



DEAKIN
UNIVERSITY AUSTRALIA

MELBOURNE GEELONG WARRNAMBOOL

School of Medicine

RESEARCH PROJECTS &
INFORMATION FOR PROSPECTIVE STUDENTS
2012
HONOURS, MASTERS, PHD

| GEELONG WAURN PONDS CAMPUS |

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Information for prospective Honours students

An overview of the Honours program H413

The Honours program in the School of Medicine is designed to build upon the skills and knowledge obtained from the completion of a three year undergraduate degree. The program aims to provide students with the opportunity to pursue an independent investigative research project in the areas of health and medicine along with relevant course work. This will enable students to expand their depth of knowledge in their chosen research area and provide a suitable qualification for entry into a higher degree by research program (Masters or PhD).

The School of Medicine program is a Type A Honours Degree, leading to award of a Bachelor of Health and Medical Sciences (Honours) (course code H413). This program, which comprises both coursework units and a research thesis, is undertaken over one year full-time. Each student is allocated a primary research supervisor and in some circumstances a co-supervisor.

Entrance requirements

- An undergraduate degree appropriate to the area of study from any Australian University or international equivalent.
- At minimum, 65% average for the 3rd year of undergraduate study.
- Availability of an appropriate supervisor with adequate resources to support the research project.

Course Structure of H413

The course comprises three Units, worth a total of eight credit points to be taken over one year of full-time study. The requirements include: an independent research project/thesis worth four credit points conducted under the supervision of the nominated supervisor for that project, a two credit point unit in research methods, and a two credit point unit in developing research skills in health and medical sciences. The course will be structured in the following way:

HM401: Developing Research Skills	2 credit points (Trimester 1)
HBS400: Research methods	2 credit points (Trimester 1)
HM402: Honours Research Project	4 credit points (Trimester 2)

HM401: This Unit will provide you with a thorough understanding of your research field through the generation of a research proposal whilst at the same time helping you to

develop skills essential to research, including online literature searching, presentation skills and critical analysis of literature. Assessment involves the development of a research proposal, the completion of a literature review and an oral presentation of the research findings prior to submission of the thesis.

HBS400: This is a Faculty-wide Unit comprised of a series of modules, in which the students must complete a required number of modules. Students select modules that are the most relevant to their project and in areas in which they require support. All modules are completed and assessed in Trimester 1.

HMH402: This Unit involves the implementation of the research project. While the enrolment is in Trimester 2, students will actually commence their research project in Trimester 1. The assessment for this Unit is writing up the research up in a thesis format that includes a literature review, research methodologies, research results and a discussion of the findings. The literature review (which is undertaken as part of HMH401) will be only assessed in relation to the relevance to the project and the hypothesis and aims.

- Developing Research Skills Trimester 1 2 credit points
- Research Methods Trimester 1 2 credit points
- Research Project/Thesis Trimester 2 4 credit points

The Honours year is an exciting year because it provides the first real opportunity to get a feel for research and students develop a wide range of research and problem-solving skills. However, students should be aware that this year is a challenging and demanding year, involving at least 35 hours per week of study and/or research work.

Honours Scholarships

Commencing Honours students are eligible to apply for merit-based Scholarships to the value of \$1,000 and \$2,000.

Contact details

For further information please contact the Honours coordinator:

Dr John Stambas
Phone: (03) 52275740
Fax: (03)52275555
Email: john.stambas@deakin.edu.au

Applying for Honours

To apply for Honours in the School of Medicine please follow the steps below:

1. Select a research project

Examine the list of research projects that the school is offering for 2012. For those projects that you are interested in, you must personally contact the named supervisor to discuss the proposed project. The supervisors contact details are provided together with the project description. This will enable you to gauge whether the research project aligns with your career goals, and enables the supervisor to establish whether you have the appropriate academic background to undertake and complete the research project.

2. Complete the project preference form

This form is provided in this booklet. Either hand in to the School of Medicine reception staff, or alternatively fax (03-5227 2945) or post to Lili Smilevski, Admission and Selection Coordinator (School of Medicine, Deakin University, Locked Bag 20000 Geelong, Vic. 3220) by **November 18, 2011**. This form MUST be filled out so that projects can be allocated to students based on the criteria outlined below.

3. Submit an on-line application

All prospective honours students MUST also apply directly to Deakin University. Submit an online application at <http://applicantportal.deakin.edu.au/connect/webconnect>. Closing dates for applications is **November 18, 2011**.

- You will need to register as a user in order to apply. Select the 'Register' link to activate a username and password to gain entry to the online application. NOTE: Current Deakin students – your Deakin username and password will not gain you access to the online application.
- Complete all of the questions on the online application. NOTE: Referee details are not required
- Complete the final step **ONLY** if your undergraduate studies were **NOT** undertaken at Deakin University. This final step requires applicants to upload scanned and certified copies of their University academic transcript(s).

4. Project allocation

Students will be allocated a project based on a combination of student preferences, supervisor's student preferences and the student's weighted average mark (WAM) of 3rd year. Successful candidates will be advised of their offer during end Nov-early Dec 2011.

The projects on offer within the School of Medicine reflect the expertise and research that is currently undertaken by the prospective supervisors at Deakin and at our affiliate institutes. It must be noted that due to the nature of research, the focus and direction of a research group may change over time and the final project may not necessarily be exactly as described.

**Please refer to the website for any further information on Honours in the School of
Medicine: <http://www.deakin.edu.au/hmnbs/medicine/research/research-projects>**

2012 Honours Project Preference Form

Your name: _____

Address: _____

_____ Postcode _____

Contact Phone Numbers: Mob _____

Home _____

Email: _____ Deakin student ID: _____

Applicants are advised that allocation to research projects is a competitive process and an applicant cannot be assured of being assigned to their choice of research projects.

Please nominate below three preferences, in order, for an Honours project (and supervisor) for 2012 from the list of projects on offer.

1st preference - Project number: _____

Project title: _____

Supervisor: _____

Have you personally spoken with the supervisor about the project? Yes No

2nd preference - Project number: _____

Project title: _____

Supervisor: _____

Have you personally spoken with the supervisor about the project? Yes No

3rd preference - Project number: _____

Project title: _____

Supervisor: _____

Have you personally spoken with the supervisor about the project? Yes No

If you are NOT offered one of the above projects would you consider an offer of an Honours project in a related area? Yes No

Please hand this form in to the School of Medicine reception staff, or alternatively fax (03-5227 2945) or post to Lili Smilevski, Admission and Selection Coordinator (School of Medicine, Deakin University, Locked Bag 20000, Geelong, Vic 3220) by November 18, 2011 for timely applications. In some circumstances, late applications will be considered depending on availability of appropriate supervisors, projects and places up until January 31, 2012.

Doctor of Philosophy and Master by Research

The key to entry (besides meeting entry qualifications) into a PhD or Masters by Research program is the support of a School of Medicine staff member to supervise you. It is essential, therefore, that you discuss your application for one of the listed projects with the relevant supervisor(s) prior to applying. Note the application form requires an applicant to provide a one page outline of their proposed research program.

Applying

Applications for candidature are accepted at **any time**; however for applicants seeking scholarships please note the appropriate closing dates shown below. With the support of a supervisor, submit an application.

The application and scholarship process for Australian and New Zealand Citizens and Australian Permanent Residents can be found at: www.deakin.edu.au/current-students/research/forms-and-guidelines. Applications for scholarships close at the end of **June** and **October** each year.

The application and scholarship process for International applicants can be found at: www.deakin.edu.au/internationalisation/hdr. Applications for scholarships from International students close at the end of **June** and **September** each year.

Top-Up Scholarships

Commencing PhD students who have been awarded a Scholarship are eligible to apply for a one-off Top-Up Scholarship of \$5,000 based on merit.

Index of projects for 2012

METABOLISM & MUSCLE BIOLOGY

1. The effects of nitric oxide on the extracellular matrix during repair of skeletal muscle injury

Supervisors: Nicole Stupka, Dan McCulloch and Liz Liberts

Location: Metabolic Research Unit, School of Medicine, Deakin University, Geelong Waurin Ponds Campus

Project Description:

Following skeletal muscle injury there is degeneration of damaged tissue and inflammation, followed by activation of muscle stem cells and regeneration. Nitric oxide signalling is thought to have an important role in inflammation and activation of muscle stem cells (satellite cells). For muscle repair to be successful, fibrosis and scar tissue formation need to be limited so that functional skeletal muscle mass is maintained. However, with severe trauma, muscular dystrophy and aging, fibrosis can exceed repair leading to dysfunction.

The balance between muscle repair and fibrosis is largely regulated by the extracellular matrix (connective tissue) surrounding muscle fibres. There is emerging evidence that nitric oxide is also very important in regulating extracellular matrix function and remodelling during regeneration.

Using cell and mouse models, this project will investigate the role of nitric oxide has on activating key enzymes involved in extracellular matrix remodelling (for example, “ADAMTS”) and the implications of this on skeletal muscle repair.

Summary of techniques to be used:

- Cell culture
- Transfection and lentivirus over-expression
- Real-time PCR and western blotting for gene and protein expression
- Nitric Oxide and Oxidative stress assays with fluorescent probes in living cells
- Cell viability assays using flow cytometry or fluorescent microscopy
- Seahorse Bioscience XF Analyzer measurement of mitochondrial function and cell metabolism

Contact details of supervisors:

Dr. Nicole Stupka (Deakin Medical School): nstupka@deakin.edu.au 5227 1360

Dr. Dan McCulloch (Deakin Medical School): daniel.mcculloch@deakin.edu.au 5227 2838

Dr. Liz Liberts (Deakin School of Exercise and Nutrition Sciences):
liz.liberts@deakin.edu.au 52272631

2. Examining mechanisms of skeletal muscle regeneration in muscular dystrophy

Supervisors: Daniel McCulloch and Nicole Stupka

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurn Ponds Campus

Project description:

Newborns with muscular dystrophy begin life with a debilitating disease, the symptoms of which rapidly exacerbate as they approach their teenage years. The most common form of muscular dystrophy is Duchenne muscular dystrophy (DMD), affecting ~1:3500 boys. Patients with DMD are wheelchair bound by 12-15 years of age and die of respiratory or cardiac muscle failure in their early thirties. Muscle damage and its inadequate repair leads to fibrosis and atrophy in children with muscular dystrophy. The balance between muscle repair and fibrosis is largely regulated by the extracellular matrix (connective tissue) surrounding muscle fibres. Using cell, zebrafish and mouse models, this Project will investigate the role of extracellular matrix enzymes called “ADAMTS” in promoting muscle development and repair, and assess their use as therapeutic agents to improve muscle health in muscular dystrophy.

Summary of techniques to be used:

Cell culture (*in vitro* muscle development):

- Examining molecular interactions between cells and their external environment.

Construction of mammalian lentiviral delivery systems:

- Over express and/or silence genes of interest in cell culture and animal models using state of the art gene delivery/therapy techniques.

Animal models of muscular dystrophy:

- The use of established mouse and zebrafish models to define *in vivo* mechanisms of muscle development and regeneration.

Contact details of supervisor:

Dr. Daniel McCulloch (Deakin Medical School): daniel.mcculloch@deakin.edu.au 5227 2838

3. Role of the antioxidant protein SEPS1 in skeletal muscle health

Supervisors: Ken Walder, Nicole Stupka

Location: Metabolic Research Unit, School of Medicine, Deakin University, Geelong Waurm Ponds Campus

Project Description:

Type 2 diabetes (T2D) exacerbates muscle mass loss with ageing leading to frailty and poor quality of life. In diabetic muscle excess nutrients, especially excess free fatty acids, increase cellular stress and compromise metabolism and repair following injury. Both are crucial for optimal muscle function.

SEPS1 is selenoprotein which was discovered at the Metabolic Research Unit and found to be implicated in the development of T2D. We hypothesize that SEPS1 can protect skeletal muscle cells from oxidative and ER stress. In this project we will investigate the effect of upregulating SEPS1 has on skeletal muscle glucose metabolism and repair processes using relevant cell culture models.

We have shown that muscle cells increase SEPS1 levels in response to elevated fatty acid concentrations, probably as a protective strategy against metabolic stress. We are interested in investigating the underlying cellular mechanisms by which SEPS1 protects cells against oxidative and ER stress and whether over-expression of SEPS1 improves cellular function following metabolic stress.

In this project, levels of SEPS1 will increased in the cultured skeletal muscle using a lentivirus over-expression system. The effects of altering SEPS1 levels on cellular sensitivity to fatty acids will be determined by measuring oxidative and ER stress responses, cell viability, differentiation, insulin and glucose responsiveness, and mitochondrial function. All of these techniques are conducted regularly in our laboratories. The results of these studies will help to determine whether modulating the levels/activity of SEPS1 is a viable strategy for the development of new ways to treat patients with diabetes.

Summary of techniques to be used:

- Cell culture (skeletal muscle or β -cells)
- Transfection and lentivirus over-expression
- Real-time PCR and western blotting for gene and protein expression
- Oxidative stress assays with fluorescent probes in living cells
- Cell viability assays using flow cytometry or fluorescent microscopy
- Seahorse Bioscience XF Analyzer measurement of mitochondrial function and cell metabolism

Contact details of supervisors:

Dr. Nicole Stupka (Deakin Medical School): nstupka@deakin.edu.au 5227 1360

Prof. Ken Walder (Deakin Medical School): ken.walder@deakin.edu.au 5227 2883

4. Functional analysis of new candidate proteins in Type 2 diabetes

Supervisors: Nicky Konstantopoulos and Kelly Windmill

Location: Metabolic Research Unit, School of Medicine, Deakin University, Geelong Waurin Ponds Campus

Project description:

Impairment of insulin action leads to type 2 diabetes. However, there are multiple and redundant metabolic pathways that control the actions of insulin. The incidence of type 2 diabetes is still rising worldwide and there is a critical need to characterise new proteins involved in the development of type 2 diabetes in order to help in the long-term prevention of this disease and/or provide alternative targets for additional therapeutic approaches. This project will focus on how novel candidate proteins that have been identified at the Metabolic Research Unit impact insulin action by suppressing their endogenous expression levels in fat, liver and/or muscle cells using a powerful approach known as RNA interference (RNAi). The consequences of this protein knock down on insulin action will be assessed by a range of biochemical approaches. Effects on insulin action will be determined by examination of the phosphorylation status of key insulin sensitive proteins and regulation of glucose and lipid metabolism using enzymatic and metabolic bioassays. This study will determine if the candidate protein is involved in insulin action, obesity and type 2 diabetes.

Summary of techniques to be used:

Techniques such as the design and generation of RNAi molecules and/or shRNA plasmids, mammalian cell culture, gene expression manipulation by RNAi or overexpression systems using transient transfection and/or retroviral or lentiviral infection of cells, RNA and protein extraction, real-time PCR, immunoprecipitation, SDS-gel electrophoresis and immunoblotting, promoter transactivation, protein-protein interactions and metabolic assays to measure glucose transport, glucose production and glycogen synthesis will also be used.

Contact details of supervisor:

Dr. Nicky Konstantopoulos (Deakin Medical School): nickyk@deakin.edu.au 5227 2513

5. Effects of exercise on skeletal muscle metabolism in Israeli sand rats (*Psammomys obesus*)

Supervisors: Ken Walder and Sean McGee

Location: Metabolic Research Unit, School of Medicine, Deakin University, Geelong Waurin Ponds Campus

Project description:

Type 2 diabetes is one of the major health problems facing Australia today, and insulin resistance in skeletal muscle is a significant factor in the development of this disease. Exercise programs, in combination with dietary manipulation, can alleviate insulin resistance and eradicate type 2 diabetes in some, but not all patients. Therefore we need a better understanding of the effects of exercise training on skeletal muscle to enhance our ability to successfully manage type 2 diabetes, and develop new therapeutic approaches. Israeli sand rats are a unique animal model of the metabolic syndrome. In the wild, these animals remain lean and healthy, but when housed in the laboratory and fed a normal (low fat) rodent diet, a proportion of sand rats develop obesity, insulin resistance and type 2 diabetes. Previous studies in our laboratory have shown that either dietary restriction or exercise training can ameliorate insulin resistance and diabetes in these animals. In this study, we will investigate the effects of both acute exercise bouts at different intensity levels, and longer exercise training regimes on metabolic disease in sand rats. These studies will reveal the mechanisms involved in the development and resolution of insulin resistance and type 2 diabetes, and highlight the most appropriate exercise approaches to maximize health benefits for patients.

Summary of techniques to be used:

- Exercise training in animals
- Indirect calorimetry
- RNA extraction and purification from skeletal muscle samples
- Real-time PCR for measurement of gene expression
- Western blotting for measurement of protein expression
- Seahorse analysis of mitochondrial function

Contact details of supervisors:

Prof. Ken Walder (Deakin Medical School): ken.walder@deakin.edu.au 5227 2883

Dr. Sean McGee (Deakin Medical School): sean.mcgee@deakin.edu.au 5227 2519

6. You are what your mother (or grandmother) ate: Dietary epigenetic effects in Israeli sand rats (*Psammomys obesus*)

Supervisors: Ken Walder and Sean McGee

Location: Metabolic Research Unit, School of Medicine, Deakin University, Geelong Waurin Ponds Campus

Project description:

There has been much recent interest in the role of the maternal diet during pregnancy on susceptibility to metabolic disease in the offspring. Several recent studies have shown that changes in the transcriptional activity of DNA can produce sustained metabolic adaptations. Within key tissues such as hypothalamus, adipose tissue, skeletal muscle and liver, metabolic function in offspring can be affected by alteration to the maternal diet via modulation of DNA methylation and histone acetylation, which suggests epigenetic programming. In this project, we will utilize a unique animal model of metabolic disease, the Israeli sand rat, to investigate how changing the maternal diet affects metabolic function in the offspring, and we will use cutting edge methods to assess genome wide methylation and gene expression in tissues of interest. These studies will provide new information on the effects of maternal diet on long term consequences for the offspring, and will highlight key genomic regions, genes and pathways that mediate these effects.

Summary of techniques to be used:

- Animal husbandry and manipulation of diet
- RNA extraction and purification from tissue samples
- Genome-wide gene expression profiling
- Real-time PCR for measurement of gene expression
- Genome-wide DNA methylation profiling
- Bisulphite sequencing
- Bioinformatics analysis of large datasets

Contact details of supervisors:

Prof. Ken Walder (Deakin Medical School): ken.walder@deakin.edu.au 5227 2883

Dr. Sean McGee (Deakin Medical School): sean.mcgee@deakin.edu.au 5227 2519

7. Pancreatic beta-cell regeneration: fishing for a diabetes cure

Supervisors: Yann Gibert, Ken Walder and Alister Ward

Location: Metabolic Research Unit, School of Medicine, Deakin University, Geelong Waurm Ponds Campus

Project description:

Diabetes is a major health problem in Australia and around the world, with an estimated 250 million people suffering from the disease around the world, including 3 million Australians. A key factor in the development of diabetes is insufficient production of insulin, due to depletion of beta-cells, resulting in hyperglycemia and the need for lifelong insulin therapy. One of the current strategies to cure diabetes is the restoration of beta-cells, which in mammals are not capable of self-regeneration. However, the zebrafish pancreas has the ability to self-regenerate, although the genetic basis of this regeneration is still unknown. In preliminary studies, we have identified a number of genes that may be involved in pancreatic beta-cell regeneration in zebrafish, but their role in the mammalian pancreas has not been investigated. In this project we will characterize the precise physiological role of these candidate genes during pancreas regeneration. Furthermore, the genes identified in the zebrafish will be validated in a mammalian system to confirm their potential as therapeutic targets for diabetes in humans.

Summary of techniques to be used:

- Pharmacological manipulation of pathways of interest in developing zebrafish.
- Generation of inducible gain- or loss-of-function zebrafish mutants.
- Phenotypic characterization, including flow cytometry, immunohistochemistry, in situ hybridization
- Microarray analysis

Contact details of supervisors:

Dr. Yann Gibert (Deakin Medical School): yann.gibert64@gmail.com 5227 2547

Prof. Ken Walder (Deakin Medical School): ken.walder@deakin.edu.au 5227 2883

Prof. Alister Ward (Deakin Medical School): alister.ward@deakin.edu.au 5227 2041

8. The role of mitochondria in the development of type 2 diabetes

Supervisor: Sean McGee

Location: Metabolic Research Unit, School of Medicine, Deakin University, Geelong Waurin Ponds Campus

Project description:

The incidence of type 2 diabetes is rapidly increasing and it currently contributes to approximately 10% of all deaths worldwide. The development of type 2 diabetes involves impaired metabolism in tissues such as skeletal muscle and the liver. Impaired mitochondrial function is thought to contribute to this response. However, the exact mechanisms remain controversial. This project will use cell culture models with state of the art equipment that can examine mitochondrial function, to closely examine the relationship between mitochondria and the processes that are involved in the development of type 2 diabetes. These studies will uncover new mechanisms involved in the development of type 2 diabetes.

Summary of techniques to be used:

- Genetic manipulation of cells
- Seahorse analysis of mitochondrial function
- Analysis of insulin action
- RNA extraction and purification
- Real-time PCR for measurement of gene expression
- Western blotting for measurement of protein expression

Contact details of supervisor:

Dr. Sean McGee (Deakin Medical School): sean.mcgee@deakin.edu.au 5227 2519

INFECTION & IMMUNITY

9. Prevalence of Rickettsial bacteria in Australian ticks

Supervisors: John Stenos, Yazid Abdad and Stephen Graves

Location: The Australian Rickettsial Reference Laboratory, Barwon Health, Geelong

Project description:

Rickettsial organisms are Gram-negative obligate intracellular bacteria that are pathogenic to both humans and animals. Transmission of the organism is via ectoparasites, most commonly by Ixodid ticks. Understanding the prevalence of rickettsial organisms in their vectors will give scientists and medical professionals i) a better understanding of the risk of contracting a rickettsial disease, ii) identify areas endemic with rickettsiae and make it a part of differential diagnosis and iii) formulate effective preventative and treatment regimens specific to the genus/species most prevalent. Recent decades have seen a surge of rickettsial organisms Australia-wide. As more people venture into the bush and outback for occupational and recreational activities, the risk of rickettsial organisms to human and animal health need investigation to determine the risk of rickettsial disease.

Summary of techniques to be used:

Successful Honours student selected to be a part of the study will be trained in

- i) rickettsial diagnostics utilising qualitative PCR and serology,
- ii) isolation and maintenance of rickettsial organisms in cell culture,
- iii) cloning of gene sequences for species identification, and
- iv) speciation of ectoparasites.

Outstanding performance may lead to a PhD project upon completion. A PhD project is available and the successful candidate is expected to have good basic molecular knowledge. Other aspects of the project may involve methods in immunology, epidemiology, acarology and entomology, which will include training in speciation of ectoparasites, diagnosis of rickettsial diseases by qPCR and serology, and possible field work. Direction of any PhD projects will be tailored to suit successful candidates to exploit their strengths and personal research interests.

Contact details of supervisors:

John Stenos (Barwon Health): johns@barwonhealth.org.au 5226 7552

Yazid Abdad (Barwon Health): myazid@barwonhealth.org.au 5226 7121

10. The bubble fish: modelling severe combined immunodeficiency in zebrafish

Supervisors: Clifford Liongue and Alister C. Ward

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurn Ponds Campus

Project description:

Adaptive immunity is an integral component of host defence that relies on the group of white blood cells called lymphocytes. Therefore, the generation and maintenance of lymphocytes is an important aspect of combating pathogens. This is controlled by specific cell-cell signals mediated by proteins called cytokines, particularly the interleukin-2 family. Defects in these signals, such as mutation of the interleukin-2 receptor or the downstream Jak3 kinase, lead to severe combined immunodeficiency (SCID), characterised by a significant reduction in lymphocytes. “Bubble boy” syndrome describes one class of SCID patients, who need to be kept in sterile conditions due to their impaired immune system and increased susceptibility to infections.

We have recently identified the zebrafish interleukin-2 receptor signalling components. This Project will utilise the zebrafish animal model to explore the function of these components to gain insight into their contribution to adaptive immunity and to establish a “bubble fish” model of SCID for future therapeutic development.

Summary of techniques to be used:

This Project will employ a range of cell and molecular biology approaches utilising zebrafish as developmental model. These will include gene expression analysis using whole mount in situ hybridisation and RT-PCR, gene knockdown/knockout approaches, and detailed functional and phenotypic analysis.

Contact details of supervisors:

Dr. Clifford Liongue (Deakin Medical School): c.liongue@deakin.edu.au 5227 3071

Prof. Alister C. Ward (Deakin Medical School): award@deakin.edu.au 0401 153 277

11. Studies of anti-viral immunity in genetically modified zebrafish

Supervisors: Tim Doran, Alister C. Ward, Clifford Liongue and Mark Tizard

Location: CSIRO (Australian Animal Health Laboratory), Geelong and Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurn Ponds Campus

Project Description:

Zebrafish are an excellent model in which to study the role of genes in complex biological processes, such as the immune response to disease. Recent advances in technology, such as the use of zinc finger nucleases (ZFNs), have enabled the precise genetic modification of animal genomes. The Ward laboratory has considerable experience in applying these technologies in the zebrafish to generate modified animals, while the Gene Modulation Group at the Australian Animal Health Laboratory has expertise in the use of RNAi and microRNA to control viral disease in transgenic animals.

This collaborative Project between the Ward laboratory and the Gene Modulation Group will use ZFN technology to knock out microRNA genes in zebrafish and study their impact on immune cell function and their role in anti-viral immune responses. This will have major implication in understanding the role of these important molecules in anti-viral immunity in both humans and in livestock species.

Summary of techniques to be used:

Generation, characterization and maintenance of transgenic zebrafish using zinc finger nuclease technology, and phenotypic analysis via Real-time PCR, immunological assays and viral infection models

Contact details of supervisors:

Prof. Tim Doran (CSIRO – AAHL): timothy.droan@csiro.au 5227 5788

Prof. Alister C. Ward (Deakin Medical School): award@deakin.edu.au 0401 153 277

Dr. Clifford Liongue (Deakin Medical School): c.liongue@deakin.edu.au 5227 3071

Dr. Mark Tizard (CSIRO – AAHL): mark.tizard@csiro.au 5227 5753

12. Development of a novel zebrafish model to investigate the extra gastric effects of *Helicobacter pylori* infection

Supervisors: Melanie Thomson and Alister C. Ward

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurn Ponds Campus

Project description:

The direct consequences of a gastric colonisation of the bacterial pathogen *Helicobacter pylori* are well described, and include stomach ulcers and gastric cancer. However, clinical epidemiological evidence has implicated *H. pylori* infection with range of extra gastric diseases, most notably with iron deficiency anemia. Preliminary studies in rodent models suggest that chronic gastric *Helicobacter* infection can lead to a systemic change in iron metabolism regulation in the host.

The aim of this Project is to develop a novel model of *Helicobacter* infection using zebrafish (*Danio rerio*) to investigate the effects of infection on the molecular pathways of iron metabolism regulation in the host.

Summary of techniques to be used:

Bacterial culture and genetic manipulation of *Helicobacter pylori*, infection of zebrafish and subsequent phenotypic analysis, including gene expression studies.

Contact details of supervisors:

Dr. Melanie Thomson (Deakin Medical School): m.thomson@deakin.edu.au 5227 2722

Prof. Alister C. Ward (Deakin Medical School): award@deakin.edu.au 0401 153 277

13. Ross River virus infection: How does the *Culex annulirostris* mosquito respond?

Supervisors: Jean-Bernard Duchemin and Prasad Paradkar

Location: CSIRO (Australian Animal Health Laboratory), Geelong

Project description:

Culex annulirostris is a local vector of arboviruses, like Ross River virus (RRV) and Murray Valley encephalitis virus (MVEV). The recent intense weather conditions in Australia have resulted in a surge in activity of arboviruses infections of both livestock and humans and the appearance of Murray Valley encephalitis virus in Victoria and South Australia for the first time since 1974. Increased travel and trade, and climate change and associated extreme weather events, are presenting opportunities for viruses and vectors to invade new regions and for viruses to adapt to new vector species. How the virus could escape the natural immune systems of its poorly known. Mainly four immune pathways are known in insects: The Toll, the Imd (immune deficiency), the Janus kinase-signal transducer and activator of transcription (JAK-STAT) and the RNAi pathways.

Previous studies examining the innate immune response of fruitfly (*Drosophila*) to viral infections indicate that different viruses differentially activate the immune signaling pathways and thus different effector genes. This may suggest that the specific aspects of viral lifecycle may define the host response. The reason for this differential response is largely unknown.

This proposed study intends to understand and characterize the innate immune response of mosquitoes, to clinically significant Ross River virus infection. Live mosquito manipulations in addition to molecular biology approaches will be used to study the mosquito's responses and defenses against viral infections. Using dsRNA injections targeting specific genes in the known immune signaling pathways, significant immune responses during viral infections will be characterized. A better understanding of these responses and underlying mechanisms may lead to identification of factors responsible for vector competence. This knowledge, in turn will provide tools for prediction of viral emergence.

This project will study the immune response of *Culex annulirostris*, as a laboratory colonised vector, to challenging with Ross river virus. Each of the four pathways will be studied either by knock-down of one of the pathways effectors, making the vector more susceptible to infection or by silencing a negative regulator of each of the pathways, increasing the resistant phenotype of the vector. The phenotypes of the general immune response will be the infection load of insect organs and the downstream expression of effector proteins.

Summary of techniques to be used:

- Monitoring of a mosquito colony (*Culex annulirostris*)
- Infections of live mosquitoes
- *In-vivo* gene silencing in live mosquitoes
- Molecular biology: Cloning, overexpression
- qPCR

Contact details of supervisor:

Dr. Jean-Bernard Duchemin (CSIRO AAHL): Jean-Bernard.Duchemin@csiro.au 5227 5612

14.Improved molecular diagnosis of avian influenza viruses

Supervisor: Jianning Wang

Location: CSIRO (Australian Animal Health Laboratory), Geelong

Project description:

Devastating outbreaks of avian influenza in poultry as well as wild birds, caused by highly pathogenic avian influenza (HPAI) viruses (e.g. H5N1 virus), has been posing serious threats to animal and human health. The disease not only causes significant economical losses, but also leads to lethal infections in humans. Since pandemic influenza virus has its origins in avian influenza viruses, HPAI H5N1 virus has to be considered as a potentially serious pandemic threat. Control of the infection relies on rapid detection and identification of the causative virus strain. Currently, molecular diagnosis of HPAI is primarily conducted by real-time RT-PCR and conventional RT-PCR following sequence analysis of amplified products. The type specific real-time PCR can detect the subtype of the virus involved within a short time (hours), while pathogenicity determination (pathotyping) of the virus is only obtained from sequence analysis, which normally takes days. In the situation of disease outbreak, rapid and accurate diagnosis is crucial for disease control measures to be applied. In addition, analysis of large numbers of samples is required. The aim of this study is to establish improved molecular diagnostic assay(s) that can provide rapid detection and reliable identification of HPAI simultaneously, with high through-put capacity. Different PCR detection platforms including TaqMan probe based real-time PCR and high resolution melting analysis, as well as conventional PCR methods, will be investigated for rapid subtyping/pathotyping avian influenza viruses.

Summary of techniques to be used:

- Nucleotide isolation
- PCR, real-time PCR
- DNA Sequence analysis
- Virus isolation

Contact details of supervisor:

Dr. Jianning Wang (CSIRO AAHL): jianning.wang@csiro.au 5227 5431

15. Dissecting the function of essential malaria genes

Supervisor: Tania de Koning-Ward

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurin Ponds Campus

Project description:

Malaria remains one of the most devastating infectious diseases of humans and is caused by infection of the blood with unicellular *Plasmodium* parasites. *P. falciparum* is the most pathogenic malaria species, causing ~800,000 fatalities amongst the hundreds of millions of people that contract clinical malaria each year. Understanding the biology of the malaria parasite is crucial towards the rationale development of vaccines and drugs to target this deadly pathogen. Despite the fact that several *Plasmodium* genomes have been fully sequenced, almost one-half of the 5,500 predicted genes still lack characterized orthologues in other systems and thus we still know very little about the function of most proteins. Whilst reverse genetic approaches are often used to assign function to *Plasmodium*-specific genes, one of the obstacles in malaria research is that the most promising targets for vaccine and drug targeting are essential to parasite survival inside red blood cells and thus cannot be inactivated and characterized for function. Recently, a powerful new conditional gene knockout system has been developed for rodent malaria parasites that permits dissection of function of essential genes for the very first time. This project will be utilizing this latest technology to conditionally regulate the expression of several key malaria proteins predicted to be involved in the invasion of red blood cells and trafficking of virulence proteins. Resulting transgenic parasites will be analysed using a raft of biological assays to finally shed light on the function of these proteins.

Summary of techniques to be used:

Molecular biology (including PCR, cloning, sequencing, Southern blotting), parasite transfection, Western blotting, immunofluorescence and live cell imaging, growth assays, pathogenicity studies.

Contact details of supervisor:

Dr. Tania de Koning-Ward (Deakin Medical School): taniad@deakin.edu.au 5227 2923

16. Potential role of F glycoprotein cleavage in the pathogenesis of the deadly henipaviruses

Supervisors: Glenn Marsh and Linfa Wang

Location: CSIRO (Australian Animal Health Laboratory), Geelong

Project description:

Hendra and Nipah viruses are two deadly zoonotic bat-borne viruses for which no vaccines or therapeutics have been approved for human or livestock use. Several unique characteristics have resulted in these two viruses being classified in their own genus, Henipavirus. One of these unique characteristics is the cleavage of the inactive F glycoprotein into two active subunits, which for the henipaviruses requires a cellular enzyme cathepsin L. This project aims to identify the sequences of the F protein that are essential for cleavage and activation. An additional aim is to create mutant forms of the F protein that either have altered or no cleavage mechanisms, with an overall goal of understanding why these viruses have evolved to utilise this unique cleavage mechanism and whether change of the cleavage site will result in change in pathogenesis of these highly virulent viruses.

Summary of techniques to be used:

DNA cloning, site-directed mutagenesis, cell culture, transfection, Western blotting, immunofluorescence

Contact details of supervisors:

Dr. Glenn Marsh (CSIRO): glenn.marsh@csiro.au 5227 5125

Prof. Linfa Wang (CSIRO): linfa.wang@csiro.au 5227 5121

17. Role of ADAMTS7 in influenza virus infection

Supervisors: John Stambas and Dan McCulloch

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurin Ponds Campus

Project Description:

Influenza viruses are responsible for high rates of morbidity and mortality worldwide. Prophylaxis can be obtained through seasonal vaccination or via administration of antivirals (tamiflu or releanza) that target the neuraminidase expressed on the surface of the virus. Although effective use requires prior knowledge of circulating strains, a 6 month lag period for vaccine production and in the case of anti-virals lack of resistance, is required. Therefore, targeting the host may be a more effective method by which influenza epidemics and pandemics can be controlled prior to the vaccine production.

ADAMTS7, a recently discovered enzyme whose biological functions are largely uncharacterised, comprises several domains that undergo extensive post-translational modifications. Of particular interest to influenza biology is its so-called mucin domain whereby several attachment sites are predicted to be modified with sialic acid, and may be targeted by viral neuraminidases to mediate infection. Moreover, the importance of ADAMTS7 was recently discovered and validated following a novel siRNA screen of a human protease library where it was shown to play a pivotal role in controlling influenza virus replication. Subsequent cellular pathway analyses suggest that changes in ADAMTS7 expression influence inflammatory responses via the NF- κ B pathway.

Aims

To assess the contribution of ADAMTS7 to influenza immunity by:

- 1) Silencing ADAMTS7 *in vitro* using siRNA and measuring infectivity.
- 2) Over expressing wildtype ADAMTS7 and corresponding ADAMTS7 mucin domain deletion mutants and measuring infectivity.
- 3) Challenging ADAMTS7 knockout animals with influenza virus and characterising viral replication and immunity.

Summary of techniques to be used:

Gene silencing by siRNA or over-expression using mammalian expression constructs, confirmation of silencing or over-expression by immunodetection (western blotting), localization of ADAMTS7 expression by immunofluorescence microscopy, cell culture, virology (virus amplification, plaque assay, HA assays), flow cytometry, immunology (tetramer staining, intracellular cytokine staining, antibody ELISAs).

Contact details of supervisors:

Dr. John Stambas (Deakin Medical School & AAHL/CSIRO):

john.stambas@deakin.edu.au 5227 5740

Dr. Daniel McCulloch (Deakin Medical School): daniel.mcculloch@deakin.edu.au 5227 2838

18. Modulating Influenza virus immunity using miRNAs

Supervisors: John Stambas and Leonard Izzard

Location: CSIRO (Australian Animal Health Laboratory), Geelong

Project Description:

In 2009, the emergence of pandemic swine-origin H1N1 influenza virus highlighted to the scientific community and to governments worldwide, the ongoing, unpredictable and very real threat influenza viruses pose to human health. Improving current live vaccine strategies is critical to ensure adequate protection for future pandemics. This project will use cutting edge technology, known as reverse genetics to insert microRNA (miRNA) sequences into influenza viruses in order to regulate the physiological development of immune cell populations following infection. MiRNA are short RNA molecules ~18-22 nucleotides in length that regulate expression of many genes at a post-transcriptional level by inhibiting the translation of messenger RNA (mRNA) to protein. They achieve this by binding to mRNA through the RISC complex causing either degradation of the mRNA (if a perfect complementary sequence) or inhibition (if an imperfect complementary sequence). This regulation of gene expression is believed to be involved in the development and physiology of all eukaryotes. By inserting our miRNAs of interest (mir-21, mir-146a and mir-150) into the virus itself for delivery to the host, we aim to more efficiently eliminate virus following infection through the deliberate expansion of specific immune cell populations.

Aims

- 1) To generate influenza viruses expressing miRNAs using cutting edge reverse genetics technology
- 2) To assess influenza immunity in a mouse model following expression of our miRNA of interest.

Summary of techniques to be used:

Molecular biology, Influenza reverse genetics, virology, immunology, flow cytometry, tetramer staining, intracellular cytokine staining.

Contact details of supervisors:

Dr. John Stambas (Deakin Medical School & AAHL/CSIRO):

john.stambas@deakin.edu.au 5227 5740

Dr. Leonard Izzard (CSIRO): Lenny.Izzard@csiro.au 5227 5051

19. Generation of genetically engineered influenza viruses expressing malaria T and B cell epitopes for inducing immunity against malaria

Supervisors: Tania de Koning-Ward and John Stambas

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurn Ponds Campus

Project description:

Malaria is one of the world's major public health problems. It is caused by infection with parasites of the genus *Plasmodium*, of which *P. falciparum* infects an estimated 500 million people annually, resulting in at least 800,000 deaths. Resistance to anti-malarial drugs is very widespread and a licenced vaccine to prevent infection is still not available. There is now a growing realization of the limitations of recombinant-based malaria vaccines and subsequently alternate vaccine strategies are required. Previous experimental data indicates that recombinant live viruses can induce protective immunity against viral and bacterial infections. Thus, a recombinant live influenza virus expressing malaria epitopes might serve as an attractive delivery system as influenza vaccines are already mass-produced globally for human use, they are effective at stimulating the immune response and the virus can be genetically engineered by reverse genetics permitting the introduction of foreign epitopes and antigens. This research project aims to manipulate the genes of influenza viruses and introduce CD4+ T cell, CD8+ T cell and/or B cell epitopes of antigens present in different lifecycle stages of the malaria parasite to determine if the immune response of mice vaccinated intranasally with these engineered viruses can be stimulated. Subsequently, this project will also explore whether the lymphocytes generated following vaccination of the influenza virus are sufficient to prevent vaccinated mice from being infected with malaria parasites or whether vaccination of malaria-infected mice protects against severe malaria disease.

Summary of techniques to be used:

Molecular biology (including PCR, cloning, sequencing), reverse genetics, amplification of virus, infections studies in mice, flow cytometry, intracellular cytokine staining.

Contact details of supervisors:

Dr. Tania de Koning-Ward (Deakin Medical School): taniad@deakin.edu.au 5227 2923

Dr. John Stambas (Deakin Medical School & AAHL/CSIRO):

john.stambas@deakin.edu.au 5227 5740

20. Any old iron? Novel host iron sources utilised by human pathogen *Helicobacter pylori*

Supervisor: Melanie Thomson

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurn Ponds Campus

Project description:

The competition for bioavailable iron between invading bacteria and the host is central to the colonisation strategies of many human pathogens. The gastric pathogen, *Helicobacter pylori*, requires large amounts of sequestered iron to help survive and colonise the harsh acidic environment of the mammalian stomach. *H. pylori* lacks the ability to produce and export iron binding proteins called siderophores that are used by other gram negative pathogens to harvest iron from the host. However, the outer membrane of *H. pylori* does have many of the structures to bind iron-loaded siderophores to enable iron absorption. This project aims to investigate the ability of *H. pylori* to utilise host catecholamines – ‘fight or flight’ hormones often described as ‘mammalian siderophores’, to support bacterial growth in an iron restricted environment. It will explore which of the iron responsive outer membrane proteins (IROMPs) described in *H. pylori* support growth on this specialised iron source.

Summary of techniques to be used:

- Bacterial culture of human pathogen *Helicobacter pylori*
- Molecular biology techniques – construction of mutant strains of *H. pylori*
- *In vitro* growth assays in liquid bacterial culture

Contact details of supervisor:

Dr. Melanie Thomson (Deakin Medical School): m.thomson@deakin.edu.au 5227 2722

21. Impact of stress on immunity to infection

Supervisors: John Stambas and Laura Gray

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurin Ponds Campus

Project description:

Physiological stress is thought to alter immune responses and increase susceptibility to infection. Recent evidence under experimental conditions has demonstrated perturbations in both innate and adaptive immunity following stress. We will use a well characterized mouse model of influenza virus infection to ascertain the impact of stress on cytotoxic CD8+ T cell and CD4+ T helper cell effector function and antibody production. Mice will be exposed to stressful stimuli over short and long periods, and before and after infection occurs. Changes in stress hormones will be measured, and correlated with any changes in measures of immune function. Mice will also be challenged with synthetic stress hormones, to further dissect the specific pathways involved. The expression of stress hormone receptors on T cells will be measured after stress or stress hormone administration. Together these studies will provide important insights into the interactions between stress response systems and immune function.

Summary of techniques to be used:

Students will develop skills in cell culture, animal handling and injections, ELISA, flow cytometry, virology and immunology.

Contact details of supervisors:

Dr. John Stambas (Deakin Medical School & CSIRO AAHL):

john.stambas@deakin.edu.au 5227 5740

Dr. Laura Gray (Deakin Medical School): l.gray@deakin.edu.au 5227 2852

22. Studies of anti-viral immunity in genetically modified zebra fish

Supervisors: Alister Ward, Tim Doran and Mark Tizard

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurin Ponds Campus and CSIRO (Australian Animal Health Laboratory), Geelong

Project description:

Zebra fish are an excellent model in which to study the role of genes in complex biological processes such as the immune response to disease. Recent advances in technology, such as the use of zinc finger nucleases (ZFNs), have enabled the precise genetic modification of animal genomes. The Ward laboratory has considerable experience in applying these technologies in the zebra fish to generate modified animals. This project will be a collaboration between the Ward lab and the Gene Modulation Group at the Australian Animal Health Laboratory which has expertise in the use of RNAi and microRNA to control viral disease in transgenic animals. The specific aim of the project will be to use ZFN technology to knock out microRNA genes in zebra fish and study their impact on immune cell function and their role in anti-viral immune responses. This will have major implication in understanding the role of these important molecules in anti-viral immunity in both humans and in livestock species.

Summary of techniques to be used:

- Zinc finger nuclease technology for genome modification.
- Generation, characterization and maintenance of transgenic zebra fish.
- Real-time PCR characterization of modified organisms.
- Immunological assays of modified organisms.
- Viral infection models.

Contact details of supervisor:

Prof. Alister Ward (Deakin Medical School); alister.ward@deakin.edu.au 5227 2041

Prof. Tim Doran (CSIRO): timothy.doran@csiro.au 5227 5788

Dr. Mark Tizard (CSIRO): mark.tizard@csiro.au 5227 5753

23. Development of novel anti-viral therapeutics

Supervisors: Andrew Bean and Cameron Stewart

Location: CSIRO (Australian Animal Health Laboratory), Geelong

Project Description:

Highly pathogenic avian influenza viruses have acquired the unprecedented and alarming capability to infect humans and pose a continuous risk for poultry and fatal human infections. Attempts to avoid or contain outbreaks have been largely unsuccessful and this may be directly linked to our lack of fundamental knowledge about the host-pathogen interaction. Therefore, it is essential to increase our knowledge of avian influenza virus infections to develop new approaches to dealing with this virus.

Summary of techniques to be used:

This project aims to investigate various aspects of virus-host interactions for the development of new therapeutic strategies. This project utilizes a number of different techniques, ranging from quantitative real time PCR, viral protection assays, haemoagglutination assays, nitrite assays and luciferase-reporter assays. To evaluate and compare host-pathogen interactions histopathological descriptions, gene analysis and flow cytometry approaches will be used.

Contact details of supervisor:

Dr. Andrew Bean (CSIRO): [andrew.beam@csiro.au](mailto:andrew.bean@csiro.au) 5227 5000

24. Investigating the role of *Mycobacterium avium* subspecies *paratuberculosis* in Type I diabetes

Supervisors: Wojtek Michalski, James Wynne, and Mark Kotowicz

Location: CSIRO (Australian Animal Health Laboratory), Geelong

Project description:

An increasing body of experimental and clinical research suggests that *Mycobacterium avium* subspecies *paratuberculosis*, a proven pathogen of animals, may pose a significant threat to public health in Australia. This pathogen is believed to be transmitted to humans through certain animal derived food products, such as milk. However the role of *M. a. paratuberculosis* in human disease remains unclear. A number of studies have demonstrated that *M. a. paratuberculosis* infections are significantly more common in patients suffering chronic illness such as Crohn's disease and ulcerative colitis, compared to health controls. This raises the question, is *M. a. paratuberculosis* involved in other chronic conditions such as Type I diabetes (T1D)? To address this question the proposed project will investigate the frequency of *M. a. paratuberculosis* infection in Type I diabetes patients within Victoria, Australia. The incidence of infection will then be compared to the frequency of infection in non-diabetic control subjects. By utilising proven research methods this project will provide valuable knowledge surrounding the role of *M. a. paratuberculosis* in T1D.

Summary of techniques to be used:

- DNA and RNA isolation
- PCR
- Recombinant DNA cloning
- DNA sequencing

Contact details of supervisor:

Dr. Wojtek Michalski (CSIRO): Wojtek.michalski@csiro.au 5227 5772

25. Virus Bioreagent Development - Expression, purification and characterization of zoonotic viral proteins

Supervisors: Grantley Peck, Wojtek Michalski and John Stambas

Location: CSIRO (Australian Animal Health Laboratory), Geelong

Project description:

Recent outbreaks of emerging zoonotic viral diseases (e.g. Lyssavirus and Hendra virus) have demonstrated a need for the development of bioreagents suitable for use as diagnostics or vaccines. The aim of this project is to produce recombinant protein bioreagents in forms suited to use in diagnostic assays or as immunogens. In addition, the student will investigate the effect on protein solubility of various affinity tags and expression systems.

To avoid risks associated with live virus work, recombinant genetic techniques will be employed. The successful student will produce a number of plasmid expression constructs encoding viral proteins fused to affinity tags. The proteins will be produced using bacterial, baculoviral and/or mammalian expression systems and will be affinity purified and characterised using a number of biochemical techniques.

Summary of techniques to be used:

Molecular biology - primer design, PCR, cloning, nucleic acid purification, electrophoresis.

Recombinant protein expression - bacterial, baculoviral or mammalian expression.

Protein purification and characterization - affinity purification, SDS PAGE, Western blotting and solubility testing.

Contact details of supervisor:

Dr. Grantley Peck (CSIRO): grant.peck@csiro.au 5227 5793

26. Evaluation of zebrafish as a novel allergy model system

Supervisors: Cenk Suphioglu and Alister Ward

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurin Ponds Campus

Project description:

In this project, adult zebrafish will be exposed to different pollen and nut allergens (different concentrations and exposure time points) and its response to the different allergens will be monitored for allergen specific antibody and cytokine production, in comparison to the untreated negative controls. In addition, immunocytochemistry and flow cytometry will be used to evaluate populations of mast cells, basophils and eosinophils between the treated and untreated groups. Such experiments will yield novel information on the usefulness of zebrafish as an allergy model system for future use in inhibitor/drug discovery for allergy treatment.

Summary of techniques to be used:

This Project will employ a range of cell and molecular biology approaches utilising zebrafish as developmental model. These will include gene expression analysis using whole mount in situ hybridisation and RT-PCR, bioinformatics, gene knockdown/knockout approaches, and detailed functional and phenotypic analysis.

Contact details of supervisors:

Prof. Cenk Suphioglu (Deakin School of Life & Environmental Sciences):

cenk.suphioglu@deakin.edu.au 5227 2886

Prof. Alister C. Ward (Deakin Medical School): award@deakin.edu.au 0401 153 277

27. Proteomic analysis of zebrafish in response to peanut allergens

Supervisors: Cenk Suphioglu and Alister Ward

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurin Ponds Campus

Project description:

The student will expose different groups of zebrafish to varying concentrations of peanut allergens at different exposure times, in comparison to untreated negative controls, and isolate total proteins from sacrificed zebrafish. Total proteins from the different treatment groups (and untreated controls) will be used for proteomic analysis, utilising 2-dimensional gel electrophoresis. Upon detection of proteins that have been either up-regulated or down-regulated in response to peanut allergens, trypsin-digest mass spec analysis will be used to reveal the identity of proteins of interest. These experiments will generate novel information on the allergic response of zebrafish to peanut proteins, which will open up new and exciting pathways for human allergy research.

Summary of techniques to be used:

This Project will employ a range of cell and molecular biology approaches utilising zebrafish as developmental model. These will include gene expression analysis using whole mount in situ hybridisation and RT-PCR, bioinformatics, gene knockdown/knockout approaches, and detailed functional and phenotypic analysis.

Contact details of supervisors:

Prof. Cenk Suphioglu (Deakin School of Life & Environmental Sciences):

cenk.suphioglu@deakin.edu.au 5227 2886

Prof. Alister C. Ward (Deakin Medical School): award@deakin.edu.au 0401 153 277

28. Developmental analysis of zebrafish in allergy

Supervisors: Cenk Suphioglu and Alister Ward

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurin Ponds Campus

Project description:

In this project, the student will subject zebrafish in different developmental stages to peanut allergens (at different concentrations and different time points) and monitor for markers of allergy (antibodies and cytokines) and haemopoiesis (mast cells, basophils, eosinophils, neutrophils, T cells, B cells and plasma cells). Allergen-treated embryos will be compared with untreated controls to ascertain importance of allergic response to peanut proteins at different developmental stages, post egg fertilisation. Adults from treated and untreated embryos will then be challenged with the same allergens and markers of allergy will be re-assessed. Information generated in this project will establish if exposure of developing zebrafish embryos to peanut allergens provide immune protection to allergens in adults. Such findings will then be compared with what is known for human allergies, and therefore establish usefulness of zebrafish as a novel model system for allergy research.

Summary of techniques to be used:

This Project will employ a range of cell and molecular biology approaches utilising zebrafish as developmental model. These will include gene expression analysis using whole mount in situ hybridisation and RT-PCR, bioinformatics, gene knockdown/knockout approaches, and detailed functional and phenotypic analysis.

Contact details of supervisors:

Prof. Cenk Suphioglu (Deakin School of Life & Environmental Sciences):

cenk.suphioglu@deakin.edu.au 5227 2886

Prof. Alister C. Ward (Deakin Medical School): award@deakin.edu.au 0401 153 277

29. Visualizing the movement of HIV-1 genetic materials and/or proteins in infected cells

Supervisor(s): Johnson Mak, Andrew Leis and Paul Monaghan

Location: CSIRO (Australian Animal Health Laboratory), Geelong

Project description:

Viruses are known to hijack some of the seemingly unrelated host cell machineries to further their own propagations. Investigations of virus replication often enable us to learn a great deal about the cell biology of the host cells. Advancement of imaging technology in recent time has allowed us to visualize the movement of viral components and their interactions with host cell machinery in real-time, which has enriched our understanding on the interplay between virus, host and the underline mechanism of the pathogenicity of virus. CSIRO AAHL has a state-of-the-art imaging facility as part of the NCRIS facility, which provides us the means to track of the movement of viral components in HIV-1 infected cells. The objective of this project is to use fluorescent and/or electron microscopy technology to unravel the process of HIV-1 infection at the early stage of viral infection.

Summary of techniques to be used:

- Tissue Culture
- Transfection
- Virus production and isolation
- Mutagenesis and molecular cloning
- Labeling of virion particles
- Virus infection
- Imaging analysis (Confocal or Electron Microscopy)

Contact details of supervisor:

Prof. Johnson Mak (Deakin Medical School): makj@deakin.edu.au 0439 562 574

30. Diversity of HIV-1

Supervisor: Johnson Mak

Location: CSIRO (Australian Animal Health Laboratory), Geelong

Project description:

One of the hallmarks of HIV-1 infection is the generation of diverse quasispecies that exhausts, and ultimately cripples, the immune system of the host. Conversely, limited viral diversity is associated with reduced viral pathogenicity. The rapid evolution of HIV-1 is arguably its strongest weapon against host immune pressure and anti-retroviral assault. Surprisingly, little effort has been placed to develop an inhibitor that directly constrains viral diversity. While the infidelity of HIV-1 reverse transcriptase introduces mutations into the viral genomes, it is retroviral recombination that drives viral evolution and furthers the diversity of HIV-1. It has been shown that the structure of viral RNA genome is important determinant of the retroviral recombination process, and recombination hotspots are likely to exist within the viral genome. The objective of this proposal is to dissect the mechanism that regulates the HIV diversification process. Successful completion of this project will provide important lead for the development of novel antiviral therapeutics.

Summary of techniques to be used:

- Tissue Culture
- Transfection
- Virus production and isolation
- Mutagenesis and molecular cloning
- Virus infection
- Real Time quantitative PCR
- Next Generation Sequencing

Contact details of supervisor:

Prof. Johnson Mak (Deakin Medical School): makj@deakin.edu.au 0439 562 574

31. Structural biology of HIV-1 assembly

Supervisor: Johnson Mak

Location: CSIRO (Australian Animal Health Laboratory), Geelong

Project description:

In the process of virus formation, viral genomes and proteins interact with a series of host factors in an orderly fashion for the generation of infectious virus particles. During this process, viral genomes and proteins undergo a series of structural rearrangement to achieve a series of steps along the way. These folding and re-folding of RNA and protein structures expose a number of binding pockets that could potentially be targeted for the design of novel antiviral agents. The objective of this project is to purify large quantity of viral factors (genome or protein) for biophysical and biochemical analysis. Successful completion of this project will lay the foundation of rational drug design during HIV-1 assembly.

Summary of techniques to be used:

- Recombinant protein production
- FPLC and protein isolation
- In vitro proteolytic processing assay
- In vitro virus like particle formation assay

Contact details of supervisor:

Prof. Johnson Mak (Deakin Medical School): makj@deakin.edu.au 0439 562 574

MENTAL HEALTH & NEUROSCIENCE

32. Therapeutic alliance and outcomes in eating disorders: cognitive analytic therapy vs. motivational interviewing

Supervisor: Melissa O'Shea

Location: Eating Disorder Service, Barwon Health, Geelong

Project description:

The Eating Disorder Service (EDS) provides assessment and treatment to children and young people with eating disorders aged up to 25 years. The service is in the process of implementing and reviewing a new model of care specifically looking at the outcomes of Cognitive Analytic Therapy (CAT) compared to Motivational Interviewing. As it stands at present, there is no one evidence-based treatment for Anorexia Nervosa or Bulimia Nervosa for older adolescents and young adults that stands above the rest, so research into this area is important. CAT, as an individual therapy approach for older adolescents and young adults is showing some promise in the treatment of eating disorders.

The research would specifically be interested in the comparison of the therapeutic alliance and outcomes in CAT compared to motivational interviewing in young people.

Participants will be clients of the Eating Disorder Service engaged in either CAT or motivational interviewing treatment pathways.

Summary of techniques to be used:

Clients of the service will be asked to complete a number of rating and outcome scales at the beginning, during and at the end of treatment.

Clients will complete the K-10, Eating Disorder Examination Questionnaire (EDE-Q 6.0), Health of the Nation Outcome Scale (HONOS), prior to commencing treatment and at the end of treatment to review outcomes of treatment. Clients will also complete the Scott Millar Outcome Rating Scale (ORS), Young Child Outcome Rating Scale (YCORs) or Child/ Adolescent Outcome Rating Scale (CORs) depending on age to review therapeutic alliance.

Contact details of supervisor:

Melissa O'Shea (Barwon Health): 5226 7410

33. Mechanisms of antidepressant response: serotonin synthesis and tryptophan hydroxylase 2

Supervisor: Laura Gray

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurn Ponds Campus

Project description:

Depression is currently the leading cause of years of life lived with disability according to the World Health Organisation's assessment of the global burden of disease. Only approximately 36% of patients respond to the first drug prescribed, and a substantial number are left with long-term disability. It is currently not possible to predict which patients will be unresponsive to pharmacotherapy, and why this variability occurs. Antidepressants are typically thought to increase the level of neurotransmitter, particularly serotonin, at the synapse. However, new evidence suggests that in some people antidepressants may actually reduce the amount of serotonin being produced in the brain, which may explain their lack of response to this drug. We will investigate the mechanisms by which antidepressants and other drugs regulate serotonin synthesis, and identify the specific intracellular signalling pathways involved. We will also study genetic polymorphisms which modulate the response to antidepressants and the signalling through relevant pathways. This approach will allow us to identify potential new targets for psychiatric drugs, and to examine the factors which determine why some people fail to respond to current drugs.

Summary of techniques to be used:

This project will enable students to develop a grounding in principles of biochemistry, molecular biology, pharmacology and neurobiology. Students will develop their understanding of a diverse range of techniques, including DNA construct design and generation, cell culture, pharmacology, RNA knockdown, overexpression, immunoprecipitation, western blots, microscopy, luciferase assays and high-performance liquid chromatography. Students will be encouraged to extend their theoretical and practical knowledge in a range of areas, and to develop independent but guided research.

Contact details of supervisor:

Dr. Laura Gray (Deakin Medical School): l.gray@deakin.edu.au 5227 2852

34. Oxidative stress in mood disorders: role of serotonin dysregulation

Supervisors: Laura Gray, Seetal Dodd, Michael Berk and Ken Walder

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurin Ponds Campus

Project description:

Mental Health issues, including mood disorders, are estimated to account for approximately 11% of the global health burden worldwide, and the WHO anticipates that this will rise to 15% by 2020. One of the strongest aetiological factors for mood disorders is dysregulation of serotonergic signalling, and growing evidence suggests changes in oxidative processes in bipolar disorder, including multiple findings of depleted glutathione, a critical antioxidant. We have developed novel evidence to demonstrate that lithium, a drug used in the treatment of bipolar disorder, also regulates serotonin levels in the brain by increasing the production of the enzyme which synthesises serotonin in the brain, tryptophan hydroxylase 2 (TPH2). TPH2 is known to be regulated by oxidation, and substantial evidence suggests that lithium is capable of regulating cellular oxidation pathways which elicit cellular damage, including glutathione. To investigate this hypothesis, we will utilise cells stably expressing TPH2 as a model of serotonin production. We will expose cells to lithium and factors modulating oxidative stress, and assess the expression and activity of TPH2. We will also assess which intracellular signalling pathways are stimulated by lithium and how these relate to oxidative stress pathways. We will also assess the changes in serotonin levels and oxidative stress pathways in mice administered lithium. Understanding how lithium regulates mood is important in order to develop improved therapies and expand our knowledge of disease processes.

Summary of techniques to be used:

This project will enable students to develop a grounding in principles of biochemistry, molecular biology, pharmacology and neurobiology. Students will develop their understanding of a diverse range of techniques, including DNA construct design and generation, cell culture, pharmacology, RNA knockdown, overexpression, immunoprecipitation, western blots, microscopy, luciferase assays, high-performance liquid chromatography and animal handling. Students will be encouraged to extend their theoretical and practical knowledge in a range of areas, and to develop independent but guided research.

Contact details of supervisor:

Dr. Laura Gray (Deakin Medical School): l.gray@deakin.edu.au 5227 2852

35. Qualitative analysis of the effects of N-acetyl cysteine treatment in unipolar depression

Supervisors: Olivia Dean, Michael Berk, Seetal Dodd and Renée Otmar

Location: Barwon Health, Geelong

Project description:

Very few clinical trials incorporate a qualitative component into their design. This novel project will involve the analysis of qualitative data collected as part of a study investigating the effects of N-acetyl cysteine, a natural therapy added to participants' usual treatment for unipolar (clinical) depression. As part of this study, case notes have been recorded detailing participants' subjective feelings of changes in their symptoms while on the trial. Similarly, notes have also been collected on subjective clinician opinions on how participants' symptoms have changed over the course of the trial. The project will involve the analysis clinical trial case notes of 273 participant files. This project would involve the collation and analysis of these qualitative notes to determine themes surrounding the potential benefit of the N-acetyl cysteine treatment.

Summary of techniques to be used:

Qualitative analysis to determine key themes and assess outcomes of N-acetyl cysteine treatment.

Contact details of supervisors:

Dr. Olivia Dean (Barwon Health): oliviad@barwonhealth.org.au 5260 3088

Dr. Seetal Dodd (Barwon Health): seetald@barwonhealth.org.au 5226 7666

Prof. Michael Berk (Barwon Health): mikebe@barwonhealth.org.au 5260 3154

Ms. Renée Otmar (Barwon Health): rotmar@barwonhealth.org.au 5226 7414

36. MoodSwings an online intervention on bipolar disorder: does support make a difference?

Supervisors: Seetal Dodd, Sue Lauder (and Michael Berk)

Location: Barwon Health, Geelong

Project Description:

MoodSwings is an online self help program for people with bipolar disorder. It is based on a successful face-to-face program that has been adapted to an online format. We are currently evaluating the program via a randomised controlled design comparing a MoodSwings psycho-education arm with MoodSwings Cognitive Behavioural Therapy (CBT). We are interested to further explore the effects of different levels of support to outcomes. Outcomes include such factors as attrition, mental health literacy, acceptability of the project. The scope of this project is able to be tailored to either honours or PhD requirements.

Summary of techniques to be used:

The online program is already developed. Different levels of support could include e-mail and/or telephone support, via the online discussion board.

Contact details of supervisor:

Sue Lauder (Barwon Health): suela@barwonhealth.org.au

DEVELOPMENT & CANCER

37. Dissection the function of B-Cell Lymphoma 6a in immunity and cancer

Supervisors: Clifford Liongue and Alister C. Ward

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurin Ponds Campus

Project description:

Cell-cell signaling represents an integral function of multicellular organisms. One such signalling system is based on a network of cytokines. These proteins bind to specific receptors on the surface of target cells and transmit signals rapidly to the nucleus via the so-called Janus Kinase/Signal Transducer and Activator of Transcription (Jak/Stat) signalling pathway, to mediate appropriate changes in gene transcription. B-cell lymphoma 6a (Bcl6a) protein has been shown to be misexpressed in several cancers, including B-cell lymphoma. Recently Bcl6a has been shown to negatively regulate the Jak/Stat pathway via competitive binding to Stat docking sites within the promoter region of target genes. Given that dysregulation of the Jak/Stat pathway is a hallmark of lymphomas and other blood cell diseases, this function of Bcl6a might be very important clinically. The aim of this Project is to characterise the role of Bcl6a in normal immune cell development, and to specifically examine which Stat-responsive genes are regulated by this protein, which will contribute to the understanding the aetiology of lymphomas.

Summary of techniques to be used:

This Project will utilise a range of molecular approaches utilising zebrafish as developmental model. These will include gene knockdown, detailed gene expression analysis using microarrays and RT-PCR, and bioinformatics analysis of the transcriptome and relevant genomic sequences.

Contact details of supervisors:

Dr. Clifford Liongue (Deakin Medical School): c.liongue@deakin.edu.au 5227 3071

Prof. Alister C. Ward (Deakin Medical School): award@deakin.edu.au 0401 153 277

38. Exploring the many functions of the granulocyte colony-stimulating factor receptor

Supervisors: Clifford Liongue and Alister C. Ward

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurn Ponds Campus

Project Description

The granulocyte colony-stimulating factor receptor (G-CSFR) is known to play a key role in the production of white blood cells, with a particularly important role during ‘emergency’ situations, such as in response to infections, where it can mobilize blood stem cells and aid in the production of white blood cells. Mutations in the G-CSFR also play a key role in diseases such as leukemia (Liongue et al., 2009a).

However, diverse new roles have emerged more recently. For example, we have discovered a novel function for the G-CSFR in the migration of various myeloid lineage cells (Liongue et al., 2009b), with parallels in the metastasis of tumours expressing G-CSFR, while others have identified roles in muscle development and in the protection of the brain following stroke (Liongue et al., 2009a). The aim of this Project is to investigate the mechanisms by which the G-CSFR contributes to these diverse functions. This will provide new insights into G-CSFR function, with implications for the development of novel therapeutics to control disease.

Liongue, C., C. Wright, A. P. Russell, and A. C. Ward. 2009a. Granulocyte colony-stimulating factor receptor: stimulating granulopoiesis and much more. *Int. J. Biochem. Cell Biol.* 41:2372-2375.

Liongue, C., C. Hall, B. O’Connell, P. Crozier, and A. C. Ward. 2009b. Zebrafish granulocyte colony-stimulating factor receptor signalling promotes myelopoiesis and myeloid cell migration. *Blood* 113:2535-2546.

Summary of techniques to be used

This Project will use zebrafish and other model systems to investigate the emerging novel functions of G-CSFR. This will involve gene knockdown/knockout, mutagenesis and overexpression with subsequent detailed phenotypic and molecular analyses.

Contact details of supervisors:

Dr. Clifford Liongue (Deakin Medical School): c.liongue@deakin.edu.au 5227 3071

Prof. Alister C. Ward (Deakin Medical School): award@deakin.edu.au 0401 153 277

39. Knock your Socs off: impacts on zebrafish development and disease

Supervisors: Alister C. Ward and Monique Trengove

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurm Ponds Campus

Project Description:

The proper development of multi-cellular organisms requires systems that enable cells to communicate with each other in response to stimuli. Signaling molecules, including cytokines, are chemicals produced by cells that act to transmit information between them. These molecules interact with target receptors located on the cell surface to induce a wide range of cellular effects. This is mediated via the so-called 'Jak/Stat' signaling pathway, mediating changes in gene transcription and cell function. It is essential however that signaling can be negatively regulated, without it cell functions such as proliferation and migration can become out of control, leading to devastating outcomes. It is the Suppressor of Cytokine Signaling (Socs) proteins that serve as a break to negatively regulate signaling through the Jak/Stat and other signalling pathways (O'Sullivan et al., 2007).

Socs proteins have been found to be important in blood and immune cell development, with disruption of this pathway associated with diseases including inflammation and cancer (O'Sullivan et al., 2007; O'Sullivan et al., 2011). However, the role of several Socs proteins, including Socs5, remains poorly understood. This Project will directly investigate the role of Socs5 in early development.

O'Sullivan, L. A., R. S. Lewis, C. Liongue, S. E. M. Stephenson, and A. C. Ward. 2007. Cytokine receptor signalling through the Jak-Stat-Socs pathway in disease. *Mol. Immunol.* 44:2497-2506.

O'Sullivan, L. A., S. M. Noor, M. C. Trengove, R. S. Lewis, C. Liongue, N. S. Sprigg, S. E. Nicholson, and A. C. Ward. 2011. Zebrafish *socs1* regulates embryonic myelopoiesis independently of its effects on T cell development. *J. Immunol.* 186:4751-4761.

Summary of techniques to be used:

This Project will employ a range of cell and molecular biology approaches utilising zebrafish as developmental model. These will include gene expression analysis using whole mount in situ hybridisation and RT-PCR, bioinformatics, gene knockdown/knockout approaches, and detailed functional and phenotypic analysis.

Contact details of supervisors:

Prof. Alister C. Ward (Deakin Medical School): award@deakin.edu.au 0401 153 277

Ms. Monique Trengove (Deakin Medical School): mtre@deakin.edu.au

40. Keeping a lid on it: control of cell-cell signaling by the Cis protein

Supervisors: Alister C. Ward, John Stambas, Tania de Koning-Ward, Melanie Thomson and Daniel R. McCulloch

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurm Ponds Campus

Project Description:

The Cis (cytokine inducible SH2-containing) protein was the first identified member of the Suppressor of Cytokine Signaling (Socs) family of proteins, which act as key feedback regulators of cell-cell signaling, particularly through the cytokine receptor/Jak/Stat pathway. We have recently shown that zebrafish Cis functions as a brake on cell-cell signaling during embryonic blood cell development, while others have implicated human Cis in infectious disease susceptibility via effects on immune cell development. This collectively suggests that Cis acts as an important physiological regulator.

This collaborative Project aims to characterize a Cis knockout mouse, examining the consequences of the loss of this protein on normal blood and immune cell development, as well as the response to specific infectious agents, including viruses, parasites and bacteria.

Summary of techniques to be used:

This Project will use mice as an experimental model to investigate the role of Cis. This will involve confirmation of gene knockout and detailed phenotypic and biochemical analyses, including full blood examination, immune subset determination, and analysis using established viral, parasitic and bacterial infection models.

Contact details of supervisor:

Prof. Alister C. Ward (Deakin Medical School): award@deakin.edu.au 0401 153 277

41. Role of cytokine receptor signaling in development and disease

Supervisor: Alister C. Ward

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurin Ponds Campus

Project Description:

The correct development and maintenance of multi-cellular organisms is supported by systems enabling cells to communicate to one another in response to distinct cues. Cytokines are polypeptides that are produced and secreted by cells following a variety of stimuli, and induce a range of cellular effects via specific cytokine receptors located on the cell surface. These receptors signal to the nucleus via the so-called 'Jak-Stat-Socs' signaling pathway to mediate effects on gene transcription and cell physiology that are particularly important in blood and immune cell development (O'Sullivan et al., 2007). Perturbation of this pathway is associated with several diseases, including inflammation and cancer (Lewis et al., 2006; Ma et al., 2007).

This Project aims to further our understanding of the developmental roles of the Cytokine receptor-Jak-Stat-Socs pathway at the molecular level, as well as elucidating how changes in this pathway lead to disease. This approach will provide insight into the underlying biology as well as establishing a platform for the development of therapeutics to combat relevant diseases.

Lewis, R. S., S. E. M. Stephenson, and **A. C. Ward**. 2006. Constitutive-activation of zebrafish Stat5 expands hematopoietic cell populations in vivo. *Exp. Hematol.* 34: 179-187.

O'Sullivan, L. A., R. S. Lewis, C. Liongue, S. E. M. Stephenson, and **A. C. Ward**. 2007. Cytokine receptor signalling through the Jak-Stat-Socs pathway in disease. *Mol. Immunol.* 44:2497-2506.

Ma, A. C., **A. C. Ward**, R. Liang, and A. Y. H. Leung. 2007. The role of jak2a in zebrafish hematopoiesis. *Blood* 110:1824-1830.

Summary of techniques to be used:

This Project will use zebrafish and other cell model systems to investigate the role of one or more components of the Cytokine receptor-Jak-Stat-Socs pathway by expression studies, as well as gene knockdown and subsequent phenotypic and biochemical analyses.

Contact details of supervisor:

Prof. Alister C. Ward (Deakin Medical School): award@deakin.edu.au 0401 153 277

42. When two Gods go to war: antagonistic interactions between the Pegasus and Ikaros transcription factors

Supervisors: Alister C. Ward and Liza John

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurn Ponds Campus

Project Description:

Members of the Ikaros family of zinc finger transcription factors are important for immune system development, via their effects on key genes involved in this process. Perturbation of these transcription factors can lead to various diseases, particularly lymphomas and leukemias. However, relatively little is known about the most divergent member of this family, Pegasus, which retains a more ancient function compared to the other Ikaros members (John, 2009).

Recent studies in the laboratory have identified reciprocal antagonistic interactions between Pegasus and Ikaros, which may be very important in disease. The aim of this Project is to further investigate the molecular details by expression and purification of recombinant zinc fingers for analysis of DNA binding and protein-protein interaction, and co-expression of Pegasus and Ikaros in cell lines to investigate functional interactions.

John, L. B., S. Yoong, and A. C. Ward. 2009. Evolution of the Ikaros gene family: implications for the origins of adaptive immunity. *J. Immunol.* 182:4792-4799.

Summary of techniques to be used:

This Project will use a range of biochemical and cell biological approaches, including tissue culture, transfection, immunohistochemistry, immunoprecipitation, Western blot analysis, recombinant protein production and various in vitro binding assays.

Contact details of supervisors:

Prof. Alister C. Ward (Deakin Medical School): award@deakin.edu.au 0401 153 277

Dr. Liza John (Peter Mac Cancer Research Institute): Liza.John@petermac.org

43. Aberrant cytokine receptor signaling in prostate cancer growth and progression

Supervisors: Daniel R. McCulloch and Alister C. Ward

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurn Ponds Campus

Project Description:

Prostate cancer is one of leading causes of cancer related mortalities in the Western world. In its early stages its growth is slow but late-stage prostate cancer is aggressive and highly metastatic, meaning it spreads and colonises in secondary sites such as lymph nodes and bone very quickly. Cytokines play a pivotal role in a diverse range of developmental processes and cellular responses that require cell differentiation and growth. They exert their effects via specific cytokine receptors that activate intracellular signalling pathways, including the so-called 'Jak- Stat-Socs' pathway. These effects include the development, maintenance and activation of red blood cells (via erythropoietin or EPO), white blood cells (via colony-stimulating factors or CSFs) and immune cells (via interleukins or ILs), as well as the growth of a range of cell types (via growth hormone). The dysregulation of various members of the Cytokine receptor-Jak-Stat-Socs pathway contributes to a number of diseases, including cancer, with specific perturbations in ovarian cancer.

This Project aims to determine whether aberrant cytokine receptor signaling is seen in prostate cancer, and how these alterations might contribute to its aggressive phenotype. This will be achieved by analyzing the expression and/or activation status of key Cytokine receptor-Jak-Stat-Socs pathway components in a panel of prostate cell lines, and confirming the key results primary tissue biopsies to examine possible relationships with the grade of malignancy, and cell phenotype.

Summary of techniques to be used:

Tissue culture, gene expression analysis by real-time PCR, Western blot analysis of cell signalling, *in vitro* cell migration, invasion and proliferation assays, immunofluorescence detection of cell signalling molecules in human prostate cancer biopsies.

Contact details of supervisors:

Dr. Daniel R. McCulloch (Deakin Medical School): daniel.mcculloch@deakin.edu.au
522 72838

Prof. Alister C. Ward (Deakin Medical School): award@deakin.edu.au 0401 153 277

44. Understanding the role(s) of the highly evolutionary conserved “ADAMTS” enzyme family during embryonic development

Supervisors: Daniel McCulloch and Alister Ward

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurn Ponds Campus

Project description:

Most genes involved in the pathogenesis of disease, and particularly in ageing, are highly conserved. If they are so detrimental to human health and longevity then why are they still present in the highly-evolved human genome? The answer is because they are indispensable to the processes required to create a healthy human embryo (embryogenesis). Non-mammalian vertebrate models of developmental biology are becoming increasingly popular in the pursuit to define mechanisms underlying embryonic development. Using the zebrafish as a model organism, we aim to define the role(s) of a unique family of evolutionary conserved extracellular matrix (connective tissue) remodeling enzymes called “ADAMTS” in key developmental processes such as skeletal muscle, bone and heart development. Unveiling mechanisms underpinning development can reveal profound biological processes broadly applicable to a plethora of disease states including cancer, congenital heart defects, muscle-wasting and arthritis, whereby the “ADAMTS” enzymes are major drug targets for the development of arthritis therapeutics.

Summary of techniques to be used:

Gene knockout and silencing technology:

- Zinc finger nuclease gene targeting of “ADAMTS” genes in the zebrafish embryo.
- Morpholino antisense oligonucleotide mRNA silencing of “ADAMTS” genes in the zebrafish embryo.

In situ hybridization:

- Analyse gene expression throughout embryonic development.
- Define genetic interactions during key developmental processes.

Fluorescence microscopy:

- Localisation of protein expression in the developing embryo using fluorescent antibody detection.

Contact details of supervisor:

Dr. Daniel McCulloch (Deakin Medical School): daniel.mcculloch@deakin.edu.au 5227 2838

45. Targeting cancer with chemical antibodies

Supervisors: Wei Duan and Sarah Shigdar

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurin Ponds Campus

Project description:

Our laboratory is focused on developing a cure for cancer by targeting the cancer stem cells that hide and hibernate within the body, ready to spring back into action. These cancer stem cells are refractory to traditional chemotherapy and require a more directed approach. We have been successful in developing chemical antibodies against two cancer stem cell markers, and will be adding to our repertoire in an attempt to eradicate cancer. These chemical antibodies, known as aptamers, are developed in the laboratory by a process known as SELEX, and can be directly linked to drugs, nanoparticles or radioisotopes. These smart bombs can target the tumorous tissues with high affinity and specificity, while leaving healthy tissue intact, thus minimising the toxic side effects of conventional treatment. The projects available will include the isolation and characterisation of RNA aptamers targeting a specific cancer associated cell surface marker, as well as investigating the possibility of linking several of our aptamers together in order to increase the effectiveness of our targeting system in a cancer cell model.

Summary of techniques to be used:

The techniques involved in these projects include molecular cloning, site-directed mutagenesis, mammalian cell culture, PCR, restriction enzyme digests, flow cytometry, and fluorescence and confocal laser scanning microscopy.

Contact details of supervisor:

Prof. Wei Duan (Deakin Medical School): wduan@deakin.edu.au 5227 1149

Dr. Sarah Shigdar (Deakin Medical School): Sarah.Shigdar@deakin.edu.au 5227 2846

46. The role of free radicals in the development of cancer cachexia

Supervisor: Paul Lewandowski

Location: School of Medicine, Deakin University, Geelong Waurn Ponds Campus

Project description:

An estimated 50% of cancer patients develop skeletal muscle cachexia (wasting), suffering a significant loss of up to 30% of their original body weight. In addition when cancer patients develop cachexia they also have a decreased chance of survival. Interestingly, research has shown that weight loss associated with cancer cachexia is not accounted for by a decrease in dietary intake, but rather a specific inflammatory catabolic response. Free radicals have been suggested to contribute to progressive tissue damage in other diseases of heart muscle, kidney, spinal cord, vascular smooth muscle and skeletal muscle, but to date the role of free radicals in the development of cancer cachexia has not been studied. To study cancer cachexia Dr Lewandowski's laboratory has developed a novel mouse model which they employ to study the development of the disease and its treatment.

Methodological approaches used:

This project will provide students with the opportunity to learn animal surgical techniques, cell culture and skills needed to run a dietary trial. In addition the project also incorporates Gene expression analysis, Protein electrophoresis & Immunoblotting, Biochemical analysis, Enzymatic analysis and Histological Analysis.

Contact details of supervisor:

Dr. Paul Lewandowski (Deakin Medical School): paul.lewandowski@deakin.edu.au 5227
1111

47. Novel treatments of cancer cachexia

Supervisor: Paul Lewandowski

Location: School of Medicine, Deakin University, Geelong Waurn Ponds Campus

Project description:

An estimated 50% of cancer patients develop skeletal muscle cachexia (wasting), suffering a significant loss of up to 30% of their original body weight. In addition when cancer patients develop cachexia they also have a decreased chance of survival and often must stop curative cancer therapies. Interestingly, research has shown that weight loss associated with cancer cachexia is not accounted for by a decrease in dietary intake, but rather a specific inflammatory catabolic response. Despite the prevalence of cancer cachexia, to date there is no cure or very few therapies that can slow or prevent the development of the condition. In this project novel nutritional, life style or drug therapies will be tested in an attempt to treat cancer cachexia.

Summary of techniques to be used:

This project will provide students with the opportunity to learn clinical trial experience, animal surgical techniques, cell culture and skills needed to run a dietary trial. In addition the project also incorporates Gene expression analysis, Protein electrophoresis & Immunoblotting, Biochemical analysis, Enzymatic analysis and Histological Analysis.

Contact details of supervisor:

Dr Paul Lewandowski (Deakin Medical School): paul.lewandowski@deakin.edu.au
5227 1111

48. The fate of Mesenchymal Stem Cells: Will zebrafish give the answer on what genes make the choice between fat and bone?

Supervisors: Yann Gibert and Ken Walder

Location: Metabolic Research Unit, School of Medicine, Deakin University, Geelong Waurin Ponds Campus

Project description:

Age related osteoporosis is associated with an increase of adipose tissue and a reciprocal loss of bone density. Both bones and adipocytes differentiate from a bone marrow-derived multipotent precursor cells: the Mesenchymal Stem Cells (MSCs). Differentiation of MSCs into adipocytes and osteoblasts is genetically driven. Recent studies have shown in zebrafish that normal expression of the Peroxisome proliferator-activator receptor gamma (Pparg) and retinoic acid (RA) is crucial for the proper balance of osteoblast and adipocyte differentiation. Furthermore membrane depolarization of human MSCs *in vitro* can prevent differentiation while hyperpolarization up-regulates osteogenic differentiation. However these results remain to be confirmed *in vivo* and during embryonic development. In this project we will characterize the precise developmental role of membrane potential changes on osteoblast and adipocyte differentiation using different molecular markers. Furthermore, the genetic cascade of MSC differentiation will be studied by abolishing and/or increasing candidate gene expression using specific pharmacological compounds, like Pparg and genes of the RA signaling pathway. Once identified in zebrafish, the genes implicated in the fate of MSCs will be validated in a mammalian system to confirm their potential as therapeutic targets for human obesity related diseases and osteoporosis.

Summary of techniques to be used:

- Pharmacological manipulation of pathways of interest in developing zebrafish, and phenotypic characterization
- Generation of inducible gain- or loss-of-function mutations in the zebrafish genome and phenotypic characterisation
- Immunohistochemistry, *in situ* hybridization
- Bone and adipocyte staining
- Quantitative RT-PCR from mammalian cells

Contact details of supervisors:

Dr. Yann Gibert (Deakin Medical School): y.gibert@deakin.edu.au 5227 1197

Prof. Ken Walder (Deakin Medical School): ken.walder@deakin.edu.au 5227 2883

49. Targeting Cancer Stem Cells in Brain Tumors

Supervisor: David Ashley

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurin Ponds Campus

Project description:

Brain tumors are aggressive forms of human cancers that affect both children and adults. Of those, Glioblastoma Multiformes (GBMs) and Atypical Teratoid Rhabdoid Tumours (ATRT) are resistant to current standards of care and therapy with a median patient survival period of about 14 months. Therefore, new and innovative therapeutic approaches are urgently required to improve the situation in these diseases, particularly with the children.

Cancer stem cells (CSCs) representing 6% to 29% of cells in gliomas that are capable of initiating the formation of tumors, and are thought to play a key role in promoting radio- and chemo-resistance. This project aims to use histone deacetylase inhibitors to regulate cancer stem cell cycles as a way of sensitizing them to conventional therapies. The detailed mechanisms of how these inhibitors work will be examined which include P53 pathway, target genes Gfi1, Necdin, PTEN and P21.

Summary of techniques to be used:

The techniques involved in the project include human cell culture, drug assay, flow cytometry, immunohistochemistry, Western blot analysis, PCR and qPCR

Contact details of supervisor:

Prof. David Ashley (Deakin Medical School): david.ashley@barwonhealth.org.au
5226 7855

50. Epigenetic Predictors of Outcome in Malignant Glioma

Supervisor: David Ashley

Location: Molecular Medicine Research Facility, School of Medicine, Deakin University, Geelong Waurin Ponds Campus

Project description:

Glioblastoma multiforme (GBM) is the most common illness and has a very poor prognosis, despite the use of multimodality therapy including surgery, radiation therapy and chemotherapy. Patients with GBM have an overall median survival time of 14 months. However, a subset of 5% of GBM tumors, termed secondary GBM, progress from lower-grade tumors (grade II/III), is seen in younger patients and exhibits longer survival times.

Recent studies have indicated an important role of epigenetics (DNA methylation) in predicting survival time in gliomas. While epigenetic profiling in gliomas has a demonstrated potential in prognostic stratification, epigenetic modification of the genome is reversible, and targeting tumor epigenetics presents a particularly attractive treatment possibility.

Methylguanine DNA methyltransferase (MGMT) is a highly conserved and ubiquitous DNA repair enzyme. MGMT methylation is considered to be a powerful predictive marker for positive response to alkylating agents (a type of drugs) and routinely used for prognostic stratification of patients suffering from GBM.

The goals of this project are: 1. To systematically characterize the genome-wide DNA methylation signatures specific to the subgroup of long term survivors and to gain greater insight into the role of DNA methylation in the disease. 2. To examine the relationship between long term survivors and MGMT promoter methylation status.

Summary of techniques to be used:

The techniques involved in the project include human cell culture, Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOP MS), PCR and qPCR, sequencing, Western blot analysis.

Contact details of supervisor:

Prof David Ashley (Deakin Medical School): david.ashley@barwonhealth.org.au
5226 7855

51. Does maternal antenatal folate level alter neonatal epigenetic profile?

Supervisors: Peter Vuillermin, Richard Saffery and Fiona Collier

Location: The Barwon Biomedical Research Laboratory and the Epigenetics Laboratory at Murdoch Childrens Research Institute.

Project description:

The Barwon Infant Study (BIS) is an unselected birth cohort study (n=1,250) with antenatal recruitment. It incorporates collection of internationally unique array of epidemiological data, biospecimens and biomeasurements. Limited studies (both animal and human) have directly implicated folate during pregnancy with specific changes in DNA methylation profile in progeny¹, however no prospective study linking neonatal epigenetic profile directly to measured red-cell folate levels has yet been undertaken in humans. The methyl groups required for establishment and maintenance of DNA methylation are derived solely from dietary methyl donors in association with specific enzymes and associated cofactors². Since September 2009, all flour used for bread making in Australia has been fortified with folic acid³. Additionally, a wide range of foods (such as breakfast cereals) also contain significant levels of folic acid fortification and the majority of pregnant women in Australia take folic acid supplements. In this context we have recently found that ~37% of women participating in the Barwon Infant Study (BIS) have red blood cell folate levels above the recommended range. The aim of this Honours project is to investigate the association of maternal folate levels in pregnancy and DNA methylation levels in cord blood mononuclear cells and placenta collected at birth.

1. Waterland RA, Michels KB. Epigenetic epidemiology of the developmental origins hypothesis. *Annu Rev Nutr* 2007;**27**:363-88.
2. Ulrey CL, Liu L, Andrews LG, Tollefsbol TO. The impact of metabolism on DNA methylation. *Hum Mol Genet* 2005;**14 Spec No 1**:R139-47.
3. Australian and New Zealand Food Standards. , 2011

Summary of techniques to be used:

Maternal RBC folate levels (28 weeks gestation) have been measured using a DxI 800 random access immunoassay analyser. DNA methylation levels of the *LINE-1* element and the imprinted *IGF2* gene will be measured in cryopreserved cord blood mononuclear cells and placental tissue from all available infant samples (n ~ 500). Methylation levels will be determined using previously validated assays and Sequenom MassArray epityper analysis. This high-throughput, quantitative process, is routinely used in the Epigenetics Laboratory, MCRI.

Contact details of supervisors:

Dr Peter Vuillermin (Barwon Health & Deakin University): peter.v@barwonhealth.org.au

Dr Richard Saffery (Murdoch Childrens Research Institute): richard.saffery@mcri.edu.au

Dr Fiona Collier (Barwon Health & Deakin University): fionac@barwonhealth.org.au

NUTRITION, BONE HEALTH

52. Coeliac disease and body mineral density

Supervisors: Julie Pasco and Sharon Brennan

Location: Epidemiology and Biostatistics Unit, Barwon Health, Geelong

Project description:

The aim is to investigate whether coeliac disease and gluten intolerance are associated with bone mineral density (BMD) and other components of body composition, including weight, and fat and lean tissue mass.

Summary of techniques to be used:

Body composition parameters have been measured using dual energy X-ray absorptiometry and anthropometry; DNA and serum samples are being used to identify markers of coeliac disease and gluten intolerance and linked with gastro-intestinal symptoms documented by questionnaire. Regression techniques will be used to determine associations between coeliac disease, gluten intolerance and indices of body composition.

Contact details of supervisors:

Assoc Prof. Julie Pasco (Barwon Health): juliep@barwonhealth.org.au 5226 7393

Dr. Sharon Brennan (Barwon Health): sharob@barwonhealth.org.au 5226 7915

53. Foot and ankle fractures in men

Supervisors: Julie Pasco and Sharon Brennan

Location: Epidemiology and Biostatistics Unit, Barwon Health, Geelong

Project description:

Foot and ankle fractures are among the most common nonvertebral fractures but little is known about their epidemiology or risk factors. This is surprising given that foot/ankle fractures have a poor prognosis and can have a substantial impact on quality of life. Furthermore, as lower extremity fracture patients often have co-morbid conditions, treatment can be complex. This project fulfils a major public health goal to identify specific risk factors and methods to prevent occurrence of lower extremity fractures. The aim of the study is to identify risk factors for foot and ankle fractures in men and determine the incidence of these fractures in the community.

Summary of techniques to be used:

In this study, fracture cases will be identified from radiology reports and compared with controls from men enrolled in the GOS. Assessments include bone mineral density, heel ultrasound, anthropometry, body composition, blood pressure, diet, alcohol consumption, medication use and cause of fracture. Logistic regression will be used to determine risk factors for foot/ankle fractures.

Contact details of supervisors:

Assoc Prof. Julie Pasco (Barwon Health): juliep@barwonhealth.org.au 5226 7393

Dr. Sharon Brennan (Barwon Health): sharob@barwonhealth.org.au 5226 7915

54. Fractures in preschoolers: informing policy

Supervisors: Julie Pasco and Sharon Brennan

Location: Epidemiology and Biostatistics Unit, Barwon Health, Geelong

Project description:

During the last decade there have been major reviews of children's safety in Victoria, in terms of legislation, and broad policy and practice frameworks. This innovative, cost-effective study will be the first to determine patterns of annual fracture incidence in southeastern Victoria for all children aged 5 years and under, over a period spanning 1994-2009. The identification of fracture patterns in children, and whether these patterns correspond with changes to children's health, wellbeing and safety legislation and policies, will provide important, cost-effective information to children's welfare groups, providing evidence for future intervention and changes to policy for the benefit of Victorian children.

Summary of techniques to be used:

Incident fractures will be identified at all skeletal sites for children aged 5 years and under for 1994 to 2009 from radiological reports for the Barwon Statistical Division, Victoria. Changes to Acts and legislation for the protection of children over this time period will be identified from policy databases and grey literature, and mapped against fracture incidence.

Contact details of supervisors:

Assoc Prof. Julie Pasco (Barwon Health): juliep@barwonhealth.org.au 5226 7393

Dr. Sharon Brennan (Barwon Health): sharob@barwonhealth.org.au 5226 7915

55. Childhood asthma and the risk of fracture

Supervisors: Julie Pasco and Sharon Brennan

Location: Epidemiology and Biostatistics Unit, Barwon Health, Geelong

Project description:

This is a collaborative project between the GOS and Dr Peter Vuillermin, Paediatrician. There are a number of reasons children with asthma may be more susceptible to fracture, which include the use of beta agonists and corticosteroid medications, differences in activity levels and the disease process itself. The aim is to compare fracture rates in children with asthma with fracture rates of their peers.

Summary of techniques to be used:

In 2005, the Geelong Childhood Asthma Study identified a community-based sample of primary school aged children with asthma. Fracture rates for this sample will be determined over the following years and compared with rates from the general community of primary school aged children as defined by the GOS. This project will provide the opportunity to develop skills in epidemiological methodology, abstracting and comparing data from existing large databases and analysing data using rate ratio analysis. This project presents the opportunity to utilize good quality data from two large community-based projects to generate clinically useful information.

Contact details of supervisors:

Assoc Prof. Julie Pasco (Barwon Health): juliep@barwonhealth.org.au 5226 7393

Dr. Sharon Brennan (Barwon Health): sharob@barwonhealth.org.au 5226 7915

56. Maternal vitamin D in pregnancy: does it influence offspring health?

Supervisors: Julie Pasco and Sharon Brennan

Location: Epidemiology and Biostatistics Unit, Barwon Health, Geelong

Project description:

Data are emerging from Australia and elsewhere to suggest that maternal vitamin D status in pregnancy affects intrauterine skeletal mineralisation and skeletal growth, together with muscle and lung development, and adiposity in the offspring. The aim of the study is to examine whether low maternal vitamin D levels during pregnancy are associated with the following parameters of body composition in the offspring at age nine years: bone mineral content, muscle mass, adiposity and lung volume.

Summary of techniques to be used:

This is a prospective study of children aged nine years, whose mothers were recruited before 16 weeks of gestation, between 2002 and 2003. Maternal blood samples were collected at recruitment and again at 28-32 weeks gestation. Mother-child pairs will be re-called to the study centre when the children are aged nine. Bone mineral content, muscle mass and total body fat mass will be determined for the children using dual energy x-ray absorptiometry. Anthropometry, skinfold thickness and lung volume will also be measured, and mothers will complete a questionnaire seeking information about the children's diet, exercise and sun exposure. This project would suit students interested in the effect of *in utero* conditions on childhood health.

Contact details of supervisors:

Assoc Prof. Julie Pasco (Barwon Health): juliep@barwonhealth.org.au 5226 7393

Dr. Sharon Brennan (Barwon Health): sharob@barwonhealth.org.au 5226 7915

57. Does canola oil contain toxic substances which shorten life?

Supervisor: Paul Lewandowski

Location: School of Medicine, Deakin University, Geelong Waurn Ponds Campus

Project description:

Since 1996, it has been known that canola oil has life shortening effects in rats and possibly susceptible humans, compared with other oils such as soybean and olive oil. It was initially suspected this toxic effect was due to the fats and the plant sterols in canola oil, however both these have been ruled out. The current study is trying to identify the compound(s) that lead to the life shortening effects of canola oil and investigate the mechanism that leads these effects. As part of this research program Dr Lewandowski has established the only colony of Stroke Prone Hypertensive rats in Australia and these are used to study the toxic effects of canola oil on a variety of organs.

Summary of techniques to be used:

This project will provide students with the opportunity to learn animal surgical techniques and skills needed to run a dietary trial. In addition the project also incorporates Gene expression analysis, Protein electrophoresis & Immunoblotting, Biochemical analysis, Enzymatic analysis and Histological Analysis.

Contact details of supervisor:

Dr. Paul Lewandowski (Deakin Medical School): paul.lewandowski@deakin.edu.au
5227 1111

58. Is the proportion of food outlet space allocated for fruit and vegetables related to health status in Australian farmers?

Supervisors: Paul Lewandowski, Ananda Chandrasekara and Sue Brumby

Location: School of Medicine, Deakin University, Geelong Waurun Ponds Campus and National Centre for Farmer Health, Hamilton.

Project description:

Dietary patterns may be influenced by the availability and accessibility within shops/stores of different types of foods. In urban areas it has been shown that measurements of shelf space devoted to the sale of items such as fruit and vegetables can be used by researchers to characterize the healthfulness of the food environment. However, little is known about the amount of shelf space used for healthy and unhealthy foods in different types of shops/stores in rural areas and how this relates to the health of individuals who shop there.

Summary of techniques to be used:

This project will provide students with the opportunity to travel throughout Victoria to survey the range of foods available for sale in regional supermarkets and other food outlets. This will involve collecting in store food inventories, measurements of space allocated to different foods, collection of diet diaries, carrying out food frequency surveys and data analysis.

Contact details of supervisor:

Dr. Paul Lewandowski (Deakin Medical School): paul.lewandowski@deakin.edu.au
5227 1111

59. The impact of clozapine on cardiovascular health

Supervisor: Seetal Dodd

Location: Barwon Psychiatric Research Unit, Barwon Health, Geelong

Project description:

Clozapine is a potent antipsychotic drug used to treat schizophrenia in patients whose symptoms have not been adequately managed by safer treatments. Clozapine can cause potentially fatal cardiovascular adverse events. Over 400 patients at Barwon Health are currently being treated with clozapine. In this project the honours students will use echocardiograms and blood biomarkers to investigate the cardiac health of patients being treated with clozapine.

Summary of techniques to be used:

The student will use clinical measures collected as routine clinical practice by the clozapine team at Barwon Health.

Contact details of supervisor:

Dr. Seetal Dodd (Deakin Medical School): seetald@barwonhealth.org.au 5226 7666