Immune Recognition Laboratory

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RESEARCH BACKGROUND

The academic research program within this laboratory is focused on defining the key molecular interactions underlying receptor recognition events that are the primary determinants of cellular immunity.

The laboratory's research has provided an understanding of the basis of peptide, metabolite and lipid presentation – events that underpin protective immunity and deleterious immune reactivity. The team's research on **anti-viral immunity** has provided an understanding of the factors that shape MHC-restriction (e.g. Nature Immunology 2015; Immunity 2016; Science 2021), while also demonstrating how the pre-TCR, a receptor crucial for T-cell development, functions by autonomous dimerization (Nature 2010). In relation to **aberrant T-cell reactivity**, our team has provided insight into alloreactivity (Immunity 2009), HLA and autoimmunity (Nature, 2017), Celiac Disease (Immunity 2012, NSMB 2014 & 2019, Cell 2019), rheumatoid arthritis (JEM 2013 & Science Immunol 2021) and HLA-linked drug hypersensitivities (Nature 2012). Regarding **innate and innate-like recognition**, the team has shed light into how Natural Killer cell receptors interact with their cognate ligands and viral immunoevasins (Nature 2011; JEM 2016; NSMB 2017; Cell 2017; PNAS 2018). Further, we have provided fundamental insight into TCR recognition of lipid-based antigens in **protective and aberrant immunity** (e.g. Nature 2007; Nature Immunology 2016; Nature Immunology 2018 & 2020). Most recently, our team identified the long sought after ligand for **MAIT cells**, namely showing that MAIT cells are activated by metabolites of vitamin B and can also respond to commonly prescribed therapeutics (Nature 2012, 2014; Nature Immunology 2016, 2017, 2020, Science 2019).

Nature Cancer, 2020 Cover
Bispecific nanobodies stabilize iNKT cell interactions for immunotherapy.

Image: Nanobodies targeting of a tumour cell.
Artwork: Erica Tandori
Read the full paper, DOI: 10.1038/s43018-020-00111-6

Our research program uses numerous biochemical and biophysical techniques including protein expression and purification, surface plasmon resonance and three-dimensional structure determination with the use of the Australian Synchrotron.
Further, cellular immunology techniques are taught within the laboratories of collaborators of the Rossjohn laboratory.

The lab is funded by the National Health & Medical Research Council, the Australian Research Council, National Institutes of Health and The Wellcome Trust.
A large number of students and ECRs from the lab have been awarded various fellowships/honours including the Premier's award, NHMRC PhD research scholarships, CJ Martin Fellowships, Peter Doherty Fellowships and CDA fellowships, ARC DECRA and Future fellowships, EMBO fellowship, NHMRC fellowships and Victoria Fellowships.

HONOURS PROJECTS

1) Investigating lipid-based immunity in the context of Mycobacterium tuberculosis infection.
2) Investigating the role of lipids in skin-based allergies (e.g. contact hypersensitivities).
3) A chemical/biochemical study into vitamin B metabolite recognition.
4) Investigating T cell mediated autoimmunity (e.g. Celiac Disease).
5) Investigating anti-viral immunity (eg. SARS-Cov-2, HIV and Influenza).

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Metabolite mediated T cell immunity

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RESEARCH BACKGROUND

Metabolite based T cell immunity is emerging as a major player in antimicrobial immunity, autoimmunity, and cancer. Here, vitamin B-based derivatives were identified to be captured and presented by the major histocompatibility complex (MHC) class-I related molecule MR1 to T cells, namely Mucosal Associated Invariant T cells (MAIT), and diverse MR1-restricted T cells. Both MR1 and MAIT are evolutionarily conserved in many mammals, suggesting important roles in host immunity.

Using a range of multidisciplinary approaches including protein biochemistry, x-ray crystallography, and cellular immunology, our team aim to provide ground-breaking findings on (i) the cellular machinery that modulates MR1-metabolite processing; (ii) metabolite presentation and (iii) T cell recognition of these metabolic antigens (Ag). Indeed, such studies improve our understanding of the molecular determinants of T cell immunity and pave the way for the development of innovative therapeutics based on selective modulation of MAIT cell immunity.

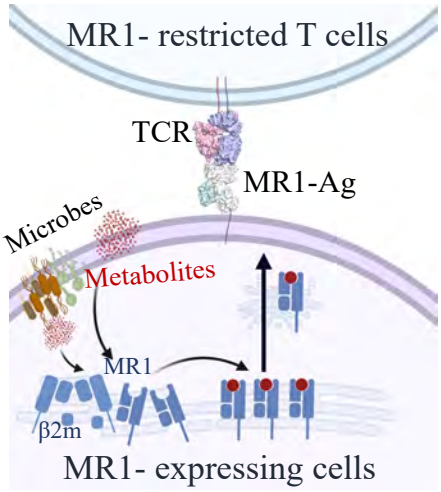

Figure 1. Metabolite antigen presentation and T cell recognition.

HONOURS PROJECTS

Project 1. Discovery of novel, microbial antigens that could modulate MAIT function

MAIT cells are modulated by intermediate metabolites derived from the riboflavin synthesis pathway in bacteria, whereby 5-OP-RU is the most potent MAIT agonist recognised so far. Recently, we have addressed the molecular basis underpinning the activation and responsiveness of MAIT cells toward 5-OP-RU (*Nature Immunology 2020 and Science Immunology 2020*). Here, we will explore the diversity within the microbial MR1-ligandome by discovering novel riboflavin and non-riboflavin related molecules that could modulate MAIT immune response.

Project 2. Non-microbial metabolic antigens and T cell immune surveillance

Recently, we have begun to appreciate the diverse nature of the small molecule metabolites that can be displayed by MR1, with several less potent synthetic drug and drug-like antigens being identified (*PNAS* 2020). Using *in-silico*, immunological & structural approaches, this project will provide insights into the range of non-microbial chemical metabolites from the universe that can be presented by MR1, thus impact T cell immunity and host defence.

Project 3. Metabolite driving diversity within human MR1-restricted T cells

A broad subset of T cells is restricted to metabolite presentation by MR1. While the αβ MAIT cells with their semi-invariant TRAV1-2^{+} T cell repertoire constitute the majority of these unconventional T cells, We and other research groups have discovered a diverse population of atypical (TRAV1-2^{-}) αβ T cells that exhibited selective reactivity toward metabolic Ags associated with MR1 (*Science 2019 & JBC 2020*). This project will tackle the molecular basis underpinning the reactivity and selectivity of the atypical MR1-restricted T cells toward diverse families of metabolic ligands including folate, and riboflavin antigens.

Lipid Mediated Adaptive Immunity

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RESEARCH BACKGROUND

Lipid antigens are presented by MHC class I like proteins, denoted as CD1 molecules, on the surface of specialised antigen presenting cells, to receptors on T cells (TCRs). Our group focuses on characterising the molecular mechanisms of Group 1 CD1 molecule lipid antigen presentation, and subsequent TCR recognition. Group 1 CD1 molecules have been found to play a role in bacterial infection, namely by Mycobacterium tuberculosis, and autoimmunity, such as in skin hypersensitivities, psoriasis, cellular stress, and cancer. Using biophysical techniques and structural biology, namely x-ray crystallography, we aim to a) elucidate the mechanisms of self- and foreign- lipid antigen presentation by CD1a, CD1b, and CD1c, b) characterise the molecular mechanisms of TCR recognition, and c) determine their roles in the context of bacterial and autoimmune diseases. Our focus will not only provide a deeper understanding of the role of lipid antigens in the context of human T-cell mediated immunity, but will provide a molecular basis for the development of novel therapeutics against targeted diseases.

HONOURS PROJECTS

Project 1: Molecular mechanisms of mycobacterial cell wall lipid antigen presentation by CD1

CD1b molecules present a range of novel lipid antigens found within the cell wall of pathogenic mycobacterial species, namely mycobacterium tuberculosis (TB). These include mycolates, including mycolic acid, a key constituent of the mycobacterial cell wall, and glucose monomycolate (GMM). Despite being the earliest lipid antigens characterised, little is known about the molecular mechanisms of lipid presentation, and recognition by T cells.

Project 2: CD1-autoreactivity and TCR gene usage bias

Recently, the importance of self-lipid antigen presentation by CD1 has become apparent. A recent and extensive analysis into the CD1b T cell repertoire of phospholipid reactive T cells has been conducted, and a bias towards T cell β-chain variable domain 4-1 (TRBV4-1) has been observed. Despite a number of CD1-TCR crystal structures previously been determined (Fig. 1), the function and molecular mechanisms of TRBV4-1 gene usage biases remain unknown.

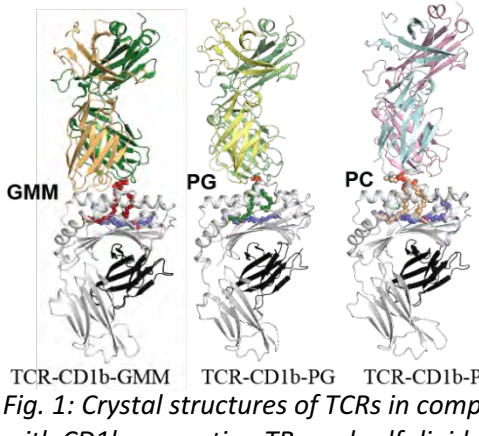

Fig. 1: Crystal structures of TCRs in complex with CD1b presenting TB- and self- lipids

Project 3: Headless lipid presentation by CD1a in contact dermatitis

CD1a, presented on skin resident dendritic cells known as Langerhans cells, can bind and present small headless lipid antigens found in cosmetics and skin products to T cells, which subsequently cause allergic contact dermatitis upon activation. Here, we seek to investigate the molecular mechanisms of CD1a presentation of small and waxy lipid antigens found in Balsam of Peru, which is a key constituent in a number of cosmetics, to investigate their role in T cell activation in skin allergies.

These projects will utilise in vitro bacterial and human tissue culture recombinant protein production, x-ray crystallography, and surface plasmon resonance, to determine the molecular mechanisms of a) lipid antigen presentation by CD1, b) role of CD1 reactive TCR gene usage bias, and b) recognition by CD1 reactive TCRs.

These projects are funded by the National Health & Medical Research Council (NHMRC), Australian Research Council (ARC), and National Institutes of Health (NIH).

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RESEARCH BACKGROUND

The adaptive arm of immune system uses lymphocytes to generate antibody and memory responses to challenges throughout life. Three lineages of lymphocytes have co-evolved over the last 550 million years: B cells, αβ T cells and **γδ T cells**. Human γδ T cells remain poorly understood and their exact role in immunity is unclear. However, human γδ T cells are frequently implicated in protective microbial and tumour immunity. γδ T cells are distributed throughout the body and form an extensive **immune surveillance network (Figure 1).** Our group seeks to explore the role of this network in health and disease.

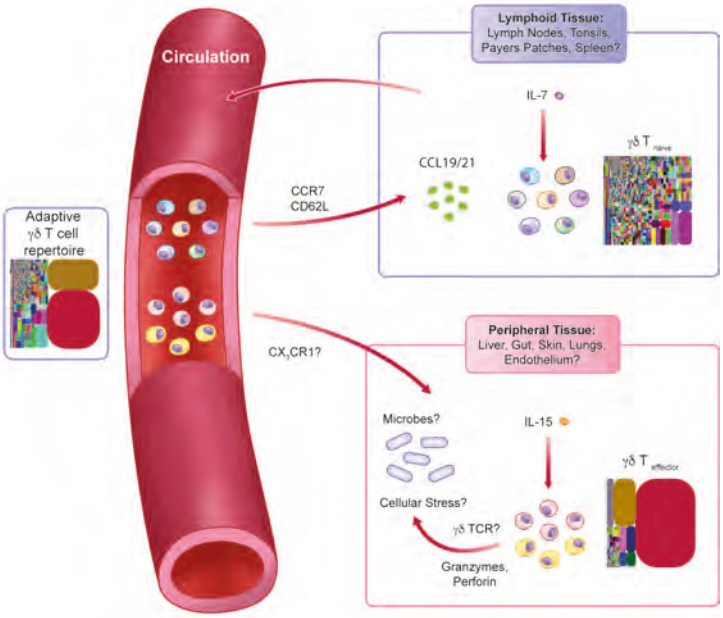

Figure 1. The circulating repertoire of γδ T cells is formed of both naïve and effector subsets. Each subset preferentially localises to the peripheral (effector) and lymphoid (naïve) tissues.

HONOURS PROJECTS

Project 1. γδ T cell memory responses in *tuberculosis* infection. Tuberculosis is caused by an infection with the bacterial pathogen *Mycobacterium tuberculosis (Mtb)*. Despite significant efforts to control and eliminate Mtb, it remains a significant global health problem. 90% of acute Mtb infections results in a state of latent *Mtb*. The student will use 17-colour flow cytometry antibody panels to track the emergence of anti-*Mtb* γδ T cell responses in longitudinal blood samples from patients either acutely or latently infected with *Mtb*. The student will then sort γδ T cell subsets and perform cutting-edge γδTCR repertoire sequencing to understand the TCR response to this pathogen.

Project 2. Transcriptional control of γδ T cells in CMV infection. Cytomegalovirus (CMV) is a human herpesvirus that infects over 80% of the population and is a major cause of mortality in immunocompromised individuals. γδ T cells make a dramatic and sustained expansion towards acute CMV infection in transplant patients, the magnitude of which has been correlated with lower morbidity and transplant failure. The student will have access to longitudinal cohorts undergoing CMV activation in different transplant scenarios (lung, kidney and stem cell). The student will undertake state-of-the-art single cell RNA sequencing to map the transcriptional trajectories of CMV-reactive γδTCRs in stem cell transplant patients.

Project 3. Human intestinal γδ T cells in inflammation. Human γδ T cells are enriched at intestinal barrier sites, where microbial infection and chronic inflammation occur. The student will have access to paediatric intestinal biopsies on a weekly basis from Monash Children's Hospital. The student will use state-of-the-art single cell TCR sequencing and RNAseq to investigate matched blood and tissue samples, allowing the identification of tissue resident γδ T cell populations. Understanding the properties of these tissue resident sentinels will allow the development of new γδ T-cell-based immunotherapeutics.

Understanding γδ T cell immune function

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RESEARCH BACKGROUND

Our team of skilled researchers investigate the ability of adaptive immune cells to respond to infections or disease. This specialised cellular system relies on recognition of self, from non-self. Understanding the protein recognition events of lymphocytes is of great importance.

Research interests

Our focus on γδ T cells, an often ignored but enigmatic lineage, holds vast implications for therapeutic development. We use pioneering techniques and state of the art equipment to probe these questions. This includes access to a advanced light microscopes, a Titan KRIOS cryo-electron microscope and the Australian Synchrotron. Using these resources we have published key immune protein complexes in journals such as Science and Nature communications.

Honours Projects

1.**Defining the architecture of a γδ T cell synapse.** The architecture of the conventional T cell synapse, the molecular machinery that initiates cellular activation, was recently determined. However, this remains unknown for γδ T cells although they play a central role in immunity. Using cellular immunology and light microscopy we aim to understand the architecture of the signalling complex within these cells.

2.**Understanding the activation of γδ T cell in disease and Tumours.** The role of γδ T cells can be perfectly illustrated in epithelial tissues such as the gut and lungs where they are the major T cell subset. These γδ T cells become more numerous in infections and diseases highlighting their central role in immunity. We aim to understand the molecular underpinnings of this immune response using protein biochemistry and structural analysis to decipher what modulates reactivity. This research will feed into our ongoing efforts to use these cells for therapeutic treatment.

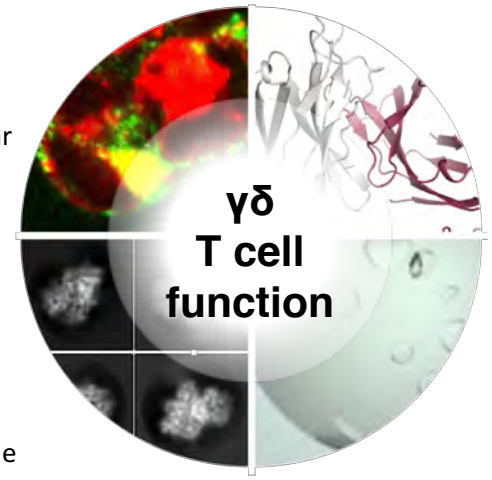

Figure 1 | (CW) Example of the experimental techniques used within the γδ T cell group, including T cell receptor structure, protein crystals, cryo-EM 2D class averages and confocal images.

3.**Using cryo-EM to probe the next generation of therapeutic antibodies.** Using advanced X-ray crystallography and cryo-EM we aim to elucidate the molecular determinants that govern reactivity and responses for a new family of therapeutic antibodies. This research will inform the basis for the optimisation and understanding of these promising protein therapies.

Infection and immunity

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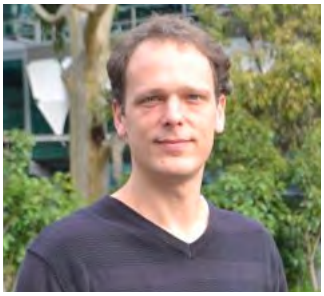

RESEARCH BACKGROUND

The ongoing COVID-19 pandemic has sparked a global effort to develop vaccines, drugs and new approaches to treat or prevent infection with the SARS-CoV-2 virus. Recent research revealed how the human immune system is able to fight this virus by producing antibodies and T cells that specifically target particular viral antigens.

Whilst the distribution and specificities of SARS-CoV-2 antibodies in acute and convalescent SARS-CoV-2 infected individuals are comparatively well characterised, our understanding of the T cell response to SARS-CoV-2 is extremely limited. T cells are known to play important roles in the detection and elimination of virus infected cells, and in the production of neutralising antibodies. By recognizing particular viral peptides presented by HLA molecules, T cells determine much of the effectiveness of the immune response to different viral components. This research is aimed at gaining an understanding of what constitutes an effective T cell response SARS-CoV-2 infection, and if, and how differences in the genetic makeup of the HLA are associated with the differential HLA presentation of important viral components to T cells. The insight gained will aid vaccine development, and provide a basis for understanding the immune response to SARS-CoV-2 and closely related viruses.

HONOURS PROJECTS

Based on the ongoing search of SARS-CoV-2 derived T cell antigens, this project aims to contribute to the fast-paced global research into the immune response in COVID-19.

The project will use protein biochemistry and X-ray crystallography to investigate T cell antigens derived from SARS-CoV-2 and from closely related coronaviruses. Peptide HLA class-I complexes will be produced via established procedures involving protein expression in bacteria, refolding in the presence of synthetic peptide and purification of the peptide-HLA complex. The resulting complexes will be characterised and crystallised to determine their 3-dimensional structure using synchrotron radiation.

Comparative Immunology

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RESEARCH BACKGROUND

While most studies in adaptive immunity have focused on peptide-mediated immunity, my research aims to explore the unchartered territory of lipid- and metabolite-mediated immunity. This aspect of immunity represents a new frontier in immunity. Indeed, there is a number of pressing fundamental questions that need to be addressed: (i) What is the extent of the chemical diversity of immunogenic non-peptidic antigens (Ags)? Are there more atypical Ags to be discovered in mammalian and non-mammalian species? (ii) How are these lipid and metabolite Ags presented and recognized? (iii) What are the molecular mechanisms that underpin the recognition event and the signalling outcomes? (iv) How did non-classical MHC molecules evolve to fulfill their molecular functions within a specific species? By applying a multi-disciplinary and highly innovative approaches that include comparative immunology, chemistry, structural biology, cell immunology, advanced atomic and molecular imaging, my research program aims to provide comprehensive and fundamental insights into molecular recognition of non-peptidic Ags, and gain an evolutionary perspective on the structure and function of MHC-like Ag-presenting molecules.

HONOURS PROJECTS

1. To explore the field of comparative immunology (Structure and function of non-classical MHC molecules (MHC-like) in evolutionary distinct species, e.g. Marsupials, frogs, chickens and bats).

In the past decade, the development of technologies has opened new exciting frontiers and novel opportunities to explore the diversity of immunity in mammalian and non-mammalian species. There is indeed tremendous value and excitement to discover how the immune system in different organisms (non-human, non-mouse) work, and more importantly to understand how distant species adapted to their immediate environment in order to survive exposure to pathogens throughout evolution. Addressing these fundamental questions may have significant impact in relation to the origin and function of the immune system. These projects aim to investigate the biological function of MHC-like molecules in evolutionary distinct species to humans and will be focusing on the functional and structural studies of families of MHC-like from a wide range of vertebrate species spanning more than 360 millions years of evolution including frogs, marsupials, guinea pigs, Tasmanian devils, bats, and rabbits. These projects will involve a number of biochemistry- and biophysical-based techniques including the recombinant expression, purification, crystallization and 3D structure determination of immune molecules using X-ray crystallography.

2. To Determine the structure/function relationship for human NKT TCRs that interact with tumour-derived lipid Ags.

This project will explore the human NKT TCR molecular recognition of human tumour-Ags that are associated with various types of human cancer and their resemblance to α-GalCer, the prototype NKT cell agonist, suggests that they may be targeted by NKT cells. Gangliosides include the disialoganglioside GD3, a tumour-associated Ag that is immunostimulatory for a subset of mouse NKT cells. We have identified subsets of NKT cells that respond to the self-tumour Ags GD3 and and α-FucCer. Furthermore, through our international collaborations, we have access to a range of synthetic analogues of α-FucCer that will enable us to explore human NKT cell recognition of this family of Ags. This project will aim to determine the structure of the NKT TCRs in complex with their CD1d-restricted, tumour-associated ligands that will permit to establish fully the specificity determinants of these NKT TCR-mediated interactions with tumour-associated Ags. This project will involve the use of a wide range of methods that include biochemical and biophysical techniques (Protein expression and purification, surface plasmon resonance (SPR) and X-ray crystallography).

Structural Autoimmunity

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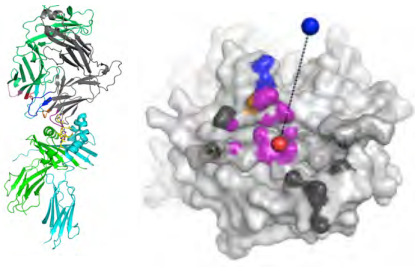
https://rossjohnlab.com/laboratory-group/research-team-hugh/

RESEARCH BACKGROUND



Human Leukocyte Antigens (HLA) molecules of the major histocompatibility complex (MHC) regulate the adaptive immune response. HLA molecules present peptides derived from self and non-self proteins to T cells as a means to detect and destroy invading pathogens. The capacity to distinguish between peptides derived from self and non-self proteins is thus a crucial feature of the immune system. However, failure of this self/non-self discrimination can result in T cell reactivity against self-peptides and, consequently, autoimmunity. Indeed, in addition to the role of HLA in protective immunity, they are also important genetic determinants in autoimmunity. We are interested in how post-translational modifications such as citrullination, deamidation and hybrid peptide generation leads to the conversion of self and innocuous environmental derived peptides (e.g. gluten peptides in celiac disease) into antigenic triggers for a deleterious immune response. We investigate how these neo-antigens are presented by MHC Class II (MHC-II) molecules and how these complexes are recognised by the T cell receptor (TCR) on CD4+ T cells that initiate these disease processes. Other projects being pursued involve understanding differences between T cell antigen recognition by regulatory and effector T cells in autoimmune disease. The projects described below will employ biochemical, biophysical, structural and cell based approaches to investigate the cellular immune response to self and modified self antigens in autoimmune and inflammatory diseases.

HONOURS PROJECTS

Project 1: The basis for T cell cross-reactivity between gluten antigens in coeliac disease

In coeliac disease (CD), the T cell response to gliadin peptides derived from gluten in wheat, barley and rye has been well characterised. Whilst some gluten peptide antigens generate a T cell response that is highly restricted to that antigen, other gluten antigens can elicit a response whereby the same T cell can recognise more than one antigen. This project will characterise how TCRs isolated from such cross-reactive T cells can recognise multiple peptides sequences presented by HLA-DQ2, the major disease predisposing allele for CD.

Project 2: The role of neoantigen generation in the pathogenesis of type 1 diabetes

A newly discovered mechanism for the generation of antigenic peptides in type 1 diabetes (T1D) involves the splicing of insulin with other pancreatic peptides to form hybrid insulin peptides (HIPs). A CD4+ T cell response to these peptides has been demonstrated in T cell clones isolated from T1D patients. This project aims to understand the structural basis for the presentation of such HIPS in HLA allomorphs associated with T1D as well as how the TCRs of responsive T cells recognises the HIP peptides bound to HLA. Furthermore we wish to determine the phenotype and TCR gene usage of the responding repertoire of CD4+ T cells to understand how HIPS shape the immune response in T1D.

Project 3: Defining key determinants of HLA mediated T cell tolerance and autoimmunity

Some HLA alleles predispose individuals to autoimmunity whereas others provide dominant protection against disease. We have have provided a mechanism for dominant protection by demonstrating in Goodpasture's Disease (GP), a kidney autoimmune disease, that HLA molecules encoded by the susceptibility and protective alleles both present the dominant autoantigenic peptide but stimulate Teff (disease causing) and Treg (protective) cells, respectively. This project will determine the phenotype and function of GP peptide specific Treg cells, how different HLA presentations of the same peptide affect T cell repertoire and phenotype, and to define how peptide-HLA/TCR interactions determine phenotype and function.

Molecular Immunology

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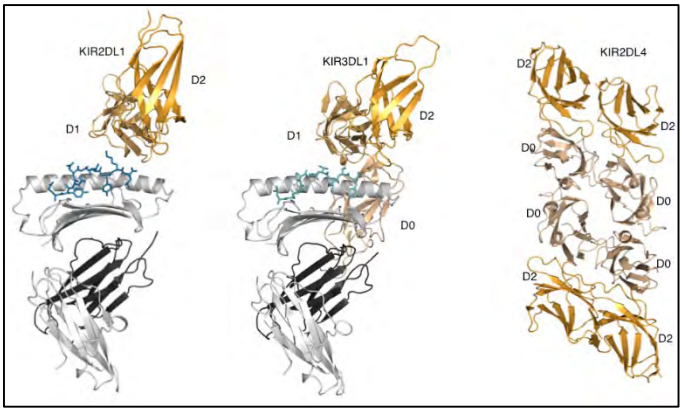
RESEARCH BACKGROUND

The projects centre broadly on the role of Natural Killer Cell receptors in disease progression. The projects will focus on the role of KIR receptors in the control of HIV replication and progression of haematological malignancies. It is well established that KIR receptors are grouped into activating and inhibitory sub-types that together dictate the cellular immune response. Yet, how these two receptor sub-types differ in terms of ligand recognition and how this plays out with regard to sensing and controlling HIV infection and other diseases is unknown. We are interested in characterising these receptors at the cellular, molecular and atomic level. See reference Vivian *et al.,* Nature (2011) 479:401-5

Techniques and the Lab:

The projects will involve challenging and multi-disciplinary approaches. They will provide an opportunity to learn bacterial, insect and mammalian techniques for protein expression. Biophysical techniques for protein characterisation including small-angle X-ray scattering, analytical ultracentrifugation, surface-plasmon resonance and atomic resolution protein structure determination by X-ray crystallography. Also, immunological techniques including cell culture and flow cytometry. The laboratory is exceptionally well funded and well equipped and is host to a large number of helpful researchers with expertise in a diverse set of disciplines. In all, it provides an excellent research environment for students.

HONOURS PROJECTS



Project 1: The enigmatic receptor KIR2DL5.
KIR2DL5 is the least understood member of the KIR family. By sequence, KIR2DL5 is a hybrid of KIR3DL1 (see Vivian *et al.,* Nature (2011) 479:401-5) and KIR2DL4 (see Moradi and Vivian *J Biol Chem*. (2015) 290(16): 10460–10471). Yet, KIR2LD5 has the properties of neither. This project will involve biophysical and functional characterisation of KIR2DL5. This is a an opportunity for the candidate to learn protein Chemistry X-ray crystallography and SAXS. The function of KIR2DL5 will be probed by cellular assays. This project is a collaboration with Prof. John Trowsdale, Cambridge Uni. UK.

Project 2: KIR3DL1 in acute myeloid leukaemia. This project centres on KIR3DL1 polymorphism and how it translates to improved outcomes in hematopoietic stem cell transplantation for the treatment of haematological malignancy (Vivian et al. J. Exp. Med (2016)) Combining functional and clinical data, the aim is to understand KIR in donor selection for HSCT treatment of AML.

Project 3: The activating receptor KIR2DS5 KIR2DS5 is an activating KIR that was long thought to be a receptor without a ligand. We have recently identified the ligand for KIR2DL5 (*unpublished*). This project is an opportunity for the student to learn the structural/functional techniques listed above to validate these preliminary results and establish the framework for the field to understand KIR2DS5. This project is a collaboration with Prof. Peter Parham, Stanford Uni. USA and Prof. Andrew Brooks, Melb Uni.