Murdoch UNIVERSITY

2017
HONOURS, PHD & POSTGRADUATE STUDENT PROJECTS

Biomedical Science and Health Research

IIID

Building 390
Discovery Way
Murdoch University
Murdoch WA 6150
http://www.iiid.murdoch.edu.au

WACTH
Western Australian Centre for Thrombosis and Haemostasis

CENTRE FOR COMPARATIVE GENOMICS
Western Australia

INSTITUTE FOR IMMUNOLOGY & INFECTIOUS DISEASES

INSTITUTE FOR IMMUNOLOGY & INFECTIOUS DISEASES

The research groups at IIID work to prevent and reduce the impact of disease on people and communities around the world, while advancing medical and scientific knowledge in global healthcare with a focus on immunology and infectious diseases. The Institute's mission is to pursue excellence and productivity in health by undertaking world-class clinical and research programs with the best clinicians, researchers, facilities and services, with a focus on clinical practice altering research in high-needs patients. To support these programs, IIID actively pursues wide collaborations, practical outcomes and the creation of an enduring legacy. The Institute's broad agenda encompasses research that will reveal interactions between adaptable pathogens, drugs and the human host at genetic, cellular and clinical levels. Current activity includes studies in biostatistics, laboratory science, drug hypersensitivity, neurocognitive health, autoimmune myositis, multiple sclerosis, HIV infection, and hepatitis C infection.

CONTENTS

BARRIERS TO UPTAKE AND PERSISTENCE WITH STATIN THERAPY

Research area/s:	Health Sciences, Psychology, Nursing
Supervisors:	Dr Susan Herrmann, Dr Vance Locke, Professor Merrilee Needham, Dr Helen Keen
Project suitable for:	Masters or PhD
Essential qualifications:	BSc
Start date:	2017

Project outline:

Background: Since the 1970s drugs commonly known as 'statins' have been prescribed to lower cholesterol and prevent cardiovascular disease but controversy over safety and perceived side-effects has led to people abandoning or avoiding treatment. Side effects, health beliefs and deficits in health literacy have contributed to poor uptake and non-persistence with treatment in other contexts but the problem is not well articulated and there is a need for pragmatic studies in real world settings.

Aims: The aim of this study is to explore to explore patient and treatment-related factors contributing to poor uptake and intolerance of statin drugs.

Methods: A dedicated research clinic for the evaluation and management of statin-associated intolerance will be established in the IIID Academic Medical Centre in 2017. Working in a multidisciplinary team, the successful applicant will use qualitative and quantitative research methods; become competent in the use of research software, including NVIVO and REDcap; and develop contemporary assessment tools.

Importance: Although lifestyle plays an important role in preventing CVD, evidence-based medicine indicates that statin drugs remain the mainstay of treatment and prevention of cardiovascular and ischaemic cerebrovascular disease. However, the definition and incidence of true statin-associated intolerance is not known and people who might benefit from treatment are missing out.

References:

1. Bates TR, et al. Non-adherence to statin therapy: A major challenge for preventive cardiology. Expert Opinion on Pharmacotherapy. 2009;10(18):2973-85.
2. Keen HI, et al. Statin myopathy: The fly in the ointment for the prevention of cardiovascular disease in the 21st century? Expert Opinion on Drug Safety. 2014;13(9):1227-39.
3. Baigent C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet (London, England). 2005;366(9493):1267-78.

Contact:
Susan Herrmann
Murdoch University
s.herrmann@iiid.murdoch.edu.au

ESTABLISHMENT OF A NATIONAL INCLUSION BODY MYOSITIS (IBM) REGISTRY

Research area/s:	Muscle Disease and Autoimmunity
Chief supervisor:	Professor Merrilee Needham
Other supervisors:	Professor Frank Mastaglia, Dr Susan Herrmann
Project suitable for:	PhD
Essential qualifications:	BSc (including Nursing)
Start date:	Flexible

Project outline:

Background: IBM although an uncommon disease, is the most common acquired muscle disease of aging. It has been proposed to involve both immunological and degenerative mechanisms involving abnormal protein metabolism. The prevalence figures vary from between 14-50 per million population within Australia, so clinical studies and clinical trials involve collaboration between centres. IBM is a poorly understood disease, which requires collaboration to generate the numbers required to more fully understand the disease.

Aims: (1) To ascertain all consenting patients diagnosed with IBM across Australia; (2) To establish a clinical database to centrally collect phenotypic data prospectively; (3) To establish a platform for collection of natural history data, to provide a basis for future clinical therapeutic trials can be held; (4) To establish a biobank to facilitate future studies of disease pathogenesis

Methods: (1) Collaboration with other investigators across Australia; (2) Establishment of a common database to collect clinical data; (3) Establishment of a central repository of biological specimens including PBMC's, serum and DNA.

Importance: Once there is a central registry of consenting patients diagnosed with IBM, and an associated biobank, this will form a platform on which future scientific and clinical studies can be performed.

References:

1. Needham, M., et al. Sporadic Inclusion Body Myositis: Phenotypic variability and influence of HLA-DR3 in a cohort of 57 Australian cases. J Neurol Neurosur and Psych 2008; 79(9):1056-60.
2. Needham, M., et al. Prevalence of Sporadic Inclusion Body Myositis and Factors Contributing to Delayed Diagnosis. Journal of Clinical Neurosciences 2008; 15(12):1350-1353.
3. Mastaglia FL, et al. Sporadic inclusion body myositis: HLA-DRB1 allele interactions influence disease risk and clinical phenotype. Neuromuscular Disorders 2009;19:763-765.

Contact:

Professor Merrilee Needham
Merrilee.Needham@health.wa.gov.au

GOUT AS A RISK FACTOR FOR HOSPITALIZATION, EMERGENCY CARE, CANCER & MORTALITY IN WA

Research area/s:	Gout / Epidemiology
Chief supervisor:	Professor Helen Keen
Other supervisors:	Dr Hans Nossent, TBA
Project suitable for:	Masters or PhD
Essential qualifications:	BSc, statistics knowledge essential
Start date:	Flexible

Project outline:

Background: Gout is the most common inflammatory arthritis. It is a chronic arthritis affecting joints, causing pain, dysfunction and damage. It is also associated with morbidity and mortality from cardiovascular and renal disease. The burden of gout in WA is unknown. The WA Data Linkage System (WADLS), commissioned in 1995, is one of the most comprehensive and well-established population-based data linkage systems in the world. It brings together around 30 million records and consists of data from over 40 population-based health data collections including all hospital inpatient data, birth and death records, mental health services data, cancer registrations and midwives' notifications extending to the 1970s. Studies involving linked administrative data have demonstrated enormous potential to investigate disease aetiologies, identify factors influencing health and utilisation of health services.

Aims: To utilize the WARDER research resource - a derivative of the WADLS:

1. to describe the overall trends in comorbidities, mortality and use of hospital resources for patients with gout in WA over the period 1980-2012.
2. to compare comorbid conditions associated/ mortality use of hospital resources of gout patients in WA in stratified for age, gender, ethnicity, remoteness and equity

Methods: The Department of Health WA maintains a set of core databases. We will use core datasets which have already been extracted to the West Australian Rheumatic Disease Epidemiological Resource (WARDER) (HREC#2015/12). The core datasets include:

1. WA Hospital Morbidity Data Collection (HMDC) contains patient demographics, co-morbidities, primary and secondary admission diagnoses and codes for procedures undertaken or complications arising during admission.
2. WA Cancer Registry records all incident cases and type of cancer in WA
3. WA Emergency contains data on all presentations including a final discharge diagnosis to emergency departments at public hospitals in WA and WA.
4. Death registrations record date and primary as well as secondary causes of death in WA.
5. The Electoral Roll will be used to generate data for a control population.

The WA Data Linkage Branch will search in these core datasets for individuals with ICD-codes relevant for gout and will subsequently perform data linkage for individuals across the various datasets using probabilistic matching (WADLS; Holman et al. 1999).

Importance: The prevalence of gout is Australia is uncertain, as is the burden of the disease on the health system. Understanding this burden can inform funding models: linked data is ideally suited to provide the evidence necessary for the planning and allocation of resources.

Contact:
Professor Helen Keen
Murdoch University
Helen.keen@uwa.edu.au

HLA INTERACTIONS IN RISK FOR DRUG HYPERSENSITIVITY AND HIV PROGRESSION (ERAP1)

Research area/s:	Drug Hypersensitivity
Chief supervisor:	Dr Rebecca Pavlos
Other supervisors:	A/Professor Alec Redwood
Project suitable for:	Honours, Masters or PhD
Essential qualifications:	BSc
Start date:	Flexible

Project outline:

Background: The HLA-B*57:01 gene is strongly associated with life-threatening hypersensitivity to the HIV drug, abacavir (ABC HSR), as well as long-term non-progression of HIV disease. Despite this only 55% of those carrying the HLA-B*57:01 gene will develop ABC HSR and not all of those carrying HLA-B*57:01 will have superior long-term control of HIV disease. We seek to understand the mechanism behind this. Variations in the Endoplasmic reticulum aminopeptidases genes (ERAP1/2) have been implicated in the pathogenesis of several autoimmune diseases. In this study we will investigate the mechanisms by which variation in ERAP1/2 leads to abacavir tolerance in HLA-B*57:01 carriers and we will also investigate an association between ERAP 1/2 and control of HIV replication in those carrying HLA-B*57:01 and other HLA alleles associated with long-term non-progression of HIV.

Aims:

1. To investigate the role of ERAP peptide processing on the repertoire of peptides presented by HLA-B*57:01 in the presence or absence of ABC.
2. To examine the effect of ERAP on the efficiency of presentation of known HLA-B*57:01 restricted peptides in the presence or absence of ABC.
3. To explore whether ERAP allotypes correlate with lower viral load in HIV infected individuals with protective HLA alleles.

Methods: This project will utilise a range of molecular and cellular immunology techniques including PCR, sequencing, CRISPR technology, site-directed mutagenesis, western blotting, ELISpot and flow cytometry.

Importance: Understanding the mechanisms driving immunologically mediated adverse drug reactions (ADRs) will be key to the development of future predictive and preventive strategies. Furthermore, knowledge of the role of HLA-ERAP on HIV control will assist in a better understanding of the immunopathogenesis of HIV. This will be important for future aid research in personalised approaches to HIV vaccine design and/or HIV eradication strategies.

References:

1. Hattori A, et al. Journal of biochemistry. 2013;154(3):219-28.
2. Mallal S, et al. N Engl J Med. 2008;358(6):568-79.
3. Ostrov DA, et al. Proc Natl Acad Sci U S A. 2012;109(25):9959-64.
4. Fellay J, et al. Science. 2007;317(5840):944-7.
5. Altfeld M et al. Aids. 2003;17(18):2581-91.

Contact:

Dr Rebecca Pavlos
IIID, Murdoch University
r.pavlos@iiid.murdoch.edu.au

INVESTIGATING THE IMMUNOLOGICAL MECHANISMS OF INCLUSION BODY MYOSITIS

Research area/s:	Muscle Disease and Autoimmunity
Chief supervisor:	Professor Merrilee Needham
Other supervisors:	A/Professor Alec Redwood, Dr Rebecca Pavlos
Project suitable for:	PhD
Essential qualifications:	BSc
Start date:	Flexible

Project outline:

Background: Inclusion Body Myositis (IBM) is the most common acquired myopathy in patients over the age of 50 years, leading to progressive muscle loss and weakness. The biopsy demonstrates three major features; Inflammatory changes including cytotoxic lymphocytes invading non-necrotic fibres and pro-inflammatory changes including MHC-I upregulation and expression of chemokines and cytokines (e.g CCL-2, CCL-3, CCL-4, CXCL-9, IL-1b, TNF-a and TGF-b); Degenerative changes including vacuoles and accumulation of misfolded proteins including TDP-43, b-amyloid, phosphorylated tau; and mitochondrial changes.

Aims:

1. Detailed immunophenotyping of the inflammatory infiltrate in muscle tissue in IBM.
2. Isolation and functional characterization of T-cell clones from IBM muscle biopsies.
3. Investigate the reactivity of T cell clones against muscle-specific antigens.

Hypothesis: Activation of the immune system is vital for the development of this disease, and it is likely activated against a skeletal-muscle-specific protein.

Methods: This project will utilise a range of molecular and cellular immunology techniques including flow cytometry, and single cell T-cell Receptor sequencing and phenotyping.

Importance: A better understanding of the immunopathogenesis of IBM is necessary to develop more effective treatments.

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References:

1. Schmidt K, et al. Molecular treatment effects of alemtuzumab in skeletal muscles of patients with IBM. BMC Neurology 2016;16:48.
2. Dalakas MC. Review: An update on inflammatory and autoimmune myopathies. Neuropathology and Applied Neurobiology 2011:37;226-242.
3. Dalakas MC. The molecular and cellular pathology of inflammatory muscle disease. Curr Opinion in Pharmacol; 2001:300-30.

Contact:

Professor Merrilee Needham
Murdoch University
Merrilee.Needham@health.wa.gov.au

INVESTIGATION OF VIRAL RISK FACTORS FOR MULTIPLE SCLEROSIS

Research area/s:	Immunology, Genetics, Virology
Chief supervisors:	Dr Monika Tschochner
Other supervisors:	Dr David Nolan
Project suitable for:	1 Honours student & 1 Masters student
Essential qualifications:	BSc
Start date:	Earliest: November 2016, latest: March 2017

Project outline:

Background: Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system that affects about 20,000 Australians. Similar to other autoimmune diseases the exact cause of the disease is unknown but both a person's genetic makeup and the environment contribute to MS risk. In particular, associations between Epstein-Barr virus (EBV) infection and multiple sclerosis risk are strongly supported by epidemiological data.

Aims: This project seeks to provide new insights into the contribution of EBV infection to MS disease. We aim to investigate specific characteristics of EBV-infected B-cells in MS cases and controls, in particular the role of B lymphocytes as antigen-presenting cells in active and inactive MS disease and to investigate if alterations in B cell activation status and/or EBNA-1 expression are associated with disease activity. We also aim to study T cell immune responses to autologously-expressed EBNA-1 epitopes.

Methods: This project will involve a variety of immunological and genetic methods including Flow Cytometry, ELIspot assays, cell culture experiments, PCR and sequencing including new deep sequencing technology, confocal microscopy, Western Blots, ELISA and protein arrays.

Importance: Our investigations in particular aim to identify, understand and link different risk factors for MS and subsequently utilising these findings to improve diagnosis and development of novel therapeutic strategies that can be applied in clinical practice to improve patient outcome.

References:

1. Tschochner, M., Leary, S., Cooper, D., Strautins, K., Chopra, A., Clark, H., Choo, L., Dunn, D., James, I., Carroll, W.M., Kermode, A.G., Nolan, D. Identifying patient-specific Epstein-Barr Nuclear antigen-1 genetic variation and potential autoreactive targets relevant to multiple sclerosis pathogenesis. PLoS One 2016.
2. Strautins K, Tschochner M, James I, Choo L, Dunn DS, Pedrini M, Kermode A, Carroll W, Nolan D. Combining HLA-DR and anti-Epstein-Barr antibody profiles to stratify multiple sclerosis risk. Multiple Sclerosis Journal, 2014, Mar;20(3):286-94.
3. Nolan D, Castley A, Tschochner M, James I, Qiu W, Sayer D, Christiansen F, Witt C, Mastaglia F, Carroll W, Kermode A. Contributions of Vitamin D response elements and HLA promoters to multiple sclerosis risk. Neurology, 2012, Aug 7;79(6):538-46

Contact:
Dr Monika Tschochner
Murdoch University
m.tschochner@iiid.com.au

MECHANISMS OF ANTI-HMGCR ANTIBODIES IN NECROTISING AUTOIMMUNE MYOPATHY

Research area/s:	Muscle disease and autoimmunity
Chief supervisor:	Professor Merrilee Needham
Other supervisors:	A/Professor Alec Redwood, Dr Rebecca Pavlos
Project suitable for:	PhD
Essential qualifications:	BSc
Start date:	Flexible

Project outline:

Background: Necrotising Autoimmune Myopathy (NAM) is a serious and disabling immune-mediated muscle disease often associated with autoantibodies to the hydroxyl-methylglutaryl CoA receptor (HMGCR). This occurs in both statin-naïve patients and more commonly in statin-exposed patients. There is a known HLA association with HLA-DRB1*1101. However, the mechanisms of disease are poorly understood and the condition is often resistant to treatment.

Aims:

1. Establish the pathogenic role of the anti-HMGCR antibodies.
2. Elucidate the immunological mechanism of disease.

Hypothesis: The anti-HMGCR Antibodies have a pathogenic role and are causative of this immune-mediated myopathy.

Methods: In vitro cytotoxicity studies using high-titre anti-HMGCR sera; studies of role of complement, B cells and CD4 Th cells.

Importance: Working out the pathogenic mechanisms are vital for the development of specific treatments.

References:

1. Kassardjian CD, Lennon VA, Alfugham NB, Mahler M and Milone M. Clinical Features and Treatment Outcomes of Necrotizing Autoimmune Myopathy. JAMA Neurol. doi:10.1001/jamaneurol.2015.1207.
2. Andrew Mammen. Statin-associated Autoimmune Myopathy. NEJM 2016;374:664-9.

Contact:

Professor Merrilee Needham
Murdoch University
Merrilee.Needham@health.wa.gov.au

MEMORY NK CELLS FOR TUMOUR IMMUNOTHERAPY

Research area/s:	Tumour Immunology
Chief supervisor:	A/Professor Alec Redwood
Other supervisors:	Dr Scott Fisher
Project suitable for:	Honours, Masters or PhD
Essential qualifications:	BSc, (BSc plus honours for PhD)
Start date:	Flexible

Project outline:

Background: Tumour immunotherapy harnesses one's own immune response to fight cancer. Several drugs which target the immune system's 'molecular brakes' are now in use for a range of cancers[1]. This approach exploits the anti-cancer role of the acquired immune system, specifically CD8 T cells, which 'learn' to recognize cancer cells. Once these cells can recognize cancer cells they retain this capacity as memory cells. In contrast, natural killer (NK) cells—a component of innate immunity—are capable of killing cancer cells without prior education, however their capacity for memory is an area of contention. Murine cytomegalovirus (MCMV) encodes gene m157, which directly activates NK cells via activation receptor, Ly49H[2]. NK cells activated via this axis retain memory for Ly49H and exhibit enhanced killing function[3]. This project will determine if NK cells can kill tumour cells transfected with m157, using memory NK cells from mice infected with MCMV to determine if these are better at killing than cells from uninfected mice. Finally, as some alleles of m157 bind NK cell inhibitory receptors, we will determine if cancer cells expressing suppressive m157 variants are protected from NK cell mediated killing, and if this is exacerbated whether the NK cells acquire memory via inhibitory receptors. These studies will help identify features of memory NK cells required for effective cancer immunotherapy.

Aims: (1) To produce stable tumour cell lines that express the viral protein m157; (2) To test the capacity of these stable cell lines to induce tumours in C57BL/6 mice; (3) To determine if memory NK cell raised during MCMV infection inhibit tumour growth.

Methods: (1) Molecular biology to produce plasmids expressing variants of m157 genes that target NK cell activation receptors (Ly49H) or inhibitory receptors; (2) Cellular techniques to produce stable cell lines from tumours transfected with the m157 expression plasmids; (3) Animal experiments performed to determine if stably transfected cells establish tumours; (4) Virus work to produce memory NK cells for adoptive transfer into tumour bearing mice.

Importance: Immunotherapy is gaining traction as a viable alternative to traditional anti-cancer therapies. However a proportion of patients treated with immune checkpoint inhibition fail to respond to treatment. Therefore other forms of immunotherapy, relying on the innate immune system, may provide additional options for patients. This study seeks to determine if memory NK cells can be harnessed in a model system. This system will allow us to identify which features of NK cell memory will be required for effective use in patients.

References: 1. Steven A, et al. Immunotherapy for lung cancer. Respirology. 2016;21(5).
2. Redwood AJ, et al. Murine and other nonprimate cytomegaloviruses. In: Mahy BWJ, Van Regenmortel MHV, eds. Encyclopedia of Virology 1. 3rd ed. Oxford: Elsevier; 2008.
3. Sun JC, et al. Adaptive immune features of natural killer cells. Nature. 2009;457(7229).

Contact: A/Professor Alec Redwood
Murdoch University
a.redwood@iiid.com.au

NEUROCOGNITIVE HEALTH & QUALITY OF LIFE FOR PEOPLE LIVING LONG-TERM WITH HIV (PLWH)

Research area/s:	Health Sciences, Psychology
Supervisors:	Dr Vance Locke, Dr Helen Correia and Dr Susan Herrmann
Project suitable for:	Masters or PhD
Essential qualifications:	BSc
Start date:	End 2016, first semester 2017

Project outline:

Background: Maintaining quality of life in the setting of HIV is a key component of clinical care and diminished cognitive function can affect quality of life directly and indirectly. Between 15% and 50% of people affected by HIV are reported to experience cognitive impairment (NCI), however testing is not routine and impairment may go undetected and/or be confounded by psychosocial stressors including stigma-associated depression. There is a need to develop evidence based interventions specifically tailored for PLWH to optimise mental health outcomes.

Aims: To develop a psychological intervention designed to support patients with or at risk of cognitive impairment**.**

Methods: The successful candidate will work in a multidisciplinary team and directly with patients. Both qualitative and quantitative research methods will be used to analyse data, in our hands, from a contemporaneous longitudinal study. There will also be an opportunity to work with the team researching, developing and evaluating a patient-centred digital communication tool.

Importance: Maintaining cognitive function is critical for managing health and optimum lifestyle. In the setting of HIV, the effects of impaired cognitive functioning take on a particular relevance affecting critical medication adherence and other healthful behaviours. Developing targeted psychological interventions and supportive therapies will be key to maintaining health-related quality of life long-term.

References:

1. Heaton RK, et al. The impact of HIV-associated neuropsychological impairment on everyday functioning. J Int Neuropsych Soc. 2004;10(3):317-31.
2. Blashill, et al. Mental Health: A Focus on Stress, Coping, and Mental Illness as it Relates to Treatment Retention, Adherence, and Other Health Outcomes. Current HIV/AIDS Reports. 2011 8(4), 215-222.
3. Woods SP, et al. Timing is everything: antiretroviral nonadherence is associated with impairment in time-based prospective memory. J Int Neuropsych Soc. 2009;15(1):42-52.

Contact:

Dr Susan Herrmann
Murdoch University
s.herrmann@iiid.murdoch.edu.au

TARGET-SPECIFIC B CELLS AND DERIVED ANTIBODIES AGAINST THE HUMAN HEPATITIS C VIRUS

Research area/s:	Identification of functional B cells and derived antibodies against the Human Hepatitis C Virus
Supervisors:	A/Professor Mark Watson and Dr Abha Chopra
Project suitable for:	Honours
Essential qualifications:	BSc
Start date:	Start or Mid Semester

Project outline:

Background: Hepatitis C virus (HCV) is a common notifiable infection that is a major economic burden for the health system in Australia and globally. Treatment failure occurs in 20 - 50% of cases leading to a chronic infection associated with progressive liver disease which can lead to liver cancer. If the liver fails, liver transplant is the only treatment but this almost inevitably results in HCV infection of the new liver due to persisting virus. In treatment of hepatitis B virus (HBV), passive therapy with HBV-specific antibody is used. However, this is not available for HCV as there is currently no vaccine. There are also technical limitations in working with HCV whereby the virus does not replicate in animals other than primates and until recently, could not be grown routinely in culture.

Antibody that neutralizes HCV infection would be useful therapeutically for: 1) preventing infection of grafted liver in the transplant group, 2) decreasing incidence of liver cirrhosis and liver cancer, and 3) prophylactic treatment for those at risk of person-to-person and blood-to-blood disease transmission. The gold standard therapeutic would consist of human immunoglobulins with strong activity against HCV even in those with immunosuppression. It would reduce viraemia, and cross react between viral genotypes without generating immune escape variants.

The goal of this application is to produce a panel of human monoclonal antibodies (MAbs) against HCV with formulation as cocktails for clinical use.

Aims: 1) To clone HCV reactive antibodies from the patients. 2) To identify target ligands for the antibodies and assess neutralization ability in vitro. 3) To use second generation sequencing technologies to sequence target antibodies for subcloning purposes.

Methods: PCR, RT PCR, DNA sequencing, Illumina, cell culture and viral neutralization assays, ELISA, molecular cloning, antibody purification, and fluorescence microscopy.

Importance: While drugs for HCV are helping with treatment success there is still no effective vaccine for HCV. It is clear that antibody plays a key role in anti HCV immunity and clearance and has cross genotype neutralising activity. Understanding the target antigens and antibodies involved will help inform vaccine design and offer new therapies and diagnostic tools.

Contact:
A/Professor Mark Watson, Dr Abha Chopra
Murdoch University
labman@iiid.com.au

USE OF EVOLUTIONARY CONSERVATION TO INFORM HIV VACCINE DESIGN

Research area/s:	Infectious Disease, HIV
Chief supervisor:	A/Professor Mina John
Other supervisors:	A/Professor Silvana Gaudieri, Dr Abha Chopra
Project suitable for:	PhD
Essential qualifications:	BSc (Hons) 1st Class
Start date:	January 2017

Project outline:

Background: Therapeutic vaccination offers patients living with HIV infection the potential for their own immune systems to control their infection as an alternative to life-long, daily, expensive drug treatments. The success of such vaccination depends on the extent to which patients' virus has already escaped immune responses by mutation before drugs were started or even before transmission. We have mapped areas of HIV that have never mutated over many thousands of years of evolution from its animal ancestor viruses. We seek to test peptides containing these evolutionary conserved areas that are resistant to mutation as being good targets for the immune system.

Aims:
1. Generate HIV-1 Gag, Pol-derived peptides optimized for EvC and overlapping peptides based on full length proteins as controls.
2. Compare phenotype and specificity of epitope-specific responses stimulated by EvC peptides versus full length control peptides using PBMC derived from HIV-infected individuals.

Methods: We will test whether EvC-optimised epitopes will be more functionally effective compared with standard epitopes in an in-vitro system using PBMC derived from treated, aviremic individuals. We will use next generation deep sequencing of single T cell mRNA on the nextSeq Illumina platform to determine molecular phenotype of single epitope-specific responses.

Importance: An EvC immunogen could deliver the dual objectives of a vaccine that is resistant to viral escape and highly immunogenic. This design approach is novel and not incorporated into existing conserved preventative vaccine candidates in preclinical and clinical development. The approach is well suited to therapeutic vaccines where induction of strong CD8 T cell immunity is requisite for control, and if associated with successful therapeutic vaccination may help expedite the pathway to HIV eradication or functional cure.

References:

1. Stephenson KE et al. J Virol. 2012, 86(21):11434-40.
2. Carlson J et al. Nat Med. 2016, 22; 606–613.
3. Keane NM et al. Immunol Cell Biol 2012;90:224-234.
4. Almeida CA et al. J Immunol 2011;187;2502-2513.
5. Brockman M et al. J, Virol 2010, 84, No. 22; 11937–11949.

Contact:

Dr Abha Chopra
Murdoch University
a.chopra@iiid.murdoch.edu.au