OCTOBER 2020

2020 HONOURS AND PHD STUDENT INFORMATION

For Prospective Honours and PhD Students starting in 2021

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Projects Available in 2020 for 2021

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HEALTH RESEARCH

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INSTITUTE FOR IMMUNOLOGY & INFECTIOUS DISEASES
Murdoch UNIVERSITY

WACTH
Western Australian Centre for Thrombosis and Haemostasis

Murdoch UNIVERSITY

Project available at the
Institute for Immunology and Infectious Diseases
Discovery Way, Murdoch University
Murdoch, WA 6150

Development of an adapted sequencing-based cell screening platform to define epitopes responsible for drug hypersensitivity reactions.

Suitable for: PhD students

Essential qualifications: BSc

Start date: 2021

Research area/s: Drug hypersensitivity

Chief Supervisors: Dr Andrew Gibson, Prof Elizabeth Phillips

Co-supervisors: Dr Ramesh Ram, A/Prof Mark Watson, A/Prof Abha Chopra

Research Area and Clinical Importance: In drug development, efficacy and safety are of equal importance. Nonetheless, many compounds elicit off-target immune mediated adverse reactions, which are rarely identified in the pre-clinical or pre-marketing phase of drug development and associated with significant ethical, scientific and financial burden. Drug hypersensitivity reactions (DHR) have diverse phenotypes but those with lifelong immunity that are life-threatening, and treatment-limiting are T-cell mediated with drug-responsive T-cells identified in the at the site of tissue damage. An extreme example is Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN), where drug-associated skin damage culminates in epidermal detachment, and mortality rates are 50%. These reactions are further characterized by hemorrhagic erosion of mucous membranes and severe secondary acute and long-term complications including sepsis, blindness, respiratory, reproductive and mental health complications. Significant unmet needs exist to understand the mechanisms of these hypersensitivity reactions to define the molecular and cellular signatures that would define with greater precision risk factors for prediction, prevention, prognostication and more targeted therapies.

Research background: For many drugs, specific human leukocyte antigen (HLA) alleles have now been strongly associated with different phenotypes of T-cell mediated drug hypersensitivity syndromes. Studies in SJS/TEN have highlighted the involvement of a single or dominant T-cell receptor (TCR) clonotype as shown to be expressed on activated CD8+ T cells in the blister fluid from patients expressing key HLA risk alleles for carbamazepine- and allopurinol-induced SJS/TEN, respectively. Interaction of both factors, specific HLA class I and TCR, is critical for CD8+ cytotoxic T-cell activation thought to mediate the tissue-damage associated with drug hypersensitivity reactions. Here, drug antigen is endogenously processed by antigen presenting cells before loading of drug-antigen derived peptides onto HLA molecules for presentation at the cell surface for recognition by passing T-cells with corresponding TCRs. For many drugs these responses can be modelled using parent compound or drug metabolites, but the structure and origin of the immunogenic epitope(s) remains undefined. While peptides may be of human origin through the formation and processing of drug haptens or the expression of an altered self-peptide repertoire as a result of drug binding to the HLA-TCR complex, further complexity lies in that peptides may have pathogenic origin/cross-reactivity. Indeed, in the case of hypersensitivity to the HIV drug abacavir, abacavir-responsive CD8+ T-cells can be expanded from both the naïve and memory T-cell subsets of healthy donors expressing the HLA-B*57:01 risk allele. This activation of pre-existing memory T-cells in donors who are abacavir unexposed implicates cross-reactivity with a previously encountered foreign antigen which was responsible for the initial priming of naïve T-cells (heterologous immunity). Understanding the epitope(s) responsible for T-cell activation in the context of drug hypersensitivity will further our understanding of disease pathogenesis and develop tools for screening risk epitopes.

Specific Aim of project: This project will harness a pre-existing biobank of DNA and cellular samples from patients with T-cell mediated drug hypersensitivity reactions. Deep immune phenotyping of these patients will include HLA, KIR and ERAP genotyping with state-of-the-art single cell technologies from paired blister fluid, skin and PBMC samples to define the TCR repertoire in samples from clinically well-defined patient cohorts with drug hypersensitivities linked to key HLA risk alleles. The project will then be defined by inclusion of these cells into the development of a novel *in vitro*, cellular screening platform for high throughput identification of immunogenic epitopes responsible for activation of the cytotoxic T-cell response. T-cells responsive to drug antigen will be cultured with discovery cells expressing single, drug-associated HLA class I risk alleles. Importantly, discovery cells

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will be designed to express a known antigen library, encoding human or pathogenic proteomes, which when expressed undergo normal endogenous processing and loading onto HLA class I for translocation to the cell surface. This allows for unbiased discovery of antigens at genome scale. Discovery cells activated through stable formation of an HLA-peptide-TCR complex can be isolated through expression of a fluorescent granzyme B reporter. Subsequent PCR of the antigen cassette followed by next-generation sequencing identifies enriched peptides containing epitopes responsible for T-cell activation. Critically, peptides containing identified epitopes can be synthesized and fed back into *in vitro* cell cultures incorporating risk HLA and TCR specificities for confirmation of immunogenicity.

Significance: Understanding the epitope(s) responsible for activation of cytotoxic T-cells in the context of drug hypersensitivity has been a missing link which will further our understanding of disease pathogenesis. The unbiased determination of immunogenic epitopes modelled within current drug hypersensitivity patient cohorts with defined HLA associations will (1) define the propensity of different human proteins to form drug-protein adducts, (2) the extent of response driven by heterologous immunity, (3) confirm utility of the platform as a tool to screen new compounds using a battery of cells expressing key risk alleles, and (4) add to development of diagnostic tools for these complex hypersensitivity reactions. Compounds that contribute to risk epitope production may be removed from the developmental pipeline at an early stage, preventing the future development of drugs likely to induce drug hypersensitivities.

This project is suitable for a PhD student or as a shortened version for an honours student. The research work will be undertaken at the Institute for Immunology and Infectious Diseases (IIID, Murdoch University Campus). The team within the research institute have diverse skills applicable to the project including genetic cloning, next-generation sequencing, and molecular methods for TCR repertoire analysis at the single cell level.

Contact: Dr Andrew Gibson **Email: a.gibson@iiid.com.au** **Telephone: 9360 1379**

Project available at the
Institute for Immunology and Infectious Diseases
Discovery Way, Murdoch University
Murdoch, WA 6150

Delineating immunological risk in drug tolerant versus hypersensitive patients; application of cutting-edge technologies for deep single cell immune profiling.

Suitable for: Honours / PhD students

Essential qualifications: Background in biology, computer science / bioinformatics experience preferred

Start date: 2021

Research area/s: Drug hypersensitivity

Chief Supervisors: Dr Andrew Gibson, Prof Elizabeth Phillips

Co-supervisors: Dr Ramesh Ram, A/Prof Abha Chopra, A/Prof Mark Watson

Research Area and Clinical Importance: In drug development, efficacy and safety are of equal importance. Nonetheless, many compounds elicit idiosyncratic adverse reactions, which lack mechanistic understanding and so are unable to be screened-out preclinically imposing healthcare providers and pharma with a significant ethical, scientific and financial burden. Drug hypersensitivity reactions (DHR) may have incidences of up to 50% in patients with disease-related immunosuppression and have an immunological aetiology, with drug-responsive T-cells identified in the blister fluid, blood, and tissue of patients with mild and severe drug-induced skin and liver injury. These immune-mediated reactions vary in phenotype, and while many are mild, reactions may be life-threatening. Indeed, for Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN), where drug-associated skin damage culminates in epidermal detachment, mortality rates are 50%. These reactions are further characterized by hemorrhagic erosion of mucous membranes and severe secondary complications including sepsis, blindness, respiratory, reproductive and mental health complications. The risk factors that skew certain patients toward drug hypersensitivity remain undefined.

Research background: For many drugs, specific HLA alleles have been associated with onset of hypersensitivity. Preventive genetic screening has had some impact, but genetic risk factors with 100% negative predictive value (NPV) across populations have not been identified for the most common drugs globally associated with SJS/TEN. Other risk factor definition has highlighted the involvement of a single or dominant TCR clonotype as shown to be expressed on activated CD8+ T cells in the blister fluid from patients expressing key HLA risk alleles for carbamazepine- and allopurinol-induced SJS/TEN, respectively. Thus, while identified HLA risk alleles may be able to narrow in on the affected demographic, other immunological parameters with inter-individual variation must additionally define susceptibility but remain to be defined. However, the critical differences that define tolerant from reacted patients may not lie in the periphery, but within the targeted tissues themselves.

Specific Aim of project: This project will combine HLA screening with state-of-the-art single cell technologies and carefully curated, clinically well-defined blood and tissue samples from patients allowing for the matrix of immunological cells and signals to be teased apart at both the gene and expressed protein levels. Computational analysis using the centers specifically-designed software packages, across different drugs and affiliated reaction phenotypes, will provide understanding of the key differences between patients that tolerate drugs and those that develop mild to life-threatening hypersensitivity reactions. This single-cell, tissue-specific multidimensional approach will be necessary not only to define the antigen-driven CD8+ T cells in terms of TCR repertoire, cell surface markers and transcriptome at a single cell level but also to define the HLA-restriction and drug reactivity of TCRs from these T-cells while providing an unbiased comprehensive atlas of the cellular immune environment at the site of acute tissue damage.

Significance: The identification of tissue specific cellular and molecular signatures at a single cell level defined during this study will provide important insights into markers that can be used for earlier diagnosis, diagnosis and treatment targets.

This project is suitable for a PhD student or as a shortened version for an honours student. The research work will be undertaken at the Institute for Immunology and Infectious Diseases (IIID, Murdoch University Campus). The team within the research institute have diverse skills to ensure maximal productivity from each sample including flow cytometry, next-generation sequencing, and molecular methods for TCR repertoire and transcriptome analysis at the single cell level.

Contact: Dr Andrew Gibson **Email: a.gibson@iiid.com.au** **Telephone: 9360 1379**

Project available at the
Institute for Immunology and Infectious Diseases
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Characterising the immune response associated with Inclusion Body Myositis.

Supervisors: Dr Jerome Coudert (j.coudert@iiid.murdoch.edu.au; Ph: 9360 1366)

Inclusion Body Myositis (IBM) is one of a group of autoimmune diseases characterised by muscle inflammation and progressive weakness of quadriceps, finger flexors and ultimately pharyngeal muscles. Symptoms usually start after the age of fifty and the syndrome is more common in men. Pathologically, IBM is characterized by the combination of inflammation and degeneration, with muscle fibre infiltration by immune cells, mostly CD8 T-cells and macrophages. The mechanisms that drive the immune cell recruitment, T-cell activation and differentiation remain to be understood.

A first aspect of this project will consist in studying blood samples from IBM patients by flow cytometry in order to identify modifications that affect the leucocyte subsets and to characterise features of activation associated with the autoimmune response; this information may indicate novel blood biomarkers but also most importantly will provide an insight into the autoimmune mechanisms at play in IBM. These samples from patients will be compared to blood from age-matched healthy donors.

Also, leukocytes infiltrating the diseased muscles will be analysed after isolation from muscle biopsies taken from IBM patients. We seek to identify activation markers on these auto-aggressive cells and to determine their function by flow cytometry-based analysis of their surface and intracellular protein signature. These data will be compared to those obtained from the blood.
Another aspect of this project will consist in profiling the TCR repertoire of the dominant autoreactive clones found expanded in the muscles. To this aim, muscle-infiltrating CD8 T cells will be isolated from biopsies and their TCR sequenced.

Aims:

- To characterise profile alterations of the circulating immune cells
- To identify T cell subset activation and expansion within muscle-infiltrating leukocytes
- To characterise CD8 T cell oligoclonal response in IBM muscles.

Methods:

This project includes both cellular and molecular biology techniques.

- Processing of blood and muscle tissues and isolation of immune cells
- Flow cytometry-based analysis of leukocyte populations
- Purification of T cell subsets
- Sequencing of TCR and identification of dominant TCR gene recombination

Hypothesis:

The autoimmune response associated with IBM is characterised by a selective expansion of specific T cell subsets

Importance:

IBM patients are resistant to conventional immunotherapies or show only a transient response, as a result, treating this progressive disease remains a major clinical challenge. This project seeks to provide a better understanding of the modifications that occur within the immune system and has the potential to identify immune targets for novel therapies.

Candidate:

This project is suitable for a **Honours student**.
This research work will set crucial foundations for future development aiming at unravelling the antigen targeted by the autoreactive T cells, which will be suitable for development into a PhD project.
Alternatively, a **PhD candidate** who may be interested by this area of research can contact me to discuss our multiple research directions.

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Institute for Immunology and Infectious Diseases
Discovery Way, Murdoch University
Murdoch, WA 6150

MicroRNAs in Thrombosis and Haemostasis

Research Group:	Western Australian Centre for Thrombosis and Haemostasis (WACTH)
Location:	Building 390, Discovery Way, Murdoch University
Start Date:	2021

Principal Supervisors: **Dr Jim Tiao**

Other Supervisors: **Prof Ross Baker, A/Prof Murray Adams**

Short project description & main objectives: Haemostasis is a fine balance of coagulation and anticoagulant proteins (e.g. Protein S, Tissue Factor, Factor VIII etc.) in individuals. An individual with imbalances of these proteins have a higher risk of developing potentially fatal thrombotic disorders, such as stroke, DVT. Venus thromboembolism (VTE) and Pulmonary Embolism (PE).

Our laboratory is interested in understanding the molecular regulation of these blood proteins, and identifying targets we can develop into therapeutic reagents. Our projects aim to understand regulatory mechanism involving microRNAs, a class of small non-coding RNAs within our genome known to be strong effectors of gene transcript levels. These small microRNAs bind with high specificity to the 3` untranslated regions (3`UTRs) of target transcripts, resulting in degradation of target transcript or translational halt. We've identified several key microRNA binding sites in the 3`UTR of selected genes in the coagulation and anti-coagulation pathway, and the project will involve molecular and biochemical characterisation of these interactions to develop an enhanced understanding of thrombosis and haemostasis.

Techniques utilised in this project include: specialised coagulation assays, molecular and cellular biology, DNA and RNA manipulations, transfection, quantitative reverse transcription PCR, western blotting and nucleic acid probe design.

Project suitable for:	Honours ☒ Masters ☐ PhD ☒
Essential Qualifications for Applicants:	Honours: Success completion of all third year BSc units; completed a BSc degree with a GPA of 2.5 or greater
Available part time?	No
Available to International students?	Yes
Additional funding/scholarship provided?	Upon application

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Project available at the
Institute for Immunology and Infectious Diseases
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Murdoch, WA 6150

Quality assessment of rapid plasma testing of microangiopathic thrombocytopenia patients

Research Group:	Western Australian Centre for Thrombosis and Haemostasis (WACTH)
Location:	Building 390, Discovery Way, Murdoch University
Start Date:	2021

Principal Supervisors: **Ms Grace Gilmore**

Other Supervisors: **Dr Jim Tiao, Prof Ross Baker, A/Prof Murray Adams**

Short project description & main objectives: Thrombotic thrombocytopenic purpura (TTP) is a rare but acute life-threatening disease requiring urgent medical intervention characterised by thrombotic microangiopathy. (TMA) Two main molecular players involved in TTP are ultra large molecular weight von Willebrand factor (ULVWF) multimers and its protease, ADAMTS13. In the microcirculation, von Willebrand factor (VWF), platelet (thrombocyte) and ADAMTS13 act in concert to induce clotting when required and prevent excessive clotting following vesicle wall repair. TTP is induced when ADAMTS13 function is impaired and cannot cleave ULWVF. This leads to the formation of ULVWF multimers to increased platelet deposition in the microcirculation which, in turn, causes the mechanical destruction of red blood cells. This process ultimately leads to fragmentation of red blood cells, a morphological feature readily recognisable on the blood film of TTP patients.

Accurate diagnosis of TTP remains challenging, and clinical decisions are currently based on patient ADAMTS13 activity levels. An activity level <10% confirms a TTP diagnosis, whereas an activity of >10% suggests other TMA cases such as Atypical Hemolytic-Uremic Syndrome. Precision and clinical interpretation of the ADAMTS13 activity assay around the 10% cut off level is still problematic and often lead to variation in clinical decisions and management. More scientific data, therefore, is required on the current 10% activity level cut-off to improve diagnosis precision.

This project will involve handling of human plasma samples collected from TTP patients. These patient samples will be important in validating the clinical interpretation of laboratory results.

Project suitable for:	Honours ☒ Masters ☐ PhD ☒
Essential Qualifications for Applicants:	Honours: Success completion of all third year BSc units; completed a BSc degree with a GPA of 2.5 or greater
Available part time?	No
Available to International students?	Yes
Additional funding/scholarship provided?	Upon application

Contact for further information:

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Project available at the
Institute for Immunology and Infectious Diseases
Discovery Way, Murdoch University
Murdoch, WA 6150

Understanding platelet dysfunction in Chronic Lymphocytic Leukemia (CLL)

Research Group:	Western Australian Centre for Thrombosis and Haemostasis (WACTH)
Location:	Building 390, Discovery Way, Murdoch University
Start Date:	2021

Principal Supervisors: **Dr. Pat Metharom and Prof. Ross Baker**

Other Supervisors: **Omar Elaskalani**

Short project description & main objectives: Chronic Lymphocytic Leukemia (CLL) is a type of blood cancer that develops slowly over months or years. CLL, rarely observed in children, is the most common type of leukaemia in adults. In the majority of cases, the overproduction of immature blood cells (blast cells) is of B-lymphocyte lineage. Many individuals with CLL show little or no symptoms and are often only diagnosed during a routine blood test. One of the symptoms of CLL is increased incidents of bruising and prolonged bleeding. This is due to the overpopulation of white blood cells in the bone marrow that prevents sufficient generation of platelets. Platelets are small anucleate blood cells that are critically important in clot forming, wound healing and innate immunity. Recent studies indicate that platelets from CLL patients are not only present in reduced number but are also functionally defective. Notably, CLL platelets display a significantly diminished response to physiological stimuli such as adenosine diphosphate (ADP). As the activities of ectonucleotidases CD39 and CD73, enzymes responsible for the generation of the immune-suppressive adenosine from ATP and ADP, are known to be elevated in several cancers, we hypothesise that purinergic metabolism and signalling (molecular communication mediated by purine nucleotides and nucleosides such as adenosine, ADP and ATP) are altered in CLL and contribute to the formation of defective platelets. This project aims to examine platelets from healthy and CLL individuals to understand better the mechanisms underpinning platelet dysfunction in CLL, which may lead to better anti-cancer treatment strategies.

Project suitable for:	Honours ☒ Masters ☐ PhD ☒
Essential Qualifications for Applicants: with a GPA of 2.5 or greater	Honours: Success completion of all third year BSc units; completed a BSc degree
Available part time?	No
Available to International students?	Yes
Additional funding/scholarship provided?	Upon application

Contact for further information:

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Further information of available projects in 2021

Please see the IIID website and access the student information and open day pages where additional projects suitable for both honours and PhD may be listed as and when they become available