. This provides an opportunity to dissect gene regulatory networks and distinguish network-specific, but tolerated gene expression changes, from those that affect organismal development and health.

PUBLICATIONS

The gene regulatory basis of genetic compensation during neural crest induction.
Dooley CM, Wali N ... Busch-Nentwich EM; bioRxiv 2018; doi.org/10.1101/314534

Placenta defects are highly prevalent in embryonic lethal mouse mutants.
Perez-Garcia V ... Busch-Nentwich EM ... Hemberger M; Nature 2018; doi: 10.1038/nature26002

A high-resolution mRNA expression time course of embryonic development in zebrafish.
White RJ, Collins JE ... Busch-Nentwich; eLife 2017; DOI: 10.7554/eLife.30860

The age of heterozygous telomerase mutant parents influences the adult phenotype of their offspring irrespective of genotype in zebrafish.
Sahill CM, Digby Z ... Busch-Nentwich; Wellcome Open Research 2017; DOI: 10.12688/wellcomeopenres.12530.2

Loss of the chromatin modifier Kdm2aa causes BrafV600E-independent spontaneous melanoma in zebrafish.
Sahill CM, Digby Z ... Busch-Nentwich; PLoS Genetics 2017; DOI: 10.1371/journal.pgen.1006995

emb81@cam.ac.uk
We are a newly established research group that focuses on the antibody response to rotavirus infection and vaccination.

**Protective rotavirus antibodies:** Rotavirus is a common cause of gastroenteritis in children, especially in low-income countries. An estimated 215,000 children under five years old die from rotavirus infection every year. Fortunately rotavirus vaccines have recently become available, but the exact mechanisms by which these vaccines work are poorly understood. This means that predicting vaccine efficacy is a challenge.

We elucidate the mechanisms of antibody-mediated protection to rotavirus using molecular techniques. In collaboration with clinical partners this enables the development of accurate tests to predict rotavirus vaccine effectiveness, and help to develop the next generation of rotavirus vaccines.

**Maternal antibodies:** Rotavirus vaccines are negatively affected by the presence of maternal antibodies that are transferred from the mother to infant and protect the infant from infection. It is not known how maternal antibodies prevent vaccines from inducing protective immune responses in infants. We are using different models for rotavirus infection, combined with genetic approaches and deep sequencing to unravel the mechanisms of maternal antibody vaccine blockade. It is anticipated that understanding the activity of maternal antibodies will lead to rational design of improved neonatal vaccines.

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**PUBLICATIONS**

Complement C4 prevents viral infection through capsid inactivation. *Cell Host Microbe* 2019

Characterization of innate immune viral sensors in patients following allogeneic hematopoietic stem cell transplantation. 

Caddy SL et al; *Innate Immunity* 2018; DOI: 10.1177/1753425918757898

Genogroup IV and VI canine noroviruses bind to histo-blood groups antigens. 

Caddy S et al; *Journal of Virology* 2014; DOI: 10.1128/JVI.01008-14

Norovirus-Mediated Modification of the Translational Landscape via Virus and Host-Induced Cleavage of Translation Initiation Factors. 

Emmott E ... Caddy S ... Goodfellow; *Molecular Cell Proteomics* 2017; DOI: 10.1074/mcp.M116.062448

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slc50@cam.ac.uk
We research humoral immunity in humans, how this goes wrong in disease and how it can be manipulated therapeutically using experimental medicine studies. In collaboration with Glaxo-Smith-Kline we recently investigated how belimumab affects the B cell compartment in renal transplant recipients. We found it suppressed new antibody formation and skewed residual B cells to an IL10-producing, regulatory phenotype.

Autoantibodies are associated with a number of kidney diseases, and antibody-mediated rejection has a negative impact on transplant outcomes. We use human kidney tissue to profile resident immune cells using flow cytometry, mass cytometry, and RNA sequencing, and complementary mouse models to understand function. We have shown how the intrarenal sodium gradient can influence mononuclear phagocyte position and function to optimise defence against ascending infection.

Although IgA is the dominant antibody isotype found at mucosal surfaces during health, genetic variation in FcγRs can influence susceptibility to inflammatory bowel disease (IBD), suggesting that IgG may be important during inflammation. We are currently investigating how the induction of IgG in the gastrointestinal tract can activate gut-resident cells, how this is regulated, and whether this is important in IBD.

Increasing evidence shows immune cells change their metabolism in response to activation signals and that some of these changes may be required for their function. We investigate how IgG immune complexes affect macrophage metabolism and influence IgG-associated tissue inflammation.

PUBLICATIONS

Single-cell transcriptomes from human kidneys reveal the cellular identity of renal tumors. Young MD ... Clatworthy MR ... Behjati S; Science 2018; DOI: 10.1126/science.aat1699

PI3Kδ hyper-activation promotes development of B cells that exacerbate Streptococcus pneumoniae infection in an antibody-independent manner. Stark AK ... Clatworthy MR ... Okkenhaug K; Nature Communications 2018; DOI: 10.1038/s41467-018-05674-8

Belimumab in kidney transplantation: an experimental medicine, randomised, placebo-controlled phase 2 trial. Banham GD, Flint SM ... Clatworthy MR; Lancet 2018; DOI: 10.1016/S0140-6736(18)30984-X

Renal Sodium Gradient Orchestrates a Dynamic Antibacterial Defense Zone. Berry MR, Mathews RJ ... Clatworthy MR; Cell 2017; DOI: 10.1016/j.cell.2017.07.022

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Menna Clatworthy
We use complementary genomics and phenotypic approaches to explore host/pathogen interactions, and are interested in how pathogens colonise and cross mucosal surfaces and then spread and survive in the deeper tissues of the body. We use the analysis of microbe populations to identify candidate evolutionary signatures that we can then analyse to determine their contribution to phenotype, if any.

In one aspect of our work we perform clinical studies that enable us to develop methods to analyse the pathogen, microbiota and host response simultaneously, and to bring genomics into clinical practice. We have interests in antibiotic resistance, how pathogens evade therapies, and in vaccines. Our focused research topic for many years has been typhoid, or enteric fever, and the Salmonella bacteria that cause it.

Our clinical work has enabled clinical teams to track infections by sequencing pathogens as they enter the hospital. We also look at environmental microbial contamination using genomics and informatics approaches, to link specific environmental contexts with patient isolates. This allows us to monitor antibiotic resistance, with the ambition of promoting the appropriate use of antibiotics.

Our work on typhoid has led to the creation of the global whole genome database for Salmonella Typhi which houses over 5,000 isolates from around the world. This database monitors the spread of typhoid and identifies novel antibiotic resistant populations. With other groups we investigate typhoid pathogenesis using microbial genetics linked to field studies, and human challenge models using stem cells. The value of these models lies in our ability to challenge them with pathogens and compare functional readouts to clinical outcomes.

**PUBLICATIONS**

Phylogeographical analysis of the dominant multidrug-resistant H58 clade of Salmonella Typhi identifies inter- and intracontinental transmission events.
Wong V, Baker S... Dougan G; *Nature Genetics* 2015; doi: 10.1038/ng.3281

Identification of enterotoxigenic *Escherichia coli* (ETEC) clades with long-term global distribution.
von Mentzer A, Connor TR ... Dougan G; *Nature Genetics* 2014; DOI: 10.1038/ng.3145

Emergence of host-adapted Salmonella enteritidis through rapid evolution in an immunocompromised host.
Klemm E ... Dougan G ... Kingsley RA; *Nature Microbiology* 2016; DOI: 10.1038/nmicrobiol.2015.23

Interleukin-22 promotes phagolysosomal fusion to induce protection against *Salmonella enterica* Typhimurium in human epithelial cells.
Forbester JL, Lees EA ... Dougan G; *Proceedings of the National Academy of Sciences* 2018; DOI: 10.1073/pnas.1811866115
We study drug-pathogen and host-pathogen interactions to inform successful global HIV control/cure strategies. This includes identification of novel determinants of drug resistance in both treated and untreated patients infected with diverse HIV-1 subtypes. We also seek and understanding of how HIV is able to infect non-dividing myeloid lineage cells that form a reservoir of HIV in the central nervous system and is therefore a barrier to cure.

**PUBLICATIONS**

HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation. Gupta RK et al; *Nature* 2019; DOI: 10.1038/s41586-019-1027-4

DNA damage induced by topoisomerase inhibitors activates SAMHD1 and blocks HIV-1 infection of macrophages. Mlochova P, Caswell SJ ... Gupta RK; *EMBO* 2018; DOI: 10.15252/embr.201796880

A G1–like state allows HIV–1 to bypass SAMHD1 restriction in macrophages. Mlochova P, Sutherland KA ... Gupta RK; *EMBO* 2017; DOI: 10.15252/embr.201696025


Wide variation in susceptibility of HIV–1 subtype C isolates to protease inhibitors and association with in vitro replication efficiency. Sutherland KA, Collier DA ... Gupta RK; *Scientific Reports* 2016; DOI: 10.1038/srep38153

rkg20@cam.ac.uk
The metabolic repertoire of immune cells, which encompasses metabolic enzymes/pathways, the available nutrient sensors and metabolic checkpoint kinases, and the epigenetic programming of metabolic genes, enables and modulates specific immune functions.

Our goal is to delineate the molecular basis of how cellular metabolism is regulated, and itself regulates, immune-function in health and disease states, and to define how environmental cues are integrated at the cellular level by immune cells to shape cellular metabolism and function.

PUBLICATIONS

The spectrum of T cell metabolism in health and disease.
Bantug GR, Galluzzi L ... Hess C; Nature Reviews Immunology 2018; DOI: 10.1038/nri.2017.99

Mitochondria–ER contact sites are immunometabolic hubs that orchestrate the rapid recall response of memory CD8+ T cells.
Bantug GR, Fischer M ... Hess C; Immunity 2018; DOI: 10.1016/j.immuni.2018.02.012

Memory CD8+ T Cells Require Increased Concentrations of Acetate Induced by Stress for Optimal Function.
Balmer ML, Ma EH ... Hess C; Immunity 2016; DOI: 10.1016/j.immuni.2016.03.016

Complement Regulates Nutrient Influx and Metabolic Reprogramming during Th1 Cell Responses.
Kolev M ... Hess C ... Kemper C; Immunity 2015; DOI: 10.1016/j.immuni.2015.05.024

Rapid effector function of memory CD8+ T cells requires an immediate-early glycolytic switch.
Gubser PM, Bantug GR ... Hess C; Nature Immunology 2013; DOI: 10.1038/ni.2687
We conduct clinical trials and associated biomarker work in primary systemic vasculitis and systemic lupus erythematosus. It has led global clinical trials in ANCA vasculitis aimed at optimising current therapies and first into disease studies to repurpose therapies licensed for other indications. A focus has been B-cell targeted therapy with rituximab and belimumab, alone or in combination, and the development of joint working between industry and academia.

Our biomarker studies have defined the role of ANCA in clinical practise and the nature of rituximab-induced secondary immunodeficiency, and we are exploring the nasal microbiome in granulomatosis with polyangiitis and urine proteome in lupus nephritis. Through development of an international collaborative research network our group has supported genomic and transcriptomic studies in ANCA vasculitis, led by Ken Smith, that have changed our understanding of these conditions.

David Jayne leads a clinical service in severe autoimmune diseases, especially vasculitis and lupus, at Addenbrooke’s Hospital, Cambridge and is the current President of the European Vasculitis Society. Through the society he has initiated a series of international training courses aimed at the autoimmune disease physicians of the future.

**PUBLICATIONS**

B cell therapy in ANCA-associated vasculitis: current and emerging treatment options.
McClure M ... Jayne D ... Jones R; *Nature Reviews Rheumatology* 2018; DOI: 10.1038/s41584-018-0065-x

Effect of disease activity at three and six months on long-term outcomes in ANCA associated vasculitis.
Gopaluni S, Flossmann O ... Jayne D; *Arthritis & Rheumatology* 2018; DOI: 10.1002/art.40776

Nasal carriage of Staphylococcus pseudintermedius in patients with granulomatosis with polyangiitis.
Kronbichler A ... Jayne D ... Harrison EM; *Rheumatology* 2018; DOI: 10.1093/rheumatology/key317

Efficacy and Safety of Belimumab and Azathioprine for Maintenance of Remission in ANCA-Associated Vasculitis: A Randomized Controlled Study.
Jayne D et al; *Arthritis & Rheumatology* 2019; DOI: 10.1002/art.40802

dj106@cam.ac.uk
Disease association of genetic variation may pinpoint pathophysiologic mechanisms and can give insight into protein function, particularly for receptors whose ligands are unknown or controversial. Coding variants often affect pathways of wider biological importance.

The orphan G-protein coupled receptor Gpr35 is one such gene, where a coding variant has been associated with an increased risk for inflammatory bowel disease, and primary sclerosing cholangitis that has an increased cancer risk. We investigate GPR35’s function, and in particular the communication of immune cells expressing this receptor and their environment.

We are also interested in GPR35’s molecular interactions with other cell membrane proteins and its implications on signalling events and cell function.

PUBLICATIONS

GPR35 promotes glycolysis, proliferation, and oncogenic signaling by engaging with the sodium potassium pump.
Schneditz G, Elias JE ... Kaneider NC; Science Signaling 2019;
DOI: 10.1126/scisignal.aau9048

Reversal of murine alcoholic steatohepatitis by pepducin-based functional blockade of interleukin-8 receptors.
Wieser V, Adolph TE; Gut 2017;
DOI: 10.1136/gutjnl-2015-310344

A matrix metalloprotease-PAR1 system regulates vascular integrity, systemic inflammation and death in sepsis.
Tressel SL, Kaneider NC; EMBO Molecular Medicine 2011;
DOI: 10.1002/emmm.201100145

‘Role reversal’ for the receptor PAR1 in sepsis-induced vascular damage.
Kaneider N et al; Nature Immunology 2007;
DOI: 10.1038/ni1525

Reversing systemic inflammatory response syndrome with chemokine receptor pepducins.
Kaneider N et al; Nature Medicine 2005;
DOI: 10.1038/nm1245
A single layer of intestinal epithelial cells separates the complex and densely populated habitat of the microbiota from the sterile host tissue of the gut, which itself harbours the majority of the host's bona fide immune cells. A loss of the mutualistic relationship between host and microbiota is thought to be at the basis of the inflammatory bowel diseases Crohn's disease and ulcerative colitis.

Using a variety of techniques, including complex genetic models, we explore the major biological mechanisms that are affected by risk genes of inflammatory bowel disease. This approach opens up a window to explore the environmental factors that may trigger disease in genetically susceptible individuals, and which are the cause for the steep increase in incidence and prevalence of these diseases around the world.

Following this path, we have reported mechanisms of how hypomorphic autophagy and mediators of the unfolded protein response lead to inflammatory bowel disease, defining a key pathway of Crohn's disease pathogenesis. Further following this paradigm, we have more recently discovered an entirely novel immunometabolic pathway that determines risk for Crohn's disease, leprosy, and systemic juvenile idiopathic arthritis.

**PUBLICATIONS**

The road to Crohn's disease.
Kaser A & Blumberg RS; *Science* 2017;
DOI: 10.1126/science.aao4158

Intestinal epithelial cell endoplasmic reticulum stress promotes MULT1 up-regulation and NKG2D-mediated inflammation.
Hosomi S ... Kaser A ... Blumberg R; *Journal of Experimental Medicine* 2017; DOI: 10.1084/jem.20162041

A role for oncostatin M in inflammatory bowel disease.
Kim WM, Kaser A & Blumberg RS; *Nature Medicine* 2017;
DOI: 10.1038/nm.4338

Defective ATG16L1-mediated removal of IRE1α drives Crohn’s disease-like ileitis.
Tschurtschenthaler M ... Kaser A ... Adolph TE; *Journal of Experimental Medicine* 2017; DOI: 10.1084/jem.20160791

C13orf31 (FAMIN) is a central regulator of immunometabolic function.
Cader MZ, Boroviak K ... Kaser A; *Nature Immunology* 2016;
DOI: 10.1038/ni.3532

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Genetic studies have successfully identified many regions of the human genome that alter an individual’s risk of autoimmune or inflammatory disease, but the molecular mechanisms that underpin these associations – and hence the reason they increase disease susceptibility – remain largely unknown.

We uncover the biology responsible for genetic associations in immune-mediated disease by combining genetics, genomics, molecular biology, and immunology-based approaches. We have a particular focus on the non-coding genome, including enhancers and non-coding RNA, and the role that they might play in regulating immune responses. Our goal is to not only shed new light on pathways involved in disease pathogenesis, but to also provide novel therapeutic opportunities. Other interests include better understanding the genetic and biological determinants of prognosis in autoimmune, inflammatory and infectious diseases - as distinct from those pathways that drive disease development.

James currently holds a Wellcome Trust Intermediate Clinical Fellowship, and has recently spent 2 years at Harvard as part of this. He is also a member of the UK and International IBD Genetics Consortia.

**PUBLICATIONS**

Genome-wide association study identifies distinct genetic contributions to prognosis and susceptibility in Crohn’s disease.
Lee JC *et al,* Nature Genetics 2017; DOI: 10.1038/ng.3755

Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease.
de Lange KM *et al,* Nature Genetics 2017; DOI: 10.1038/ng.3760

Genome-wide association studies in Crohn’s disease: past, present and future.
Verstockt B, Smith KG & Lee JC, Clinical &Translational Immunology 2018; DOI: 10.1002/cti2.1001

Human SNP links differential outcomes in inflammatory and infectious disease to a FOXO3-regulated pathway.
Lee JC *et al,* Cell 2013; DOI: 10.1016/j.cell.2013.08.034

Gene-expression profiling of CD8 T-cells predicts prognosis in patients with Crohn disease and ulcerative colitis.
Lee JC *et al,* Journal of Clinical Investigation 2011; DOI: 10.1172/JCI59255
As the ultimate intracellular parasites, viruses target their host cell machinery to enable replication and avoid elimination. Understanding how viruses manipulate cellular processes provides unique insights into host immune pathways, informs us about viral evasion and offers novel therapeutic targets.

We use functional genetic and proteomic technologies to identify novel cellular pathways appropriated by viruses. Retroviruses, like HIV, integrate into host chromosomal DNA allowing unintegrated, poorly expressed retroviruses to escape extrachromosomal silencing. All cells defend their genome against viral invasion through innate immune system activation, and by silencing incoming viruses through chromatinisation. In HIV, it is the silenced integrated HIV provirus that defies eradication and mandates lifelong HIV treatment.

Our studies have provided unique insight into chromatin regulation and opportunities for manipulating chromatin silencing pathways, and viral cures. Our discovery of HUSH (Human Silencing Hub), a novel epigenetic transcriptional repressor complex which silences HIV and endogenous retrotransposons, provides a potential route to HIV eradication.

PUBLICATIONS

- Epigenetic silencing by the HUSH complex mediates position-effect variegation in human cells.
  Tchachvnikarova IA, Timms RT ... Lehner PJ; *Science* 2015; DOI: 10.1126/science.aaa7227

- Hyper-activation of HUSH complex function by Charcot-Marie-Tooth disease mutation in MORC2.
  Tchachvnikarova IA, Timms RT ... Lehner PJ; *Nature Genetics* 2017; DOI: 10.1038/ng.3878

- CMTM6 maintains the expression of PD-L1 and regulates anti-tumour immunity.
  Burr ML ... Lehner P ... Dawson MA; *Nature* 2017; DOI: 10.1038/nature23643

- The HUSH complex cooperates with TRIM28 to repress young retrotransposons and new genes.
  Robbez-Masson L ... Lehner P ... Rowe HM; *Genome Research* 2018; DOI: 10.1101/gr.228171.117

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Vaccines are one of the most powerful tools to prevent infectious diseases. New vaccines are currently planned or already in the development pipeline. Epidemiological and clinical studies are necessary to determine the burden of existing diseases, the level of vaccine protection and identification of target populations. They can improve existing vaccination schemes and quantify the add-on benefits such as herd protection and vaccine effects pertinent to the reduction of antimicrobial resistance.

Jointly with the International Vaccine Institute in Seoul, Republic of Korea, and other institutions, we operate field sites in 14 African and 12 Asian countries capable of conducting multi-center epidemiological field studies that provide well-characterized samples for basic research and as a platform for the conduct of clinical trials.

Our research focuses on late-stage support of generating clinical data for a novel typhoid conjugate vaccine through a cluster-randomized Phase III trial in Ghana and an effectiveness trial in the Democratic Republic of the Congo, thereby generating data urgently required by the World Health Organization and Gavi, the Vaccine Alliance.

This well-established field network can be leveraged as a platform for scientists in CITIID and beyond to add-on study activities and obtain samples in high quality to execute basic sciences research.

**PUBLICATIONS**

What is the best immunization strategy for protecting African children against invasive Salmonella disease?
Jeon HJ, Pak GD ... Marks F; Clinical Infectious Diseases 2018;
DOI: 10.1093/cid/ciy386

Updates estimates of typhoid burden in sub-Saharan Africa.
Kim J-H, Mogasale V ... Marks F; Lancet Global Health 2017;
DOI: 10.1016/S2214-109X(17)30328-5

Incidence of invasive Salmonella disease in sub-Saharan Africa: a multicenter population-based surveillance study.
Marks F et al; Lancet Global Health 2017;
DOI: 10.1016/S2214-109X(17)30022-0

Effectiveness of the Viet Nam produced, mouse brain-derived, inactivated Japanese encephalitis vaccine in Northern Viet Nam.
Marks F et al; PLoS Neglected Tropical Diseases 2012;
DOI: 10.1371/journal.pntd.0001952

Sm-p80-based schistosomiasis vaccine: double-blind preclinical trial in baboons demonstrates comprehensive prophylactic and parasite transmission-blocking efficacy.
Zhang W ... Marks F ... Siddiqui AA; Annals of the New York Academy of Science 2018; DOI: 10.1111/nyas.13942
Evolution has produced an ‘arms race’ between viruses and the cells they infect. Studying host-virus interactions therefore provides key insights into both viral pathogenesis and cell biology, and suggests novel therapeutic approaches.

To discover processes and pathways targeted by viruses, we use Stable Isotope Labelling by Amino Acids in Cell Culture (SiLAC) and Tandem Mass Tag (TMT)-based functional proteomics to characterise changes in intracellular and cell surface proteins during viral infection.

Human Immunodeficiency Virus (HIV) infects almost 40 million people worldwide, and causes approximately 1 million AIDS-related deaths every year. We have identified dysregulation of hundreds of proteins in HIV-infected T cells, including cell surface amino acid transporters.

Amino acid metabolism is increasingly recognised to shape the immune response and our current research therefore aims to, 1) understand the importance of the pathways regulated by HIV for viral pathogenesis and T cell immunobiology, and 2) identify new host factors targeted by the virus.

As well as amino acid transport, we have broad expertise in manipulating and analysing primary human CD4+ T cells, and collaborate on proteomics and metabolism in other related settings, including different viral infections and cancer.

**PUBLICATIONS**

- Functional proteomic atlas of HIV-infection in primary human CD4+ T cells. Naamati A, Williamson JC ... Matheson NJ; eLife 2019; DOI: 10.7554/eLife.41431

- Temporal proteomic analysis of HIV infection reveals remodelling of the host phosphoproteome by lentiviral Vif variants. Greenwood EJ, Matheson NJ ... Lehner PJ; eLife 2016; DOI: 10.7554/eLife.18296

- Manipulation of immunometabolism by HIV – accessories to the crime? Matheson NJ et al; Current Opinions in Virology 2016; DOI: 10.1016/j.coviro.2016.06.014

- Cell surface proteomic map of HIV infection reveals antagonism of amino acid metabolism by Vpu and Nef. Matheson et al; Cell Host Microbe 2015; DOI: 10.1016/j.chom.2015.09.003

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The immune response is a powerful and complex system that has evolved to protect us from pathogens and from tumours. Losing control of that system results in immunopathology, manifest in a broad range of diseases including autoimmunity (such as T1D, lupus, multiple sclerosis), autoinflammatory disease (such as Crohn’s disease, Ulcerative colitis), infection and malignancy.

We use a systems immunology approach – modelling a broad range of quantitative traits as a means of discovering previously unsuspected relationships between them – to better understand the dysfunctional immune response in human disease. Our goal is to better understand what shapes an aberrant response and to use the information to indicate novel tests and/or interventions to help clinicians treating immune pathology.

Examples of the approach include, 1) the association of T-cell exhaustion with clinical outcome in numerous autoinflammatory/autoimmune diseases, 2) the use of this observation to develop a clinical assay for patient stratification, being brought to the clinic through a University start-up (PredictImmune), 3) the identification of a natural killer cell subset associated with clinical outcome in multiple sclerosis, and 4) the identification of molecular signatures predicting clinical onset of T1D in at risk children.

Ongoing projects include predicting and understanding clinical progression at various stages in T1D (in collaboration with the TEDDY consortium, TrialNet and JDRF), multiple sclerosis (in collaboration with the Immune Tolerance Network), and in human ageing (in collaboration with the SardiNIA consortium) in addition to a Wellcome-funded study investigating novel ways of modulating T cell exhaustion.

### PUBLICATIONS

| Metabolic exhaustion in cancer, infection and autoimmunity. McKinney EF & Smith KG; Nature Immunology 2018. DOI: 10.1038/s41590-018-0045-y |
| T cell exhaustion and immune-mediated disease – the potential for therapeutic exhaustion. McKinney EF & Smith KG; Current Opinion in Immunology 2016; DOI: 10.1016/j.coi.2016.09.005 |
| T cell exhaustion: understanding the interface of chronic viral and autoinflammatory diseases. McKinney EF & Smith KG; Immunology & Cell Biology 2016; DOI: 10.1038/icb.2016.81 |
| T cell exhaustion, costimulation and clinical outcome in autoimmunity and infection. McKinney EF, Lee JC ... Smith KG; Nature 2015; DOI: 10.1038/nature14468 |
Viruses depend on host cell machinery to express and replicate their genes. Viral RNA must therefore be delivered or generated in the cytosol. Some viruses also deliver genomic DNA into the nucleus, where it can be integrated into the host cell genome. The cell’s principal innate antiviral defence is an inflammatory response that is activated upon sensing cytosolic viral RNA. An additional defence mechanism is the transcriptional silencing of integrated viral DNA. Our overarching goal is to gain a mechanistic understanding at the molecular level of how the cell detects cytosolic viral RNA and how it silences viral gene expression. In pursuit of this goal we are applying a complementary set of biophysical, biochemical and cell biological approaches, with a focus on using high-resolution structural information to obtain detailed mechanistic insights with atomic-level detail. This will help establish basic principles of how viruses and cells coexist in health and disease.

Our research is focussed on, 1) how cells distinguish pathogenic viral nucleic acids from non-pathogenic endogenous nucleic acids, 2) how the inflammatory innate immune response against cytosolic viral double-stranded RNA is generated and amplified, 3) how cells recognise and silence the expression of integrated viral DNA, and 4) the cellular functions of endogenised viral sequences.

### PUBLICATIONS

MAVS oligomers smaller than 80 nm induce mitochondrial membrane remodeling and interferon signaling.
Hwang MS, Boulanger J ... Modis Y; FEBS Journal 2018; DOI: 10.1111/febs.14772

CryoEM structures of MDAS-dsRNA filaments at different stages of ATP hydrolysis.
Yu Q, Qu K & Modis Y; Molecular Cell 2018; DOI: 10.1016/j.molcel.2018.10.012

Neuropathic mutations in MORC2 perturb GHKL ATPase dimerization dynamics and epigenetic silencing by multiple structural mechanisms.
Douse CH1, Bloor S ... Modis Y; Nature Communications 2018; DOI: 10.1038/s41467-018-03045-x

Structural studies of viperin, an antiviral radical SAM enzyme.
Fenwick MK ... Modis Y ... Ealick SE; Proceedings of the National Academy of Science 2017; DOI: 10.1073/pnas.1705402114

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We use advanced bacterial genomics and metagenomics to better understand the evolution and spread of pathogens locally, nationally and globally. Realising the complexity of big data and its limited understanding in most developing and underdeveloped countries, we mine genomic data for robust, risk-informative diagnostic markers. I use these markers and design smart detection probes as field-compatible technologies. This technology-driven global health approach makes my research accessible to the communities who need it most.

PUBLICATIONS

Defining endemic cholera at three levels of spatiotemporal resolution within Bangladesh.
Domman D ... Mutreja A ... Thomson NR; Nature Genetics 2018; DOI: 10.1038/s41588-018-0150-8

Integrated view of Vibrio cholerae in the Americas.
Domman D ... Mutreja A ... Thomson NR; Science 2017; DOI: 10.1126/science.aao2136

Genomic history of the seventh pandemic of cholera in Africa.
Weill FX ... Mutreja A ... Thomson NR; Science 2017; DOI: 10.1126/science.aad5901

Retrospective Analysis of Serotype Switching of Vibrio cholerae O1 in a Cholera Endemic Region Shows It Is a Non-random Process.
Karlsson SL ... Mutreja A ... Lebens M; PLoS Neglected Tropical Diseases 2016; DOI: 10.1371/journal.pntd.0005044
A fundamental requirement for cell survival is the ability to respond to the local oxygen and nutrient environment. Our goal is to gain novel insights in oxygen and metabolite sensing pathways, providing potential new therapeutic targets for inflammatory disease and cancers.

The ability to sense and respond to changes in oxygen availability is conserved in all metazoans. Central to this process are a group of enzymes that require oxygen, 2-oxoglutarate (2-OG, also known as α-ketoglutarate), and iron for catalytic activity—the 2-OG dependent dioxygenases. The most well described function of these enzymes relates to the prolyl hydroxylases (PHDs) which sense intracellular oxygen, controlling the stability of Hypoxia Inducible transcription Factors (HIFs). However, 2-OG dependent dioxygenases have diverse functions, including altering cell phenotypes by remodelling chromatin. We aim to (i) uncover new metabolic pathways that influence the activity of 2-OG dependent dioxygenases, and (ii) gain insights into their biological relevance, focusing on HIF signalling, mitochondrial function and chromatin remodelling.

**PUBLICATIONS**

MARCH6 and TRC8 facilitate the quality control of cytosolic and tail anchored proteins.
Stefanovic-Barrett S, Dickson AS ... Nathan JA; EMBO Reports 2018; DOI: 10.15252/embr.201745603

The vacuolar-ATPase complex and assembly factors, TMEM199 and CCDC115, control HIF1α prolyl hydroxylation by regulating cellular iron levels.
Miles AL, Burr SP ... Nathan JA; eLife 2017; DOI: 10.7554/eLife.22693

Mitochondrial protein lipoylation and the 2-oxoglutarate dehydrogenase complex controls HIF1α stability in aerobic conditions.
Burr SP, Costa AS ... Nathan JA; Cell Metabolism 2016; DOI: 10.1016/j.cmet.2016.09.015

The proteasome distinguishes between heterotypic and homotypic lysine-11 linked polyubiquitin chains.
Grice GL1, Lobb FT ... Nathan JA; Cell Reports 2015; DOI: 10.1016/j.celrep.2015.06.061

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The human gastrointestinal tract houses a large number of microbes, collectively known as the microbiota that supports host metabolism, immune development and pathogen resistance. Intestinal dysbiosis, disruption of bacterial diversity in the gut, can result from antibiotic use or pathogenic infection and has been strongly linked to increased disease susceptibility. This dysbiosis-induced susceptibility indicates that normal commensal bacteria are capable of preventing disease; however, mechanisms involved in key host-commensal interactions are still largely unknown.

We seek mechanistic insights into the influence of commensal microbes on both intestinal infections and inflammation and systemic immune responses. These fundamental insights will give us a better understanding of infectious diseases, autoimmune disorders and even cancer, and will enable the development of new approaches to combat these diseases. Using in vivo models, cellular immunology, transcriptomics and proteomics and working closely with the Wellcome Trust Sanger Institute, we characterise the complex interactions between the commensal microbial community, intestinal epithelium and adaptive immune cells.

PUBLICATIONS

Intestinal epithelial and intraepithelial T cell crosstalk mediates a dynamic response to infection.
Hoytema van Konijnenburg DP … Pedicord VA … Mucida D; Cell 2017; DOI: 10.1016/j.cell.2017.08.046

Exploiting a host-commensal interaction to promote intestinal barrier function and enteric pathogen tolerance.
Pedicord VA et al; Science Immunology 2016; DOI: 10.1126/sciimmunol.aai7732

A secreted bacterial peptidoglycan hydrolase enhances tolerance to enteric pathogens.
Rangan KJ, Pedicord VA … Hang HC; Science 2016; DOI: 10.1126/science.aaf3552

Absence of MHC class II on cDCs results in microbial-dependent intestinal inflammation.
We are interested in the pathogenesis of tuberculosis and understanding both host and pathogen strategies that result in clearance or disease.

In the host we seek the basis of vastly different susceptibilities to this disease. Tuberculous infection results in the formation of granulomas, complex immune structures that are composed of differentiated macrophages, lymphocytes and other immune cells. However, bacteria can persist within granulomas despite the development of antigen-specific immunity. To understand the mechanistic basis of mycobacterial persistence, the mechanisms of granuloma formation and its role in tuberculosis, we have developed a zebrafish model to study immunity to tuberculosis. Zebrafish are naturally susceptible to tuberculosis caused by a close genetic relative of M. tuberculosis, the agent of human tuberculosis. We exploit the optical transparency and genetic tractability of zebrafish to monitor the infection process and modulate it using genetically defined host and bacterial mutants. Our research is shedding light on TB pathogenesis, fundamental mechanisms of immune cell chemotaxis, adhesion and aggregation, as well as immune regulation. Findings from the zebrafish have borne out in human populations and are informing strategies for intervention. Consequently, we are also using this zebrafish model to understand the pathogenesis of leprosy.

In bacteria, we identify and characterise virulence factors that subvert host defences and lead to drug tolerance.

**PUBLICATIONS**

A macrophage response to Mycobacterium leprae phenolic glycolipid initiates nerve damage in leprosy.
Madigan CA1, Cambier CJ ... Ramakrishnan L; Cell 2017; DOI: 10.1016/j.cell.2017.07.030

Phenolic Glycolipid facilitates mycobacterial escape from microbicidal tissue-resident macrophages.
Cambier CJ, O’Leary SM ... Ramakrishnan L; Immunity 2017; DOI: 10.1016/j.immuni.2017.08.003

lysosomal disorders drive susceptibility to tuberculosis by compromising macrophage Migration.
Berg RD, Levitte S ... Ramakrishnan L; Cell 2016; DOI: 10.1016/j.cell.2016.02.034

Host genotype directed therapies can optimize the inflammatory response to mycobacterial infections.
Tabin CM, Roca FJ ... Ramakrishnan L; Cell 2012; DOI: 10.1016/j.cell.2011.12.023

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Human cytomegalovirus (HCMV), the largest known human herpesvirus, is a major cause of disease in individuals whose immune systems are compromised or immature and is the commonest infective cause of congenital damage to the central nervous system. Similarly, it can also be life-threatening in the context of organ or bone marrow transplant or advanced HIV infection.

Unlike many other viruses, HCMV is never cleared after primary infection but persists for the lifetime of the host. In part, this is due to the profound ability of HCMV to avoid the host’s immune response.

However, this lifelong viral persistence is also underpinned by a biological property of all herpesviruses; the ability to undergo latent infection where viral genomes are carried silently in the absence of detection of infectious virions. It is now clear that that reactivation of virus from these latent pools is also a major cause of congenital infection as well as causing much of the HCMV-mediated disease observed in immunocompromised transplant patients and patients with AIDS.

We seek the molecular basis of viral latency and reactivation of this persistent human virus and how the host immune response combats virus disease. Such an understanding of how latent virus infection alters cellular functions to optimise the cell for latent carriage allows us to identify potential “Achilles heels” of the virus to enable us to target the latent viral reservoir in patient populations.

PUBLICATIONS

Defining the transcriptional landscape during Cytomegalovirus latency with single-cell RNA Sequencing.
Shnayder M, Nachshon A ... Stern-Ginossar N; MBio 2018;
DOI: 10.1128/mBio.00013-18

DeSUMOylase activity is required for Cytomegalovirus reactivation from latency.
Poole EL, Kew VG ... Reeves MB; Cell Reports 2018;
DOI: 10.1016/j.celrep.2018.06.048

Targeting the latent cytomegalovirus reservoir with an antiviral fusion toxin protein.
Krishna BA, Spiess K ... Sinclair. Nature Communications 2017;
DOI: 10.1038/ncomms14321

Latency-Associated Expression of Human Cytomegalovirus US28 attenuates cell signaling pathways to maintain latent infection.
Krishna BA, Poole E ... Sinclair JH; MBio 2017;
DOI: 10.1128/mBio.01754-17

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PUBLICATIONS

Metabolic exhaustion in cancer, infection and autoimmunity. 
McKinney EF & Smith KGC. *Nature Immunology* 2018; 
DOI: 10.1038/s41590-018-0045-y

Genome-wide association study identifies distinct genetic contributions to prognosis and susceptibility in Crohn’s disease. 
Lee JC, Biasci, D ... Smith KG; *Nature Genetics* 2017; DOI: 
10.1038/ng.3755

T cell exhaustion, costimulation and clinical outcome in autoimmunity and infection. 
McKinney EF, Lee JC ... Smith KG; *Nature* 2015; 
DOI: 10.1038/nature14468

How many memories does it take to make an SLE flare? 
Tarlinton, DM & Smith KGC. *Nature Immunology* 2015; DOI: 
10.1038/ni.3209

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Synthetic biology seeks to engineer biological processes. “Xenobiology” goes further by manipulating biological processes using artificial chemistries. For example, functional oligos have huge potential for precision medicine as they can be made to target tumours or pathogens with remarkable specificity, and are easily prepared on a standard desktop oligo synthesiser.

Unfortunately, natural processes present some serious hurdles: nucleases severely limit their stability in vivo, and their chemical uniformity impacts the type of interactions or mechanisms they can participate in. Taking lessons learnt from the medicinal chemistry of antisense therapeutics, artificial oligo chemistries – or “xeno nucleic acids” (XNAs) - offer properties beyond those of DNA and RNA, such as reduced immunogenicity and nuclease-resistance in serum.

We have established methods to evolve biostable XNAs into high affinity aptamers for specific targets, into a variety of catalysts or “XNAzymes”, and self-assembling nanoscale polyhedra. We are exploring the development of functional XNAs as a platform technology to direct or manipulate biology, for example using assemblies of XNA aptamers to target pathogens and tumor cells precisely modulate immune effector mechanisms in response to disease. XNAs have the potential to offer the molecular precision and function of biologics but the advantages of short oligos, including the ability to turn activities on & off with complementary strands as antidotes.

**PUBLICATIONS**

A synthetic genetic polymer with an uncharged backbone chemistry based on alkyl-phosphonate nucleic acids.
Arangundy-Franklin S ... Taylor AI ... Holliger P; *Nature Chemistry* 2019

Beyond DNA and RNA: the expanding toolbox of synthetic genetics, RNA Worlds.
Taylor AI, Houlihan G. and Holliger P; 2019; *CSH Press*

Nanostructures from synthetic genetic polymers.
Mutschler H, Taylor AI, ... Holliger P; *ChemBioChem* 2016; DOI: 10.7554/eLife.43022

Catalysts from synthetic genetic polymers.
Taylor AI, Pinheiro VB ... Holliger P; *Nature* 2015; DOI: 10.1038/nature13982

Synthetic genetic polymers capable of heredity and evolution.
Pinheiro VB, Taylor AI ... Holliger P; *Science* 2012; DOI: 10.1126/science.1217622

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We elucidate the aetiology of human immune-mediated diseases, to improve diagnosis and treatment. We use integrative statistical analysis of genomic data and develop statistical methods to improve inference, or adapt to new biological techniques:

*Genetic association discovery and fine mapping.* This focuses on increasing power through optimal study design, borrowing information between related diseases using the conditional False Discovery Rate, and distinguishing the variant(s) driving the association from their correlated neighbours.

*Comparative genetic studies of immune-mediated diseases.* We use co-localisation to integrate over the fine mapped posterior distributions of causal variants of different diseases to determine which diseases share which genetic risk factors

*Integrative analysis of genetic and omic data.* Co-localisation methods to enable us to understand disease mechanisms by mapping disease associated genetic variants to the genes they regulate. We also develop techniques to integrate genetic association data with maps of promoter-enhancer chromatin contacts in the cell nucleus.

*Dissection of heterogeneity within diseases.* Human diseases have been classified according to clinical presentation, but there is increasing evidence that clinical symptoms may not align to aetiological cause. This is motivating a transition towards alternative aetiological, molecular, or treatment-responsive, classifications of diseases and their subtypes. Our comparative studies of diseases can inform treatment decisions using stratified medicine approaches.

**PUBLICATIONS**

Chromosome contacts in activated T cells identify autoimmune disease candidate genes.

Burren OS, Rubio García A ... Wallace C; *Genome Biology* 2017; DOI: 10.1186/s13059-017-1285-0

A method for identifying genetic heterogeneity within phenotypically-defined disease subgroups.

Liley J, Todd JA & Wallace C; *Nature Genetics* 2017; DOI: 10.1038/ng.3751

A pleiotropy-informed Bayesian false discovery rate adapted to a shared control design finds new disease associations from GWAS summary statistics.

Liley J & Wallace C; *PLoS Genetics* 2015; DOI: 10.1371/journal.pgen.1004926

Lineage-specific genome architecture links disease variants to target genes.

Javierre BM ... Wallace C ... Fraser P; *Cell* 2016; DOI: 10.1016/j.cell.2016.09.037

Statistical colocalization of genetic risk variants for related autoimmune diseases in the context of common controls.

Fortune MD, Guo H ... Wallace C; *Nature Genetics* 2015; DOI: 10.1038/ng.3330

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Infection by human cytomegalovirus (HCMV) of immunocompetent individuals is generally asymptomatic or mild, and is self-limiting. However, HCMV is never cleared after primary infection, but persists for the lifetime of the host as a latent infection that avoids immune surveillance. While HCMV is a paradigm for viral immune evasion strategies, the resolution of primary infection is dependent on effective CD4 and CD8+ T cell responses. In contrast, infection of individuals whose immune systems are compromised (such as HIV/AIDS patients and transplant patients) or immature (such as a foetus) often leads to wide spread viral replication and dissemination and this can often be life threatening. Similarly, reactivation of the virus in individuals who are immunosuppressed also leads to significant morbidity and mortality.

We address a number of important questions concerning the immunobiology of HCMV both in lytic and during latent infection, with a particular focus on the generation, maintenance and function of memory CD4+ and CD8+ T cells and the immune evasion mechanism employed by the virus to modulate Natural Killer cell function. We establish how this human pathogen persists for the lifetime of the host in the presence of a fully competent and potent cell mediated immune response. Our view is that this knowledge will allow us to develop credible strategies to make latently infected cells immunological targets and thus lead to the elimination of latent HCMV reservoirs in vivo and in solid organ donor tissue, which would have a significant clinical benefit for transplant patients.

**PUBLICATIONS**

HCMV Specific CD4+ T Cells are poly-functional and can respond to HCMV Infected Dendritic Cells in vitro.
Jackson SE, Sedikides GX ... Wills MR; Journal of Virology 2017; DOI: 10.1128/JVI.02128-16

Diverse specificities, phenotypes, and antiviral activities of cytomegalovirus-specific CD8+ T cells.
Jackson SE, Sedikides GX ... Wills MR; Journal of Virology 2014; DOI: 10.1128/JVI.01477-14

Human cytomegalovirus latency-associated proteins elicit immune-suppressive IL-10 producing CD4+ T cells.
Mason GM, Jackson ... Wills MR; Plos Pathogens 2013; DOI: 10.1371/journal.ppat.1003635

Human cytomegalovirus latency alters the cellular secretome, inducing cluster of differentiation (CD)4+ T-cell migration and suppression of effector function.
Mason GM, Wills M ... Sinclair JH; Proceedings of the National Academy of Sciences 2017; DOI: 10.1073/pnas.1204836109

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One in every three-hundred people has inflammatory bowel disease (IBD, comprising Crohn’s disease & ulcerative colitis) in the developed world and its incidence is rising fast in developing countries. In the UK alone there are around 620,000 sufferers with an annual cost to the NHS in excess of £1bn. Around half of patients have an aggressive, relapsing disease course, while in others the disease is more quiescent.

Unfortunately, prognostic markers that can reliably identify these patients are not available in clinical practice. This hinders disease management because patients with aggressive disease will be undertreated by conventional escalating dose therapy, while those with quiescent disease can be exposed to the risks and side-effects of unnecessary immunosuppression.

Research in the Professor Smith’s lab found a transcriptional signature that is detectable within peripheral blood CD8 T-cells (a type of white blood cell) at diagnosis and which correlates with long term clinical outcome in IBD. The signature reflects a process called exhaustion, in which T-cells progressively lose the ability to sustain an effective immune response. Patients following an aggressive disease course have less exhaustion than those with a quiescent course. However, translating these findings to the clinic originally presented a technical challenge as blood cell populations needed separating to see a signal, something that is not practical in a routine clinical setting. To meet this challenge the researchers utilised novel approaches to find a whole blood biomarker that could provide the same results without the need for cell separation.

The answer was to measure gene expression using microarrays and then use machine learning to identify the suitable whole-blood biomarker. Ultimately this led to the identification of a 15 gene assay that could identify different disease courses by stratifying patients into aggressive and quiescent types of IBD, and an independent, prospective multicentre study validated these findings.

Having established these principles, a spin-out company (PredictImmune Ltd) was created through Cambridge Enterprise to translate this work into the clinic. The prognostic tests it provides for immune-mediated conditions can aid disease management and improve patient outcomes. As differing IBD patients may require different treatment regimens, the test ensures that they receive the most appropriate course of treatment and avoid excessive side effects resulting from overtreating the quiescent group, or excessive morbidity from under-treating the aggressive group. With funding from the Wellcome Trust, PredictImmune is also running a biomarker-stratified trial that is a first of its kind for inflammatory disease and will determine whether the biomarker can deliver personalised care.

The test uses a small blood sample to accurately predict each patients’ outcome at the point of diagnosis, and is available as a laboratory testing service and soon also as a kit. The group is also developing predictive tests for other immune-mediated diseases that pose long-term burdens on patients as well as imposing a financial burden society. They include tests for lupus, multiple sclerosis, diabetes mellitus and rheumatoid arthritis.

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(a) Horizontal bar plot of $-\log_{10}$ (P values) for the top 40 most enriched pathways in an analysis of 29 LD-pruned prognosis-associated SNPs (meta $P < 1 \times 10^{-5}$) across 1,751 pathways annotated by Gene Ontology. (b) Bar plot of $-\log_{10}$ (P values) for 155 specific cell-types and conditions. Significant enrichment was observed in “monocyte-derived macrophages stimulated by M-CSF” and “monocyte-derived macrophages stimulated by M-CSF and interferon-gamma”. Other non-immune cell-types included neural, skin, lung, liver, stem cells, smooth muscle, stromal cells, bone marrow progenitors, endothelial and epithelial cells. Dotted lines represent Bonferroni-corrected significance thresholds. Analyses performed using SNPsea.
Tuberculosis (TB) is an infectious disease that affects over 10 million people worldwide, of whom 10% die if the disease is untreated. Globally it is one of the top 10 diseases that causes death, and over 95% of these deaths occur in low and middle-income countries. Ending the TB epidemic by 2030 is one of the health targets of the United Nations Sustainable Development Goals, but multidrug-resistant TB (MDR-TB) is a continuing public health crisis and a health security threat.

Eradication of TB is impeded by the need for long complex treatment - six months with four drugs - for durable cure. Furthermore, this need for long treatment could be the catalyst for the development of antibiotic-tolerant TB. Researchers in Professor Ramakrishnan’s lab have found that the actively-growing bacteria become antibiotic-tolerant upon entry into host macrophages (part of our immune system, and the bacteria’s site of growth) by inducing bacterial efflux pumps. With this knowledge, the researchers are testing the therapeutic value of a several drugs that are known to inhibit these efflux pumps and are already approved for other purposes. For example, a clinical trial with verapamil (commonly used as an antiarrhythmic) as a treatment-shortening agent has been approved and funded by the Government of India and is entering Phase 2. Linked to this trial, studies to better understand bacterial efflux pump-mediated drug tolerance mechanisms are in progress through a multi-investigator collaborative grant from the British MRC and the Indian Department of Biotechnology.

Other clinical trials are also underway for studies on meningitis TB, the most severe and lethal form of this disease. In this study, Professor Ramakrishnan and her colleagues found that TB susceptibility is heightened in conditions of inadequate or excessive inflammation, and is regulated by the balanced production of steroid called eicosanoids. The balance of these steroids is maintained by an enzyme that is referred to as leukotriene A4 hydrolase (LTA4H), and it is variants of this enzyme that control the severity of TB meningitis. In collaboration with colleagues from the Oxford University Wellcome Trust Research Unit (OUCRU) in Vietnam, researchers from the Ramakrishnan lab have found that because of this variation in the enzyme, the standard therapy for meningitis TB is only effective in patients with a high inflammatory state, while patients with the low inflammatory state patients may be harmed by it.

Based on this finding, the OUCRU investigators have begun a randomised clinical trial where patients are genotyped and those with the low-LTA4H genotype are given steroid treatment or placebo. If the previous findings are confirmed, then in the future steroid treatment will be restricted to the excessive inflammation subset, improving the outcome of both groups. To address this, in the meantime, the zebrafish is being used to reveal mechanistic details of the LTA4H-mediated low and high inflammatory states. New targets for treatments are being revealed and drugs that have already been approved for other purposes have been identified. The use of personalised genomics will have consequences for guiding clinical treatments, where patients from the two LTA4H genotypes will be treated with different therapies.

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Concentrations are in picograms/milliliter for all cytokines except interleukin 6 (IL-6), for which concentrations are in nanograms/milliliter. Statistical comparisons between HIV-infected and HIV-uninfected were made by the Mann–Whitney test corrected for multiple testing across the 10 cytokines. Only P values of ≤ .05 are shown. Abbreviations: IFN-γ, interferon γ; TNF-α, tumor necrosis factor α.
The incidence of Inflammatory Bowel Disease (IBD) is doubling every ten years. The increase in the number of children diagnosed with the disease is of particular concern. Resistance to drugs and patients who do not respond to treatment is also a challenge.

However, the picture is not all bad. While there was no available treatment 30 years ago, now at least, there are several therapeutic interventions that can be used. For example, anti-TNF treatment transformed the lives of many following its approval in 1998, and antibodies against integrin and interleukin-23 have been more recently been employed.

Studies by Professor Kaser’s lab, have been partly responsible for some of these successes. These have enabled the development of experimental methods for examining the environmental stresses and microbes that could be responsible for triggering IBD. Simultaneously they have probed the genetics that are associated with the disease. They have found that of the over-200 genetic loci that are associated with IBD, variations in one protein particularly stand out. Professor Kaser and his researchers have used state-of-the-art methods to study it.

Unusually, the protein they identified was of unknown function and lacked any similarity to other known proteins. This in itself was unusual, yet it was also associated with an increased risk of juvenile idiopathic arthritis and leprosy. At the time the link between these different diseases was striking, but slowly over the last two years a number of other genetic changes have been identified that unite them, something that suggests a common cause.

The scientists named the unknown protein FAMIN, a term that is short for Fatty Acid Metabolism–Immunity Nexus. This name reflected their finding that FAMIN was highly expressed in macrophages, where it interacts with fatty acid synthase and is involved in the metabolism of cellular lipids. A change in FAMIN had a negative impact on the energy stores of these essential immune cells. Consequently, macrophages that contained mutations in FAMIN were less able to kill bacteria. What is more, these effects were seen in the cells of mice and humans, a consistency across species that provided welcoming confirmation of the causal genetic risk to IBD.

Metabolic pathways in immune cells are emerging as important determinants of immunological function and the work of Professor Kaser and his colleagues’ shows that a core metabolic regulator of immune cell function is affected by genetic variation that results in a predisposition to inflammatory diseases and infection. Such findings have profound implications for the treatment of IBD and pave the way for further studies of gene-environmental interactions. Cambridge has consequently been the epicentre for clinical trials which are ongoing throughout the UK. Importantly, the studies have been accelerated by the unique collaborative environment that is provided by Cambridge, involving researchers in other University departments, as well as other Cambridge centres such as the Wellcome Sanger Institute.

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(a) Immunoblot analysis (IB) of FAMIN and FASN (right margin) in primary human macrophages (MΦ) derived from peripheral blood mononuclear cells and in U937 and THP-1 macrophages differentiated with PMA (below blots), assessed after immunoprecipitation (IP) with antibody to FAMIN (anti-FAMIN), mouse immunoglobulin G (IgG; control) or anti-FASN (above lanes) or without immunoprecipitation (Input; far right). Left margin; molecular size, in kilodaltons (kDa). (b) PLA of FAMIN and FASN (yellow) in THP-1 macrophages also stained with the DNA-binding dye DAPI (blue throughout). (c) Immunoblot analysis of FAMIN or GAPDH (loading control) in lysates of HEK293 cells transfected to express human FAMIN(p.254I) or FAMIN(p.254V) or with vector alone (above lanes), assessed with (top blot) or without (bottom two blots) immunoprecipitation with anti-FASN. (d) Immunofluorescence analysis of the co-localization of FAMIN (red) with PMP70 (green) in primary human macrophages (enlarged from areas outlined in Supplementary Fig. 2a); far right, enlargement of the area outlined at left. (e) PLA of FAMIN and PMP70 (red) in THP-1 macrophages. (f) Immunofluorescence analysis of the co-localization of FASN (red) with catalase (green) in mFamin+/+ and mFamin−/− M1 macrophages (M1Φ) and M2 macrophages (M2Φ). (g) Quantification of the results in f. (h) PLA of FASN and catalase (yellow) in mFamin+/+ and mFamin−/− M1 and M2 macrophages. (i) Quantification of the results in h. Scale bars (b,d–f,h), 5 μm. Data are representative of three independent experiments (a–e) or one experiment with three mice and six cells (f,g) or ten cells (h,i) imaged per sample (f–i; mean + s.e.m.).

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DOI: 10.1038/ni.3532
Changes in behaviour can provide some of the most successful means of reducing the spread of disease.

In Ghana and Uganda there are often no established infrastructures for sanitation and it is common for rural communities to relieve themselves in the open environment. Researchers in Dr Mutreja’s lab are providing evidence that the use of pit-latrines can improve the health of these communities. They are taking samples from pit-latrines and individuals within the communities, to provide evidence that pathogen burdens are decreased by following simple sanitation measures. The researchers later return to the communities to explain their findings and coordinate efforts with local community leaders and government officials to promote sanitation and reduce the spread of disease.

In one arm of these studies, samples are taken from the faeces of volunteers, and from pit-latrines within village communities. By using whole genome sequencing (WGS) of these samples our researchers can examine their genetic components, to establish a highly detailed portrait of the pathogens contained within them, and to probe mechanisms of disease transmission.

Pit-latrines are a low-cost solution for reducing disease transmission and require minimal design and materials. By examining their microbial composition our researchers can determine whether the environment of the latrines kills harmful pathogens and limits the spread of disease. By collecting samples from different regions of the pit-latrines, our teams can also establish the optimal depth at which they should be dug and provide communities and local authorities with practical advice.

In a second arm of these studies the Mutreja lab trains local community health workers to create culturally sensitive digital media that that promotes WASH (clean Water, Sanitation and Hygiene) interventions. This enables these workers to share content with their communities using mobile communication platforms such as tablets and mobile phones. This approach provides a flexible solution that can incorporate new knowledge, beliefs and practices, and rapidly communicate these to local communities.

To enable this work, the researchers received an Impact Acceleration Award from the Economic and Social Research Council to foster relations between civil society, academia, NGOs and policy makers. Using a participatory approach they have joined with the community as equal partners, and have used scientific evidence to promote the use of WASH in areas of Africa where clean water and sewage systems are absent. Taking this approach means their research is more responsive to community needs, overcomes many of the cultural barriers that exist within the communities, and engages stakeholders at both local and national levels.

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SANITATION IN LOW AND MIDDLE INCOME COUNTRIES

SEE THE WORK HERE

DOI: 10.1080/17441692.2018.1536156
Infections are caused when disease-causing agents enter the body and multiply. Cholera is one of these, for which it was estimated that globally there were 1.3 – 4 million cases in 2017 that resulted in 143,000 deaths. This is the consequence of the seventh cholera pandemic that originated in South Asia in 1961 and spread throughout the globe over the course of the next 50 years. Such information can help to determine the factors that are important in the spread of a disease and allows us to gauge the impact of future interventions. However, little was known about its propagation routes in Africa, the country most affected by this pandemic.

Global-health researchers in Professor Dougan’s lab have reconstructed the spread of cholera across the African continent by analysing the genomes of 1070 cholera isolates. By mapping this data onto historical records of cholera outbreaks they found that resurgence of cholera in the 1970’s was the result of two strains, one in West Africa, and another in East Africa. The West African strain first appeared between July and September 1970 and was likely to have come from Asia. Countries such as Angola saw infection despite being over 1000 km from the closest country with cholera at the time and this then led to an outbreak in Mozambique in 1973. Subsequent reintroductions led to new outbreaks extending over many years up to 2003. The East African strain also appeared in 1970, but was more closely related to strains from the Middle East, suggesting that it may have distinct origins. This strain was associated with several outbreaks over the next 40 years, leading to 125,000 cases of cholera in South Africa in 2001-2002, and 98,000 cases in Zimbabwe in 2008-2009. Originally, even these strains had originated in Asia, but some had circulated in the then endemic Middle East before moving into the East African region. Many of the outbreaks could be linked to large migrations resulting from war or from religious practices such as pilgrimage.

This work has also provided information about antibiotic resistance. Professor Dougan and his colleagues found that African isolates became increasingly resistant over time, and while the earlier of these were recovered in the early 1980’s, only resistant forms have been collected since 2000. This finding reveals that the spread of resistance is likely to have occurred by determinants that were already in these disease-causing organisms as they spread, rather than independent local acquisitions of resistance. In other words, the bacteria already contained the genetic information they needed to overcome antibiotics and its emergence was likely to have resulted from human interventions such as the poorly coordinated use of antibiotics.

These high-resolution genomic studies show how it is possible to use modern scientific methods to monitor the spread of diseases, even long after outbreak events. The genomic data were consistent with events that were controlled by human activities, and demonstrated that human transmission chains are more important than climatic or environmental speculations. As such, these studies highlight that the long-term spread and maintenance of cholera in Africa is largely a consequence of direct, human to human transfer, or indirect infection by water polluted with human faeces. Such large-scale scientific interpretations over long time scales have an enormous impact on our ability to govern the continued spread of this disease and anticipate future outbreaks.
Maximum likelihood phylogeny of the 1070 genomes studied, including M66 as an outgroup. Branches are color-coded according to their geographic location, inferred by stochastic mapping of the geographic origin of each isolate onto the tree. (B) Maximum clade credibility tree for a subset of 228 representative isolates. Twelve introduction events (T) are shown, along with three previously described waves (3) as coloured arrows.

Inferred propagation routes of the seventh pandemic V. cholera, showing twelve introduction events (T) with median date ranges for the most recent common ancestor in years. The first number indicates the median MRCA of the African isolates and their closest relative from the source location, and the second number indicates the median MRCA of the African isolates. Introductions and inferred secondary transmission chains are indicated by thick and dashed arrows, respectively. Secondary transmission chains for West Africa in 1970 to 1971 are based on published records. The geographic presence of the various lineages is indicated by a circle, triangle, and diamond for waves 1, 2, and 3, respectively, and coloured according to the inferred transmission events. The size of the shapes is proportional to the number of genomes analysed.

SEE THE FULL ARTICLE AT

DOI: 10.1126/science.aad5901
CITIID also offers a range of scientific services. The NIHR Cambridge BRC Cell Phenotyping Hub provides state-of-the-art flow cytometry, cell sorting and single-cell technology facilities for the handling of unscreened human samples. It was established in 2011, to service the immunology community’s need for human cell sorting and flow phenotyping. In 2012, 700 hours of cell-sorting time was used. By 2018 this had increased to 3300 hours. This platform provides rapid access flow services to both fundamental and patient-based research from 8.00am - 11.00pm. In future the hub will incorporate a broader range of immunophenotyping and immunometabolic analysis, coupled to a streamlined process for analysing vaccine responses (to experimental or standard vaccination), immunomodulatory and immunosuppressive clinical trials and studies that use genetically-defined individuals recruited from the Cambridge BioResource.

The Hub offers a wide range of flow-based approaches, including single cell sorting, multicolour phenotyping (16-18 colours), multi-way sorting, concurrent sorting and phenotyping, apoptosis and proliferation assays, cell viability monitoring, assay development et cetera.

The following equipment is available as a service:

Attune NxT flow acoustic cytometer
BD Ariall cell sorter
BD Fortessa flow cytometer (four): 3 laser, 18 colour high speed flow analyser
BD FACScantoll flow cytometer: 3 laser, 8 colour analyser
BD Influx cell sorters
BD FACsaria Fusion cell sorters with 16+ fluorescent channels
BD FACsJazz cell sorter
BD FACsCalibur cell analyser
BD FACsMelody cell sorter
Cellomics Arrayscan XTI automated cellular imaging and analysis
Coulter Multisizer 3 flow cytometer for cell size & concentration
Leica Sp5 confocal
Leica LMD6 laser capture microdissection microscope
Leica SPE Confocal
Leica LM Cellomics Arrayscan XTI high-throughput screening microscope
Opera Phoenix (Perkin Elmer) high content confocal
SeaHorse XF96 measure OCR and ECAR of live cells in a 96-well plate format
Miltenyi AutoMACS Pro cell separator
Symphony analyser (5 lasers, 28 detectors)
MoFlo customised cell sorter
Biorad S3 sorter
Fortessa analyser
Cyan analyser
LSR II analyser
Aria II sorter

Find us at
https://www.med.cam.ac.uk/nihr-cambridge-brc-cell-phenotyping-hub/
The Wellcome-MRC Cambridge Stem Cell Institute Advanced Microscope Facility is able to offer imaging technologies, training and support.

The variety of instruments and image analysis options in the facility ensure that we are able to meet many imaging requirements in-house. We are able to provide invaluable tools for investigating cellular processes in both fixed and living cells in 2D and 4D. This is achieved by means of conventional imaging, HCS, confocal microscopy, time-lapse, widefield & FRAP, FRET, FCS and FLIM.

We also offer post-processing and image analysis tools for image volumes (deconvolution, 3D reconstruction, quantification) and assist users by developing custom analysis protocols.

**Our range of equipment includes:**

- 2x Leica SP5 TCS confocal microscopes
- Zeiss 710 confocal microscope with FLIM
- Zeiss 880 Multiphoton microscope
- Zeiss 700 confocal microscope
- Andor Revolution XD Spinning Disk confocal microscope
- Leica Matrix HCS screening/live cell imaging microscope
- Zeiss Imager fluorescence microscope
- GE Incell 2200 High Content Imager
- Essen Incucyte Zoom live cell imager
- Nikon Biostation IM live cell imager

**CONTACT US:** imaging@stemcells.cam.ac.uk

CITIID has a local high-performance computing (HPC) cluster and is configured similar to the University of Cambridge HPC, to which it has access via two 10Gb links.

There are 200TB of networked data storage available, which is supported by a team of four people, led by Stuart Williams.

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The CITTID immuno-metabolism facility offers cutting-edge high resolution liquid chromatography mass spectrometry (LC-MS) to solve small molecule (less than 2000 Da) analytical needs. Whether you are interested in highly bespoke hypothesis driven work, absolute quantitation, tracking stable labelled substrates through core metabolic pathways or untargeted global metabolomic profiling with fragmentation based metabolite ID, the immuno-metabolism facility can tailor the analysis to your needs.

We also have a suite of data processing packages to deliver fast turnaround and get the most information out of your data from large scale pattern recognition studies to small scale quantitative work.

We currently use Thermo Scientific orbitrap (FTMS) based high-resolution MS coupled to a best-in-class Vanquish UHPLC+ chromatography system for conventional analytes such as lipids and less polar aqueous compounds, and a Dionex Ion Chromatography system for highly polar difficult to measure species.

With over 15 years’ experience in the field of small molecule MS we can meet any analytical challenge.

The following equipment is available:

Thermo Scientific Q-Exactive Plus Orbitrap mass spectrometer
Thermo Scientific Horizon UHPLC+ liquid chromatography
Thermo Scientific Integrim ion chromatography system
Software: Excalibur V4.1, Tracefinder Clinical V4.1, Comound Discoverer V2.1

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Bio-Safety Level 3

CL-3 containment facilities in CITTID allow scientists to work with non-attenuated clinical organisms. As such, they provide a critical research capacity that allows investigators to study the emergence of lethal pathogens with global importance.

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