



THE UNIVERSITY OF
MELBOURNE

DEPARTMENT
OF
PATHOLOGY

B.Sc. (Honours)
Project Booklet

2008

The Department of Pathology B.Sc. (Honours) Program 2008

The B.Sc. (Honours) program in Pathology provides an introduction into the challenging area of investigation of disease at the molecular and cellular level. This program involves candidates undertaking a full-time research project into one of the various aspects of disease as outlined in the B.Sc. (Honours) project descriptions below, under the supervision of highly-trained clinicians or research scientists. The objectives of the course include the development of individual student's skills in the areas of acquisition, interpretation and critical analysis of laboratory data, planning and design of experiments and reporting of experimental data in a concise and scientific manner consistent with that published in scientific journals.

The B.Sc. (Honours) course in Pathology is divided into the 531-496 Research and 531-497 Coursework components. The Research Component involves the preparation of a literature review (10%) and the final research report thesis (50%) as well as the delivery of an introductory research seminar (5%) at the beginning and final "Defence of the Thesis" Seminar (10%) at the end of the research program. The Research Component accounts for 75% of the B.Sc. (Honours) assessment. The remaining 25% is contributed from the Coursework component as two Data Assessment examinations in which candidates are asked to critically analyse previously unseen research data.

To undertake B.Sc. Honours in the Department of Pathology potential candidates should consider the projects on offer in this booklet and discuss any of interest with the indicated supervisors. For convenience, candidates should make an appointment with potential supervisors in order to discuss the research work to be undertaken in detail. Candidates should decide on four projects of interest and list these in order of interest on the "**B.Sc. (Honours) 2008 List of Preferred Projects**" form which is provided within this project booklet. For students wishing to commence the B.Sc. Honours degree in February 2008, this form and the **B.Sc. Honours Application form** should be submitted to **Dr. John R. Underwood in the Department of Pathology by Friday 16th November 2007.**

Again in 2008, the Department of Pathology will accept applications for mid-year enrolments for the B.Sc. Honours degree. The Mid-Year B.Sc. Honours degree will run from July 2008 until May 2009 and applications should be made using the **B.Sc. (Honours) 2008 List of Preferred Projects** form and the **B.Sc. Honours Application form** to Dr. John R. Underwood in the Department of Pathology by 1st June 2008.

Important Dates for B.Sc. Honours Applicants

Friday, 12th October 2007

B.Sc. Honours Information Session

Time: 12.15 pm - 1.30pm

Venue: The Harry Brookes Allen Museum of Anatomy and Pathology
Level 3, Medical Centre

For students commencing B.Sc. Honours in Pathology in February 2008:

Friday, 12th October 2007 - Friday, November 16th 2007

Discussion of research projects of interest with potential supervisors

Friday, November 16th 2007

Deadline for the submission of the:

B.Sc. (Honours) 2008 List of Preferred Projects form

- from the Department of Pathology B.Sc. Honours 2008 Project Booklet*

B.Sc. Honours Application form.

- from the Faculty of Science.

NOTE:

- * Please provide contact telephone numbers and address details on these forms that will enable the B.Sc. Honours coordinator to contact you for provisional and final offers.

For additional information on the B.Sc. (Honours) course and regarding Mid-Year B.Sc. Honours enrolments in Pathology please contact:

Dr John R. Underwood

B.Sc. (Honours) coordinator

Room W643

Ph: 8344-4292/5881 (office/lab.)

043-817-4034 (mobile)

Fax: 8344-4004

Email: johnru@unimelb.edu.au

Outline of the B.Sc. (Honours) Course in the Department of Pathology

B.Sc. (Honours) Course commences:

Monday 18th February 2008 or 14th July 2008 for mid-year entry

- Introduction to B.Sc. Honours in the Department of Pathology

Safety Induction Program

Laboratory Animal Science and Animal Welfare Seminars

Department of Pathology B.Sc. (Honours) Lecture Series

Assessment:

The Course will be divided into two components, comprising the Research Component and the Course Work Component, and will be assessed as follows:

531-496 RESEARCH COMPONENT

Introductory Seminar:	5%
Review of the Literature	
Aims of the Project	
Hypotheses being tested	
Methods - Rationale for Use	
Literature Review:	10%
Final “Defence of the Thesis” Seminar:	10%
Research Report:	<u>50%</u>
Sub-Total:	<u>75%</u>

531-497 COURSE WORK COMPONENT

Data Assessment Exercise I	12.5%
critical appraisal of a published paper	
Data Assessment Exercise II	12.5%
critical appraisal of a published paper	
Sub-Total:	<u>25%</u>

Research institutes affiliated with the Department of Pathology

Burnet Institutes at the Austin (formerly Austin Research Institute)

Baker Institute

Bernard O'Brien Institute for Microsurgery, St Vincent's Hospital

Bone Marrow Transplantation Unit, Alfred Hospital

Centre for Eye Research, Australia

Howard Florey Institute of Experimental Medicine and Physiology

Ludwig Institute for Cancer Research, Austin and Repatriation Medical Centre

Mental Health Research Institute of Victoria

Peter MacCallum Cancer Institute

Department of Anatomical Pathology, Royal Melbourne Hospital

Royal Women's Hospital

Department of Clinical Neurosciences, St Vincent's Hospital

Walter and Eliza Hall Institute

Department of Pathology
University of Melbourne

B.Sc. Honours 2008**PROJECT TITLE: STUDIES OF EARLY NEUROINFLAMMATORY DISEASE****PROJECT DESCRIPTION**

Neuroinflammation produces extensive neuronal and axonal damage and is a major component of Central Nervous System disease (eg. Multiple Sclerosis (MS), Motor Neuron Disease, Alzheimer's disease, Stroke etc.) and Neurotrauma. In a mouse model of MS, generated by vaccination with a peptide homologous with a quantitatively minor myelin component, myelin oligodendrocyte glycoprotein (MOG), mapping of the spatial and temporal disease profiles has shown that pathological processes, including inflammatory infiltrate, begin very early after disease initiation, prior to the first appearance of symptoms.

We are using the model to address the following question: *what are the molecules that facilitate entry of inflammatory cells into the CNS and initiate the pathological process?* This will be investigated by using a phage display library to highlight molecules that are activated when inflammatory cells accumulate within blood vessels, followed by isolation and purification of these molecules and further investigation of their biochemical properties.

Methods: use of phage display libraries, generation of MS-like disease in mice, protein purification, immunohistochemistry.

PROJECT START TIME (indicated preferred start time):

February 2008:	Yes
July 2008 (mid-year intake):	No

PREFERRED BACKGROUND OF STUDENT: interest in Neuroscience, Biochemistry**NAME OF SUPERVISOR(S):** Dr. Margaret Ayers, Pathology, Melbourne University
Dr. Jacquie Orian, Biochemistry, La Trobe University**CONTACT PHONE & FAX NUMBERS:** 83445876, 94791113.**CONTACT EMAIL ADDRESS:** mmayers@unimelb.edu.au / j.orian@latrobe.edu.au

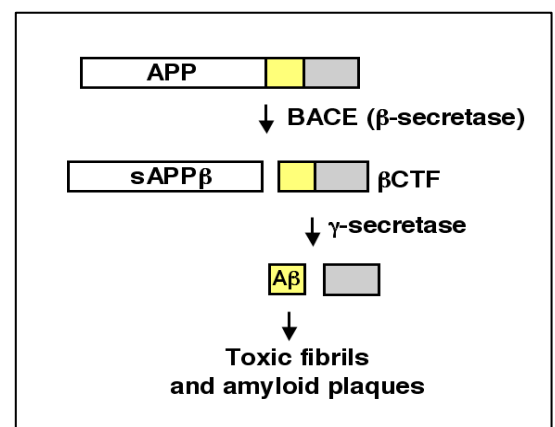
B.Sc. Honours 2008

PROJECT TITLE: Effects of Aging and Oxidative Stress on the Expression and Activity of Alzheimer's Disease BACE1

PROJECT DESCRIPTION

(including techniques to be used)

The pathological hallmark of Alzheimer's disease (AD) is the presence of abundant amyloid plaques in the brain cortex and parenchyma. These plaques are constituted by the accumulation and deposition 40-43 amino acid A β peptides. A β peptides self-aggregate and form toxic fibrils that cause neurodegeneration, resulting in AD. Research in our lab focuses at clarifying the molecular and cellular mechanisms that produce A β , particularly the regulation of the proteases responsible for their production. A β are derived from a type I membrane receptor termed amyloid precursor protein (APP) by the successive action of two proteases termed β -secretase (or BACE1) and γ -secretase. Our previous studies have shown that BACE1 protein expression and activity are increased in the frontal cortex of AD patients, with no increase in the levels of BACE1 mRNA. We hypothesize that the increase in BACE1 protein levels in AD is caused by changes in molecular associations and subcellular distribution triggered in response to ageing and oxidative stress.



You will use cell culture models to test the above hypothesis. Aged human fibroblasts and mouse primary cortical neurons cultured for up to four weeks will be analysed for changes in BACE1 activity, subcellular distribution and molecular associations. As a model of oxidative stress, human neuroblastoma SH-SY5Y and mouse cortical neurons will be treated with hydrogen peroxide and the effect of this treatment on BACE1 will be characterized. BACE1 enzymatic activity will be determined in cell lysates using a FRET assay based on cleavage of a synthetic substrate. BACE1 species will be analysed by western blotting. Subcellular organelles (Golgi and endosomes) and lipid rafts will be isolated by differential centrifugation. Immunofluorescence microscopic analysis of the cells will help determine changes in the subcellular distribution of BACE1 upon aging and oxidative stress treatment. BACE1 molecular complexes will be analysed using SDS-PAGE in non-denaturing conditions and gel filtration.

PROJECT START TIME (indicated preferred start time):

February 2008:

Yes

July 2008 (mid-year intake):

Possible if project still available

PREFERRED BACKGROUND OF STUDENT:

NAME OF SUPERVISOR(S): Dr Genevieve Evin

DEPARTMENT & INSTITUTION: Department of Pathology, Medical Building
Level 5 (Room W541)

CONTACT PHONE & FAX NUMBERS: ph 8344-4205 fax 8344-4004

CONTACT EMAIL ADDRESS: gmevin@unimelb.edu.au

B.Sc. Honours 2008**PROJECT TITLE: The role of auxiliary factors in prion disease.****PROJECT DESCRIPTION**

(including techniques to be used)

Prion diseases are transmissible, neurodegenerative disorders associated with the misfolding of the normal host encoded prion protein. In the absence of a conventional infectious agent this misfolding is believed to be responsible for the transmission and pathogenesis of the disease and to also encode different prion disease strains. However it is apparent that host contributed factors including the prion protein itself affect the disease process. My research group uses *in vivo* and *in vitro* models of prion disease and an integrated system of biochemical, molecular, cellular biology methods to investigate the contribution of the host in the transmission, pathogenesis and therapeutic impact of prion diseases. It is hoped that this research will contribute to our understanding of the molecular basis of prion disease pathogenesis and the development of effective therapeutic interventions for a disease that currently has no cure.

Honours projects offered in 2008 include:

1) investigating the effect of metal co-ordination on the capacity of the prion protein to bind to glycosaminoglycans, large negatively charged molecules that have been implicated as auxiliary factors in prion disease transmission and pathogenesis;

2) the role that glycosaminoglycans have on the trafficking of the prion protein in a cell culture model of prion disease and the effect this has on the ability of the protein to convert to a protease resistant form and susceptibility of the cell line to infection with prions.

Techniques associated with these project may include cloning and expression of the prion protein in bacterial and mammalian systems, biochemical analysis (chromatography, SDS-PAGE, protein staining and western blot), cell-free assays of prion propagation, mammalian cell culture, identification/ characterisation of binding sites and immunofluorescence.

PROJECT START TIME (indicated preferred start time):**February 2008: Yes****July 2008 (mid-year intake): Yes****PREFERRED BACKGROUND OF STUDENT: Pathology, Biochemistry, Microbiology****NAME OF SUPERVISOR(S): Vicki Lawson****DEPARTMENT & INSTITUTION: Department of Pathology, The University of Melbourne****CONTACT PHONE & FAX NUMBERS: 8344-1944 (ph) 8344-4004 (fax)****CONTACT EMAIL ADDRESS: vlawson@unimelb.edu.au**

B.Sc. Honours 2008

PROJECT TITLE:

Investigation of the role of candidate proteins in the molecular pathogenesis of frontotemporal dementia

PROJECT DESCRIPTION

(including techniques to be used)

Frontotemporal dementias (FTD) consist of a number of disorders which share similar clinical (behavioural, personality, cognitive), neuroimaging (frontotemporal atrophy) and macroscopic pathological (reduced brain size, frontotemporal atrophy, cortical thinning) changes. The clinical syndromes however do not generally provide sufficient diagnostic differentiation between the neuropathological subtypes of FTD. Diagnostic discrimination ultimately occurs at the immunohistochemical and is largely based on the presence or absence of tau or ubiquitin positive intraneuronal inclusions. The study of patients with familial FTD has shed much light on the nature of the associated genetic and biochemical disturbances. Recent advances have included the identification of mutations in the tau gene (<http://www.molgen.ua.ac.be>) and progranulin genes on chromosome 17 mutation and the identification of TDP-43 as a major constituent of inclusions in tau negative ubiquitin immunoreactive inclusions of patients with FTD.

The aims of the current project are to examine a cohort of brains from patients with young onset frontotemporal dementia for progranulin mutations and progranulin and TDP-43 expression.

Routinely used histological techniques for progranulin and TDP-43 immunoreactivity will be used to stain sections of FTD and normal control brains with antibodies to each protein. Standardised routine Western Blotting techniques will be used to identify TDP-43 and progranulin protein expression using specific antibodies. The expression pattern of tau and ubiquitin will also be studied. This project will also involve sequential fractionation of proteins based on their solubility. Screening for mutations in the progranulin gene (PGRN) will involve DNA extraction from brain tissue, PCR amplification and direct sequencing of the PCR products.

PROJECT START TIME (indicated preferred start time):

February 2008:

Yes

July 2008 (mid-year intake):

Yes only if the position is not filled in Feb

PREFERRED BACKGROUND OF STUDENT: Biochemical knowledge is preferable, but not essential. An interest in neuroscience is also favourable.

NAME OF SUPERVISOR(S): Dr. Qiao-Xin Li, Dr Dennis Velakoulis and Ms Tiffany Cowie

DEPARTMENT & INSTITUTION: Department of Pathology and Melbourne Neuropsychiatry Centre (Department of Psychiatry and Melbourne Health)

CONTACT PHONE & FAX NUMBERS: 8344-5878 or 8344-4049

CONTACT EMAIL ADDRESS: q.li@unimelb.edu.au, dennis.velakoulis@mh.org.au

B.Sc. Honours 2008

PROJECT TITLE: Isolation of Antithrombin Heparin (ATH) complex from heparinised plasma.

PROJECT DESCRIPTION:

Unfractionated Heparin (UFH) is the most commonly used anticoagulant medication in children. Over 15% of children admitted to a tertiary paediatric hospital are exposed to UFH during their inpatient care. Therefore, the interaction between UFH and the haemostatic system is of significant clinical importance. UFH binding to lysine sites on Antithrombin (AT) is enhanced by the pentasaccharide sequence which is found on approximately 30% of UFH molecules.

We have previously demonstrated that covalent complexes of Antithrombin Heparin (ATH) and Heparin Cofactor II Heparin (HCH) can form via Schiff base-Amadori rearrangement and likely form *in vivo*. ATH has increased ratio of β -AT to α -AT compared to natural adult AT. We have preliminary data that suggests neonatal AT has increased ratio of β -AT to α -AT, suggesting that neonatal AT may be more likely to form covalent complexes. Increased *in vivo* formation of covalent ATH complexes in children is one proposed explanation for the incomplete reversal of UFH observed in children during cardiopulmonary bypass (CPB).

Hypothesis: There will be age-specific differences in formation of ATH.

Specific aim: To determine a method for isolation of Antithrombin-Heparin (ATH) complex from plasma samples obtained from children receiving UFH therapy.

Rationale: ATH has increased ratio of β -AT to α -AT compared to natural adult AT. We have preliminary data that neonatal AT has increased ratio of β -AT to α -AT, suggesting that neonatal AT may be more likely to form covalent complexes. Heparin-AT covalent complex formation is likely influenced by age-related structural differences in AT.

Research Plan: ATH will be isolated from plasma samples obtained from children undergoing CPB. Children will be grouped into age-groups (<1 year old, 1-5 year old, 6-10 year old, 11-16 year old). There will be a minimum of 5 subjects per age-group. Baseline levels of AT will be assessed. ATH will be isolated and the relative quantities that have formed in each age-group will be assessed and standardised against the relative plasma levels of AT to assess whether differences in covalent complex formation represent differences in plasma protein levels, or differing propensities to form covalent complexes.

Techniques: Antibody specific purification, SDS-PAGE, HPLC, LC-MS/MS, basic haemostatic assays.

PROJECT START TIME (indicated preferred start time):

February 2008: Yes

July 2008 (mid-year intake): Yes

**PREFERRED BACKGROUND OF STUDENT: Biochemistry and Molecular Biology,
Pathology**

NAME OF SUPERVISOR(S): Professor Paul Monagle, Dr Vera Ignjatovic

DEPARTMENT & INSTITUTION:

Department of Pathology, University of Melbourne

Department of Clinical Haematology, Royal Children's Hospital

CONTACT PHONE & FAX NUMBERS: Phone: 83443750

CONTACT EMAIL ADDRESS: verai@unimelb.edu.au

Department of Pathology

The University of Melbourne

B.Sc. Honours 2008

PROJECT TITLE: Age-related differences in endothelial cell binding of Unfractionated Heparin (UFH).

PROJECT DESCRIPTION:

Unfractionated Heparin (UFH) is the most commonly used anticoagulant medication in children. Over 15% of children admitted to a tertiary paediatric hospital are exposed to UFH during their inpatient care. Therefore, the interaction between UFH and the haemostatic system is of significant clinical importance. This proposed study is a direct follow on from our previous research and considers that we need to examine not only the “effect” of UFH in children of different ages, but also the mechanism of action of UFH in children of different ages.

Hypothesis: There will be age-specific differences in UFH binding to endothelial cells.

Rationale: The observed differences in weight-adjusted dose requirements for UFH in children compared to adults suggest there is a difference in binding of UFH. Our previous study confirmed that there are clinically significant age-related differences in the anticoagulant effect of UFH. Quantitative and qualitative differences in key haemostatic proteins with age will likely alter the affinity of haemostatic proteins for UFH. Hence, differences in UFH binding to the vascular endothelium will occur. These binding differences may explain the observed differences in anticoagulant effect, and understanding them will be crucial to developing better strategies for optimal use of UFH in children.

Specific aim: To develop a technique sensitive enough to determine if there are age-specific differences in Endothelial cell binding of UFH.

Research plan: Standard endothelial cell cultures (HUVEC monolayers) will be incubated with plasma from different aged healthy children and clinically relevant concentrations of UFH. Differences in endothelial cell binding of the UFH will be determined, by measurement of free UFH remaining in the supernatant. The anticoagulant effect of the bound UFH will be assessed by measuring thrombin generation (Endogenous Thrombin Potential) on the cell surfaces using the non-continuous method which allows for specific calculation of α -2-macroglobulin inhibited thrombin (α -2-macroglobulin concentrations are greatly increased in children compared to adults).

Techniques: cell culture, basic haemostatic assays

PROJECT START TIME (indicated preferred start time):

February 2008: Yes

July 2008 (mid-year intake): Yes

PREFERRED BACKGROUND OF STUDENT: Biochemistry and Molecular Biology, Pathology

NAME OF SUPERVISOR(S): Professor Paul Monagle, Dr Vera Ignjatovic

DEPARTMENT & INSTITUTION:

**Department of Pathology, University of Melbourne
Department of Clinical Haematology, Royal Children’s Hospital**

CONTACT PHONE & FAX NUMBERS:

Phone: 83443750

CONTACT EMAIL ADDRESS:

verai@unimelb.edu.au

Department of Pathology

The University of Melbourne

B.Sc. Honours 2008

PROJECT TITLE: Characterisation of cord blood derived stem cells

PROJECT DESCRIPTION

Cord blood is the blood left behind in the placenta and umbilical cord after birth of a baby. Cells from bone marrow (BM) or cord blood (CB) are already used to treat over 75 haematological diseases. Six thousand cord blood stem cell transplants worldwide have demonstrated the safety of the procedure.

It has recently been shown that cord blood derived adult stem cells have the capacity to differentiate into cells from all three germ line layers (endoderm, ectoderm and mesoderm). This means they resemble embryonic stem cells, although “adult” in origin and completely ethical to work with. However, further characterisation and improvements in the isolation of cord blood derived stem cells is essential to enable their application. The objective of the stem cell research laboratory is to establish the scientific basis to make it possible to use these somatic stem cells for cell therapy to treat any diseased or injured tissue.

Sample Research Topics:

1. Improving the propagation of cord blood derived stem cells and testing if they change in properties as they divide over several generations.
2. Determining if cord blood stem cells can differentiate into lung cells in culture.

Techniques

Stem cell propagation and differentiation, RTPCR, antibody staining and FACS analysis

PROJECT START TIME (indicated preferred start time):

February 2008: Yes

July 2008 (mid-year intake): Yes

PREFERRED BACKGROUND OF STUDENT: Molecular and Cell Biology

NAME OF SUPERVISOR(S): Professor Bob Williamson, Dr Faten Zaibak

DEPARTMENT & INSTITUTION: Department of Pathology, The University of Melbourne

CONTACT PHONE & FAX NUMBERS: Phone: 83445908 or 83444181

Fax: 8344 4004

CONTACT EMAIL ADDRESS:

fzaibak@unimelb.edu.au or
r.williamson@unimelb.edu.auology

B.Sc. Honours 2008**EXAMINATION OF THE MOLECULAR AND CELLULAR BASIS OF IMMUNOSTIMULATION INDUCED BY BOTANICAL MEDICINALS.**

Herbal medicines or botanical medicinals have been used by primitive and civilized societies throughout the world for many thousands of years. In China, early records dating from 3000 B.C. document the use of herbal preparations for the treatment of disease. By the 16th Century the publication of *Pen t'sao Kang Mu* (*The General Catalog of Herbs*) in China documented the use of 1,871 herbs in 8,160 herbal prescriptions for the treatment of inflammation, infections, fractures, burns and cancer.

With the accelerated growth of Western medicine, the use of traditional herbal medicines has declined significantly in the past 100 years. Western medicine utilizes a "reductionist" scientific approach for the development of therapies to prevent and treat disease and rigorous clinical trialling prior to the release of newly-developed drugs. In spite of this, there are 120 distinct plant-derived substances which are currently registered for clinical treatment of inflammation, hypertension, pain, bacterial and parasitic infections and cancer.

During 2006, we have demonstrated differential effects of two Chinese herbal medicine preparations a number of normal and cancer cell lines. Current studies are aimed at the isolation of the bioactive components of these botanical preparations.

Recently, new interest in the effects of herbal medicines on immune function has emerged. Our laboratory has examined three botanical preparations and identified significantly increased immune responses to human vaccine antigens in mice treated with these preparations. Preliminary observations indicate an absence of autoimmunity to intracellular antigens, which are the common targets of autoantibodies in non-organ specific autoimmune diseases, in the mice treated with the botanical medicinals and an absence of microstructural changes in tissues and organs and inflammatory cell infiltrates. For 2008, we will extend these studies to investigate the cellular and molecular basis of the immunostimulatory responses to the vaccine antigens.

Techniques to be used in this study will include *in vitro* T and B lymphocyte stimulation and cell proliferation assays, analysis of cytokine secretion profiles induced by immunostimulatory botanical medicinals, sub-fractionation and analysis of immunoactive components of botanical medicinals, ELISA, immunoblotting and/or immunoprecipitation, immunohistochemistry, immunofluorescence, and histology.

PROJECT START TIME:

February 2008:	Yes
July 2008 (mid-year intake):	Yes

PREFERRED BACKGROUND OF STUDENT: Pathology/Immunology/Biochemistry

NAME OF SUPERVISOR/S: Dr John R. Underwood (Pathology)

DEPARTMENT & INSTITUTION: Department of Pathology

CONTACT PHONE NUMBER: 9344-4292 (office), 043-817-4034 (mobile)
9344-4004 (fax)
johnru@unimelb.edu.au

**Burnet Institute at
Austin**
(formerly Austin Research Institute)

B.Sc. Honours 2008

PROJECT TITLE: Defining mechanisms of immunoreceptor binding to pathogenic bacterial pathogens.

PROJECT DESCRIPTION

Inflammatory and infectious diseases are increasingly representing major global public health challenges. Growing resistance to antibacterial therapy contributes to continued morbidity, mortality and unmet medical need. To address these challenges, our studies aim to elucidate some of the fundamental mechanisms of bacterial pathogen pathogen-host interactions and physical interface involving immunoreceptors. Immune cells are equipped with an array of immunoreceptors to detect pathogens and to initiate innate and adaptive immunity. Ig-ITIM superfamily members are expressed by immune cells including macrophages, dendritic cells, T cells, B cells and NK cells. These include PECAM-1 and CEACAM1, which are adhesive, endocytic and signalling receptors that play an important role in innate and adaptive immunity. An understanding of how these molecules influence these mechanisms will provide the basis for understanding some of the important interactions in infection and immunity. Recent studies in the Immunoreceptor Laboratory suggest that carbohydrate moieties displayed by Ig-ITIM superfamily members are key cellular “antennas” in fine-tuning physical interactions between individual Ig-ITIM superfamily members and their physiological ligands that include bacterial microbes. The specificity of receptor:microbial interactions involving Ig-ITIM superfamily members has remained poorly understood. In this study, we will use a combination of *in vitro* and *in vivo* approaches to help define the role of Ig-ITIM superfamily members in *S. aureus* infection and immunity.

Aim 1. To define mechanisms of immunoreceptor recognition of *S. aureus* bacteria *in vitro*. This study will principally examine *in vitro* bacterial pathogen recognition of different Ig-ITIM superfamily members. We will define the physical interface between *S. aureus* bacteria (laboratory strain) and immunoreceptor binding determinants using ELISA, immunofluorescence and bacterial CFU analysis. By using recombinant immunoreceptor Ig-Domains and *S. aureus* mutants, we will map the respective binding sites on human and mouse Ig-Domains of immunoreceptors required for binding the bacteria.

Aim 2. To define mechanisms of action of immunoreceptors *in vitro*. We propose that Ig-ITIM superfamily members serve as recognition receptors arrayed on immune cells whose signalling responses are important in the modulation of endocytic/phagocytic responses. In this aim, we will investigate the response of wild-type versus PECAM-1 KO neutrophils in terms of production of pathogen killing and pathogen processing (inflammatory cytokine production and respiratory burst).

Aim 3. To define the role that immunoreceptors play in the pathogenesis of *S. aureus* infection *in vivo*. In this aim, we will investigate the biological function of Ig-ITIM superfamily members, PECAM-1 as a recognition receptor for bacterial pathogens *in vivo*, using *S. aureus* mouse models. Parameters to be measured include survival, bacterial clearance in organs and blood, clinical chemistry to monitor organ failure, cellular immunology profiles and histology of organs.

PROJECT START TIME (indicated preferred start time):

February 2008:	X	Yes	No
July 2008 (mid-year intake):	Yes		No

PREFERRED BACKGROUND OF STUDENT: Science based.

**NAME OF SUPERVISOR(S): A/Prof. Denise Jackson
Dr. Bruce Wines**

DEPARTMENT & INSTITUTION: Burnet Institute at Austin.

CONTACT PHONE & FAX NUMBERS: Ph: (03) 9287-0657; Fax: (03) 9287-0600.

CONTACT EMAIL ADDRESS: djackson@burnet.edu.au

B.Sc. Honours 2008**PROJECT TITLE: Understanding mechanisms of regulating blood clots****PROJECT DESCRIPTION**

Platelets are fragments of megakaryocytes released into the blood stream that play an important role in preventing excessive blood loss at sites of tissue injury by sticking together and forming a haemostatic plug. Excessive platelet clumping in diseased blood vessels can lead to blockages and cause thrombotic diseases such as heart disease and stroke, two of the biggest killers of humans in the western world. In this study, we will seek to understand the cognate receptor relationships of tetraspanins in platelets coupled with signaling pathways and how this impacts on thrombosis and stroke in mouse models.

Aims: 1). To define lateral binding partners of tetraspanins on the surface of platelets. In this aim, we will define the repertoire of binding partners of tetraspanins in platelets. Using several approaches including co-immunoprecipitation/western blot studies from resting, activated and aggregated human and mouse platelets, SDS-PAGE with Coomassie blue or silver protein staining, a proteomics/mass spectrometry approach and analysis of platelets from various tetraspanin, immunoreceptor, and FcR gamma chain knockout mice for cell surface expression of binding partner. We will also examine the functional consequences of tetraspanin: integrin interactions in platelet spreading on specific extracellular matrices (fibronectin, vitronectin, laminin, Type I collagen) \pm anti-integrin subunit blocking antibodies. Finally, wild-type versus various tetraspanin KO platelet adhesion on specialised extracellular matrices under *in vitro* low and high shear flow conditions will be determined.

2). To investigate mechanisms of signalling cross-talk between tetraspanins and integrins in platelets. In this aim, we will define mechanisms of signalling cross-talk between tetraspanins and cognate binding receptors by characterising several putative signalling molecule interactions with tetraspanins that occur under resting, activated platelets or integrin $\alpha_{IIb}\beta_3$ -mediated platelet aggregation.

Outcomes and Significance: Understanding the interplay, organisation and signalling events of tetraspanin interactions, and their role in thrombosis will provide new knowledge concerning the basic mechanisms of the biology of these receptors.

PROJECT START TIME (indicated preferred start time):

February 2008:	X	Yes	No
July 2008 (mid-year intake):	Yes	No	No

PREFERRED BACKGROUND OF STUDENT: Science based.**NAME OF SUPERVISOR(S): A/Prof. Denise Jackson****DEPARTMENT & INSTITUTION: Burnet Institute at Austin****CONTACT PHONE & FAX NUMBERS: Ph: (03) 9287-0657; Fax: (03) 9287-0600.****CONTACT EMAIL ADDRESS: djackson@burnet.edu.au**

B.Sc. Honours 2008**PROJECT TITLE: Exploring the roles of carbohydrates on the structures and functions of human IgM cryoglobulins****PROJECT DESCRIPTION**

Cryoglobulinemia is a “cold-sensitivity” condition that is associated with the presence of a cryoglobulin, which is reversibly insoluble at low temperatures. Clinical severity varies widely and is correlated with the type of cryoglobulin (monoclonal or mixed immunoglobulins) and the physical nature of the aggregates (precipitate, gel or crystal). We have selected two monoclonal IgM cryoglobulins (Pot and Yvo), isolated from plasma of patients with Waldenström’s macroglobulinemia, for detailed structural and functional characterization. Since up to 12% of the mass of an IgM is attributable to complex N- and O-linked glycans, it is likely that the oligosaccharides influence structural and functional properties of IgM. Using dynamic light scattering (DLS), we have shown that different processes contribute to cold-induced precipitation (Pot IgM) and gelation (Yvo IgM) of cryoglobulins [1]. In this project, the DLS assay will be used to monitor the effects on cold-induced aggregation after treatment of the IgM cryoglobulins with a variety of glycosidases. Accessibility and composition of carbohydrates in the intact IgM and antigen binding fragments (Fab) will be probed with a panel of specific carbohydrate binding proteins (lectins) using ELISA and biosensor (Biacore) techniques. Furthermore, we have determined crystal structures for the fully glycosylated antigen binding fragments (Fab) of both the Yvo [2] and Pot cryoglobulins. A goal of this project is to produce crystals of the Pot and Yvo Fab with modified N-linked carbohydrates. X-ray crystallography and molecular modeling will be used to examine the three-dimensional structures of the Fab associated glycans with regard to their possible roles in the assembly of crystalline lattices and cold-induced aggregates. In summary, this project will provide important functional and structural information for a diverse group of clinically relevant proteins (cryoglobulins), associated with a range of human diseases.

[1] Vallas *et al.*, (2007) *J Mol Recognit*, 20:90-96.

[2] Ramsland *et al.*, (2006) *Biochem J*, 395:473-481.

PROJECT START TIME (indicated preferred start time):**February 2008: Yes****July 2008 (mid-year intake): No****PREFERRED BACKGROUND OF STUDENT:** Pathology/Immunology/Biochemistry**NAME OF SUPERVISOR(S):** Drs Paul A Ramsland and Bruce D Wines**DEPARTMENT & INSTITUTION:** Structural Immunology Laboratory, Burnet Institute (Austin Campus, Heidelberg)**CONTACT PHONE & FAX NUMBERS:** Tel. (03) 9287 0686, Fax. (03) 9287 0600**CONTACT EMAIL ADDRESS:** pramsland@burnet.edu.au

**Bone Marrow
Transplantation Unit
Alfred Hospital**

B.Sc. Honours 2008

PROJECT TITLE: The novel expression of calcitonin receptor by stem cells present in normal and diseased bone marrow.

PROJECT DESCRIPTION

Haematopoietic stem cells and mesenchymal stem cells are important precursors maintained in bone marrow that provide the source of mature cells, which are mobilized in response to injury and disease.

The expression of calcitonin receptor (CTR) by sub-populations of precursor cells (blasts) is a recent discovery from our laboratory. Such CTR+ blast cells are recruited from blood into regions of the diseased vasculature, as well as providing a source of nascent cells for wound healing. Furthermore, large populations of CTR+ blast cells are found in the bone marrow aspirants of patients with leukaemia.

Novel anti-CTR antibodies have been developed in our laboratory, which have the potential for use in the purification of CTR+ blast cells. Furthermore, a cell line (HL-60), derived from a patient with acute lymphoblastic leukaemia expresses CTR and will be used in a variety of experiments (real time PCR, western blot, immunohistochemistry, cell sorting) to confirm the fidelity of the antibodies. Secondly, these anti-CTR antibodies will be used in the analyses of bone marrow aspirants and peripheral blood taken from patients with leukaemia undergoing treatment.

These studies are aimed at the investigation of the idea that CTR+ blast cells play a central role in the etiology of some forms of leukaemia.

PROJECT START TIME (indicated preferred start time):

February 2008:

Yes

July 2008 (mid-year intake):

Yes , if no suitable student can begin in Feb

PREFERRED BACKGROUND OF STUDENT: Some molecular biology and an interest in translational research

NAME OF SUPERVISOR(S): Dr Peter Wookey

DEPARTMENT & INSTITUTION: Medicine, University of Melbourne, Austin Health

CONTACT PHONE & FAX NUMBERS: 496 3584

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Genomic Diseases Research Centre

B.Sc. Honours 2008

Professor Richard Cotton of the Genomic Disorders Research Centre and Dr Finlay McRae of The Department of Colorectal Medicine and Genetics, The Royal Melbourne Hospital will be offering two B.Sc. Honours projects in Pathology for 2008. The details of the projects will be available shortly or can be obtained by contacting Professor Cotton

PROJECT START TIME (indicated preferred start time):

February 2008: Yes

July 2008 (mid-year intake):

PREFERRED BACKGROUND OF STUDENT: Science/Bioinformatics

NAME OF SUPERVISOR(S): Prof. Richard Cotton/Prof. Finlay Macrae

DEPARTMENT & INSTITUTION: Genomic Disorders Research Centre/The Department of Colorectal Medicine and Genetics, The Royal Melbourne Hospital

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**Peter MacCallum
Cancer Institute**

B.Sc. Honours 2008

Involvement of Siah proteins in the tumour/stroma microenvironment

Supervisors: Professor David Bowtell & Dr. Andreas Moeller

The induction of new blood vessel outgrowth (neo-angiogenesis) is a key hallmark of tumour progression and is caused by reduced oxygen levels in the tumour (hypoxia). Cells respond to hypoxia by the stabilization of the transcription factor, Hif-1alpha, which in turn up-regulates genes inducing neo-angiogenesis. It still remains unclear, however, whether the tumour cells themselves or the surrounding tissue is the main source of the neo-angiogenesis.

Recently our group demonstrated the involvement of Siah ubiquitin ligases in the regulation of Hif-1alpha protein levels (Nakayama et al., Cell 2004). Using our Siah knockout mice, this project aims to establish and analyse tumour models defining the tissue responsible for neo-angiogenesis in tumours and the importance of Siah and Hif proteins in this process. The project is supported by excellent mouse breeding and molecular/biochemical facilities and will be performed as part of an internationally competitive multidisciplinary team incorporating a number of innovative techniques such as microarray, quantitative real-time PCR, protein degradation assays and siRNA approaches.

References:

1. House, CM, et al., *Elucidation of the substrate binding site of Siah ubiquitin ligase*. Structure, 2006 14(4):695-701.
2. Nakayama, K., et al., *Siah2 regulates stability of prolyl-hydroxylases, controls HIF1alpha abundance, and modulates physiological responses to hypoxia*. Cell, 2004. 117(7): p. 941-52.
3. Frew, I.J., et al., *Generation and analysis of Siah2 mutant mice*. Mol Cell Biol, 2003. 23(24): p. 9150-61.
4. Dickins, R.A., et al., *The ubiquitin ligase component Siah1a is required for completion of meiosis I in male mice*. Mol Cell Biol, 2002. 22(7): p. 2294-303.
5. Frew, I.J., et al., *Normal p53 function in primary cells deficient for Siah genes*. Mol Cell Biol, 2002. 22(23): p. 8155-64.

For more information about this project contact:

Professor David Bowtell (Group Leader)

Dr. Andreas Moeller, Tel: +61 3 9656 1287, Email: andreas.moeller@petermac.org

Peter MacCallum Cancer Centre, Cancer Genetics & Genomics Laboratory

Preferred background: science, biomedical sciences

Project start time: February or July 2008

B.Sc. Honours 2008

Distinguishing recurrent breast tumours from de novo primary breast carcinomas

Supervisors: Professor Stephen Fox & A/Prof Alexander Dobrovic

Hypothesis: Profiling tumours for a series of cancer specific changes will allow the ready determination of the relationships between primary and recurrent/new primary breast cancers.

Clinical issues:

- Patients with breast cancer are at increased risk of a second breast cancer and also from local relapses in the breast. Currently we do not have the ability to accurately identify whether a new breast tumour arising in the breast is a new primary breast cancer or a recurrence of a previous tumour. This is essential since their treatments are very different.
- Recurrent breast cancer is considered a metastasis but not all recurrences have similar biological behaviour and therefore a "recurrence" breast tumour classification system on which to base treatment decisions is needed. This is likely to become more important with the further molecular characterisation of breast cancer for targeted treatment.
- The true frequency of multifocal / multicentric breast cancers is unknown. Morphology alone is not adequate in distinguishing between truly synchronous tumours and multiple deposits of the same tumour. This issue is of importance since staging and treatment decisions are based on these observations.

Methodology: Tumour specific markers based on mutation and methylation will be used to compare primary and ipsilateral second presentation. These markers have been selected because the readout is only minimally affected by the presence of contaminating normal tissue. The technique for screening is the novel methodology of high resolution melting analysis which has been recently developed in the Molecular Pathology Research Laboratory and allows rapid and sensitive 'in-tube' typing within a few hours.

Mutation Analysis: DNA will be screened for p53 and PIK3Ca mutations using high resolution melting. As PIK3Ca mutations are observed in 40% of breast tumours and mutations are likely to be of independent origin i.e. at different sites, this marker alone is likely to be informative in many cases. This marker will be uninformative if it is unmutated in both tumours. If the mutation is discordant between the tumours, it is likely that they are of independent origin. If the mutation is the same in the tumours, it is very likely that they are of common origin. Sequencing and identification of mutations will enable the relationship between primary and recurrences/new primaries to be ascertained. We have recently demonstrated that high resolution melting can be used to detect such mutations in human tumour samples, even when the mutation is present in as few as 10% of cells.

Methylation Analysis: DNA will be bisulphite modified, amplified by whole genome amplification and screened for the methylation of a panel of promoter regions commonly methylated in cancer. Tumours are unlikely to show similar profiles unless related. This is the first time that such a large panel of known promoters has been used to evaluate methylation in breast cancer and will enable us to choose a more restricted panel of methylation markers to distinguish between unrelated tumours by high resolution melting analysis of a smaller panel of markers.

For more information about this project contact:

A/Prof Alexander Dobrovic, Tel: +61 3 9656 1807, Email: alexander.dobrovic@petermac.org
Peter MacCallum Cancer Centre, Molecular Pathology Research Program

B.Sc. Honours 2008

Understanding the molecular mechanism of long term survival after radiotherapy for lung cancer

Supervisors: A/Prof Alexander Dobrovic & Dr. Michael McManus

We seek to understand why about 1% of patients with apparently-incurable non-small cell lung cancer have experienced long-term survival and even cure after low dose palliative radiotherapy at Peter Mac. This initiative builds on a highly successful research project. (MacManus MP, Matthews JP, Wada M, Wirth A, Worotniuk V, Ball DL. *Unexpected long-term survival after low-dose palliative radiotherapy for non-small cell lung cancer*. *Cancer*. 2006 106:1110-6). That study attained widespread publicity in the medical and lay press and media, both internationally and in Australia, including the Health Report with Norman Swann, and was discussed in articles in the *Lancet* and in *Nature Clinical Reviews*.

Hypothesis. The tumours in these patients are likely to have a defect with in DNA repair or in DNA damage sensing pathways which underlies their extraordinary radiosensitivity. This defect/these defects will also occur in some patients treated with conventional radiotherapy.

Experimental plan - Methylation profiling for methylated DNA repair genes: As the amount of DNA from the tumours will be limited and the DNA undergoes further degradation during bisulphite modification, a whole genome amplification method specific for bisulphite modified DNA will be used. Methylation of genes involved in the detection and repair of damage caused by ionising radiation will be assessed. These include ATM, CHK2, BRCA1, and FANCF.

Mutation status of genes determining sensitivity to radiation: DNA will be screened for p53 (exons 5-8), PTEN (exons 5-8), and PIK3Ca (exons 9, 20) mutations using high resolution melting. Inactivating mutations at any of these genes is likely to lead to radioresistance and would be more likely to be found in the control population.

Profiling expression: We will use a panel of 190 genes including all known DNA repair genes, selected anti- and pro-apoptotic genes, HIF1 alpha to assess hypoxia and genes that Ramaswamy reported as being associated with metastasis in adenocarcinoma, particularly lung adenocarcinoma.

For more information about this project contact:

A/Prof Alexander Dobrovic, Tel: +61 3 9656 1807, Email: alexander.dobrovic@petermac.org
Peter MacCallum Cancer Centre, Molecular Pathology Research Program

B.Sc. Honours 2008

Role of mitochondrial pathway to apoptosis in cytotoxic lymphocyte mediated killing

Supervisors: Dr. Nigel Waterhouse & Professor Joe Trapani

One mechanism by which cytotoxic lymphocytes (CL) kill their target cells is via granule exocytosis. During this process CL deliver perforin and granzyme B to the target cell. Purified perforin and granzyme B have been shown to induce mitochondrial damage, resulting in a specific form of cell death known as apoptosis. Little is known about how intact CL kill their target cell. We have recently established experimental models and developed specific techniques to investigate the exact nature of how intact CL kill their target cells. We have found that some CL that lack granzyme B can still kill their targets but cannot induce apoptosis. Further, cells that express specific viral proteins or mutated proteins that are integral to apoptosis are still killed by CL. This poses the question as to how CL specifically induce apoptosis and how CL can kill cells in which apoptosis is blocked.

This project will investigate how CL kill target cells in which key proteins involved in the mitochondrial pathway to apoptosis have been deleted. Our lab has developed a bank of primary lymphomas arising from various gene deficient animals, including Bid, apaf, and caspase-9. The student will investigate and compare the morphological and biochemical features of death of these lines induced by purified granzyme B, intact wild type CL and CL from granzyme B deficient mice to determine whether removing key regulators of specific apoptosis pathways can alter the death from apoptosis to alternative death mechanisms.

During this project the student will develop skills in tissue culture, primary cell isolation, apoptosis assays, CL mediated killing, and time-lapse microscopy. It is envisaged that the student will identify the key proteins involved in CL-mediated apoptosis and potentially identify novel pathways by which tumour cells can be killed.

For more information about this project contact:

Professor Joe Trapani (Group Leader), Tel: +61 3 9656 1326, Email: joe.trapani@petermac.org

Dr. Nigel Waterhouse, Tel: +61 3 9656 1657, Email: nigel.waterhouse@petermac.org

Peter MacCallum Cancer Centre, Cancer Cell Death Laboratory

Preferred background: science, biomedical sciences

Project start time: February or July 2008

B.Sc. Honours 2008

Bridging the evolution and function of perforin, a key regulator of immune homoeostasis.

Supervisors: Dr. Ilia Voskoboinik, Professor Joe Trapani & Dr. Charles Robin

Perforin is a cytolytic protein, which regulates cytotoxicity of cytotoxic T lymphocytes (CTL) and natural killer (NK) cells. These cells destroy virus infected or transformed cell targets. The lack of perforin expression or the loss of function due to detrimental mutations, or the inability of an immune cell to process perforin leads to a fatal disease in neonates, familial haemophagocytic lymphohistiocytosis (FHL). FHL is characterised by severe enlargement of the lymphoid organs, which are infiltrated by activated macrophages and T cells. Very little is known about the mechanism and structure of perforin, despite a considerable wealth of information on its key role in immune homoeostasis and immune surveillance. Understanding the structure and properties of perforin will help to elucidate the mechanism of cytotoxicity of CTL and NK cell. Perforin is a mysterious protein. It was discovered more than 20 years ago, but only recently experimental methodologies have been developed to investigate its properties. Current advances in genome projects have made available the DNA sequences from many evolutionarily distant species for comparative analysis. Interestingly, several perforin homologue genes are being identified within a single genome of various types of fish and frogs, while single copies of the gene exist in higher organisms. The starting point of the project will be a comparative genomic analysis of perforin homologues from evolutionarily distant species. On the basis of these analyses, the evolution of putative functional domains of perforin will be investigated. These hypotheses will be tested experimentally by expressing perforin homologs in immune cells and testing their ability to kill target cells. These studies are expected to further elucidate the evolution of the immune system and will provide key information on the mechanism and structure of a key player, perforin. The project involves bioinformatics and a wide range of genetic, cell biology, biochemistry and immunology techniques. The project is offered jointly by Cancer Immunology Program at Peter MacCallum Cancer Centre and Department of Genetics, The University of Melbourne. Applicants are expected to complete major in genetics and biochemistry.

For more information about this project contact:

Professor Joe Trapani (Group Leader), Tel: +61 3 9656 1326, Email: joe.trapani@petermac.org

Dr. Ilia Voskoboinik, Tel: +61 3 9656 1657, Email: ilia.voskoboinik@petermac.org

Peter MacCallum Cancer Centre, Cancer Cell Death Laboratory

Preferred background: science, biomedical sciences

Project start time: February or July 2008

B.Sc. Honours 2008

NK cell-mediated rejection of cancer

Supervisors: Prof Mark Smyth & Dr Daniel Andrews

Chronic infection and inflammation are considered to important factors contributing to tumorigenesis and tumor progression. By contrast, innate lymphocytes also play a major role in preventing spontaneous tumour formation. The innate immune system recognizes the presence of bacterial pathogens through the expression of a family of membrane receptors known as Toll-like receptors (TLR). TLRs play essential roles in innate immunosurveillance by recognizing microbial-associated pathogen-associated molecular patterns (PAMP) expressed by bacteria and viruses but also host-derived PAMPs, such as stress proteins. TLRs mediate alternative pathways by utilizing a specific combination of adapter molecules (including MyD88, TRAM, TITAP and Trif) to mount appropriate immune responses. We have recently determined that MyD88 is required for optimal tumour initiation in some tumour models. However more surprisingly, MyD88-deficient mice are less effective than wild-type mice in suppressing some experimental tumours in a natural killer (NK) cell-dependent manner. In particular we now hope to uncover a new pathway of NK cell activation and tumour rejection that requires MyD88 signalling.

We are seeking a highly motivated Hons student. A background and interest in cellular immunology is desirable and a working knowledge of cellular immunology, molecular biology, flow cytometry, and mouse experimentation would be beneficial. The project will be performed as part of an internationally competitive multidisciplinary team with access to the best reagents and many strains of gene-targeted mice. The project will incorporate a number of innovative techniques such as specialist tumour models in various gene-targeted mice, multi-colour flow cytometry and immunohistochemistry.

Reference:

1. Smyth, et al. Nature Reviews Cancer. 2:850-861, 2002.

For more information about this project contact:

Prof. Mark Smyth (Group Leader), Tel: +61 3 9656 3728, E-mail: mark.smyth@petermac.org
Peter MacCallum Cancer Centre, Cellular Immunity Laboratory

Preferred background: science, biomedical sciences

Project start time: February or July 2008

B.Sc. Honours 2008

To investigate the role of polarity proteins in asymmetric cell division of T lymphocytes

Supervisors: Dr Jane Oliaro and Dr Sarah Russell

Cellular diversity during development is often generated through the segregation of cell fate determinants predominantly into one daughter cell during cell division. During an immune response, T lymphocyte interactions with antigen presenting cells involves the formation of an immunological synapse (IS) proximal to the APC and clustering of signaling complexes at the distal pole of an axis perpendicular to the APC. Our laboratory has identified a network of polarity proteins in T lymphocytes and demonstrated that at least one polarity protein is required for IS formation and migration of T lymphocytes (1).

In general, it is thought that T lymphocytes detached from the antigen presenting cell (APC) before dividing, and that differences between the fate of daughter cells is determined by differences in their subsequent exposure to signals or chance differences in the inheritance of signalling molecules and cell fate determinants. However, using live imaging, we have been able to visualise T lymphocyte interactions with dendritic cells (DC) *in vitro* until the time of first division and observed that as T cells undergo mitosis, they remain attached to the DC with one daughter connected to the APC ('proximal' cell) and the other daughter ('distal' cell) not in contact until after division is complete. Immunofluorescent confocal microscopy of these dividing T cell-DC conjugates has revealed that there is asymmetric distribution between the daughter cells of polarity proteins, particularly those that regulate asymmetric cell division in other organisms.

This observation provides potential for generating the diversity of T lymphocytes required for an effective immune response and suggests that a conserved mechanism based on asymmetric cell division exists in immune cells (2). An Honours project is available to further investigate the role of these polarity proteins in the regulation of asymmetric cell division in T lymphocytes, and determine how this process impacts on T cell fate and function. The candidate will have the opportunity to develop skills in wide range of cell biology, immunology and molecular biology techniques, including primary cell culture, lymphocyte functional assays and confocal and time-lapse microscopy.

References:

1. Ludford-Menting & Oliaro *et al.* (2005) *Immunity* 22(6): 737-748
2. Chang & Palanivel *et al.* (2007) *Science* 315(5819): 1687-1691

For more information about this project contact:

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Peter MacCallum Cancer Centre, Cancer Immune Signalling Laboratory

Preferred background: science, biomedical sciences

Project start time: February or July 2008

B.Sc. Honours 2008

To determine the role of the hippo signalling pathway in the control of organ size, and human cancer

Supervisor: Dr. Kieran Harvey

Our laboratory is focussed on determining how the hippo signalling pathway controls organ size during development and disease. Using the vinegar fly, *Drosophila melanogaster*, we identified a number of known and potentially novel tumour suppressor genes that restrict cell growth and number. Subsequently we found the human orthologues of many of these genes to be mutated in a percentage of human cancers.

We currently have several different projects available aimed at studying the mechanism by which the hippo signalling pathway controls cell growth and proliferation, using an array of genetic, cell biological and biochemical techniques. The aims of this project are:

1. To understand how the hippo signalling pathway controls organ size during development.
2. To determine whether components of the hippo signalling pathway are mutated in human cancer.

A broad range of techniques will be employed throughout the course of this project, including confocal microscopy and light microscopy, immunohistochemistry, *Drosophila* genetics, molecular biology, cell biology. All of these techniques are routinely used by current laboratory members and training will be provided to you, to enable you to master all of these techniques. Our laboratory is looking for intelligent, motivated Honours and PhD students to join our team. You should have a willingness to learn a number of different biological techniques, and be able to integrate into a close team environment.

References:

1. Kieran F. Harvey and Nicolas Tapon (2007). The Salvador-Warts-Hippo pathway – an emerging tumour-suppressor network. *Nat Rev Cancer*. 7, 182-191.
2. F. Christian Bennett and Kieran F. Harvey (2006). Fat Cadherin Modulates Organ Size in *Drosophila* via the Salvador/Warts/Hippo Signaling Pathway. *Curr Biol*. 16, 2101-2110.
3. Kieran F. Harvey, Cathie M. Pflieger and Iswar K. Hariharan (2003). The *Drosophila* Mst ortholog, *hippo*, restricts growth and cell proliferation and promotes apoptosis. *Cell* 114, 457-67.
4. Nicolas Tapon, Kieran F. Harvey, Daphne W. Bell, Doke C. Wahrer, Taryn A. Schiripo, Daniel A. Haber and Iswar K. Hariharan (2002). *salvador* Promotes both cell cycle exit and apoptosis in *Drosophila* and is mutated in human cancer cell lines. *Cell* 110, 467-78.

For more information about this project contact:

Dr. Kieran Harvey (Group Leader), Tel: +61 3 9656 1291, Email: kieran.harvey@petermac.org
Peter MacCallum Cancer Centre, Cell Growth & Proliferation Laboratory

Preferred background: science, biomedical sciences

Project start time: February or July 2008

B.Sc. Honours 2008

Characterization of Scribble and associated genes in cancer

Supervisors: Dr. Patrick Humbert & Dr. Helena Richardson

Project description - Our laboratory has developed a collaborative research program with Drs Helena Richardson's and Sarah Russell's laboratories to elucidate the role of a novel class of tumour suppressor genes first identified in *Drosophila* that include *scribble* (*scrib*), *discs-large* (*dlg*) and *lethal giant larvae* (*lgl*). In particular, these genes appear to normally coordinate the establishment and maintenance of polarity, the property of a cell to organise itself into a spatially asymmetric structure necessary for its function.

In *Drosophila*, loss of *scrib*, *dlg* or *lgl* function in epithelial cells gives rise to tumorous overgrowth characterised by loss of polarity, impaired cell cycle exit, multilayering, invasion into adjacent tissue and when transplanted into a novel host *Drosophila*, the ability of these tumour cells to metastasise through multiple tissue layers.

Together, these tumours have many of all the hallmarks of human cancer. Genetic screens conducted in Helena Richardson's laboratory have identified a number of genes that can cooperate with *scribble* mutants or the Ras oncogene to produce tumours in *Drosophila*. Initial studies carried out in our laboratory provide proof of principle that we can exploit *Drosophila* findings to good effect in mammalian epithelial systems. *This project aims to translate the information obtained in Drosophila tumour screens to mammalian systems and the study of human cancer.*

The project will examine biological activity of mammalian homologues of newly identified *Drosophila* oncogenes and tumour suppressors in the regulation of cell polarity, proliferation and migration in 2D and 3D cultures using non-transformed epithelial cell line models. Second, mammalian homologues will be tested for cooperativity with Scribble knockdown or expression of oncogenic Ras in transformation and tumorigenicity in vitro.

This will be followed by in vivo studies using sensitised mouse cancer models. These studies will provide new insights into the development of mammalian cancer

References:

1. Humbert P, Russell S, Richardson H. Dlg, Scribble and Lgl in cell polarity, cell proliferation and cancer. *Bioessays*. 2003, 25:542-53.
2. Brumby AM, Richardson HE. scribble mutants cooperate with oncogenic Ras or Notch to cause neoplastic overgrowth in *Drosophila*. *EMBO J*. 2003, 22:5769-79.
3. Dow LE, Brumby AM, Muratore R, Coombe ML, Sedelies KA, Trapani JA, Russell SM, Richardson HE, Humbert PO. hScrib is a functional homologue of the *Drosophila* tumour suppressor Scribble. *Oncogene*. 2003 22:9225-30.
4. Brumby AM, Richardson HE. Using *Drosophila Melanogaster* to map human cancer pathways. *Nature Reviews Cancer*. 2005, 5:626-639.

For more information about this project contact:

Dr. Patrick Humbert (Group Leader), Tel: +61 3 9656 3526, Email: patrick.humbert@petermac.org

Peter MacCallum Cancer Centre, Cell Cycle & Cancer Genetics Laboratory

Dr Helena Richardson, Peter MacCallum Cancer Centre, Cell Cycle & Development

Laboratory, Tel: +61 3 9656 1466, Email: helena.richardson@petermac.org

Preferred background: science, biomedical sciences

Project start time: February or July 2008

B.Sc. Honours 2008

How do red blood cells enucleate?

Supervisor: Dr. Patrick Humbert

Project description - The terminal differentiation of erythroid cells provides an extreme example of asymmetric division where the final division gives rise to one daughter cell containing all of the genetic material whilst the other daughter cell, the “enucleated” daughter cell, will give rise to the functional erythrocyte population required to provide oxygen to the organism. We have set up a powerful in vitro erythroid differentiation system and used it to characterize the defective asymmetric division (“enucleation”) of Rb-deficient erythroid cells. This erythroid culture system now allows for the first time the systematic genetic analysis of the asymmetric division associated with terminal differentiation of erythrocytes.

This project aims to characterize erythroid “enucleation” and to use pharmacological and RNA interference approach to identify the molecular pathways involved in this terminal asymmetric division. These studies will provide fundamental insights into the regulation of erythroid differentiation.

References:

1. Clark AJ, Doyle KM, Humbert PO. Cell intrinsic requirement for pRb in erythropoiesis. 2004, *Blood* 104:1324-1326
2. Doyle KM, Clark AJ, Iazzolino RM and Humbert PO (2006) E2f4 regulates fetal erythropoiesis through the promotion of cellular proliferation *Blood* 108:886-895
3. Humbert P, Russell S, Richardson H. Dlg, Scribble and Lgl in cell polarity, cell proliferation and cancer. *Bioessays*. 2003, 25:542-53.

For more information about this project contact:

Dr. Patrick Humbert (Group Leader), Tel: +61 3 9656 3526, Email: patrick.humbert@petermac.org

Peter MacCallum Cancer Centre, Cell Cycle & Cancer Genetics Laboratory

Preferred background: science, biomedical sciences

Project start time: February or July 2008

B.Sc. Honours 2008

Molecular Radiation Biology Laboratory

Protection of radiation-induced base-damage by methylproamine and analogues

Supervisors: Dr.Pavel Lobachevsky & Associate-Professor Roger Martin

The normal tissue damage associated with radiotherapy has motivated the development at Peter Mac of a new class of DNA-binding radioprotecting drugs that could be applied topically to normal tissues at risk. Methylproamine, the lead compound, reduces radiation induced cell kill at low concentrations, apparently by reducing radiation-induced DNA damage. To date, most of our mechanistic studies with purified DNA have focussed on radiation-induced strand breaks. However experiments with a series of methylproamine analogues indicate that there is an incomplete correlation between protection of radiation-induced strand breaks and protection against radiation-induced cell kill. Accordingly, our attention has now turned to other forms of DNA damage. It is believed that the most critical for cell kill is complex DNA damage, when single- or double-strand break is accompanied by base damage.

The aim of this BSc Hons project is to investigate the radiation-induced base damage and its protection by methylproamine. The proposed experimental strategy takes advantage of the convenience of circular plasmid DNA to assay for strand breakage, but whereas we have used this assay previously to detect immediate (so-called “frank”) radiation-induced DNA breakage, in the proposed project the irradiated DNA will be treated with various endonucleases, which convert base lesions to breaks. For example the bacterial enzyme formamidopyrimidine DNA-glycosylase (FPG) recognises oxidised base lesions such as 8-oxo-7, 8-dihydro guanine (8-oxoGua) and inserts a DNA single-stranded break at the site of damage. Endonuclease III (ENDOIII) recognises oxidised pyrimidines, including thymine glycol and uracil glycol. Finally, whereas FPG recognises a variety of different base lesions, human 8-hydroxyguanine DNA-glycosylase 1 (hOGG1) is specific for 8-oxoGua. Thus the project involves irradiation of plasmid DNA, with or without added radioprotector (such as methylproamine), and subsequent treatment with one of the above endonucleases (including radiation-only control), in order to investigate the extent of radioprotection of radiation-induced base damage. Extension of the studies to a collection of methylproamine analogues will provide an indication of whether protection of radiation-induced base damage, rather than frank breaks, provides a better correlation with radiation-induced cytotoxicity.

For more information about this project contact:

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Peter MacCallum Cancer Centre, Molecular Radiation Biology Laboratory

Preferred background: science, biomedical sciences

Project start time: February or July 2008

B.Sc. Honours 2008

Molecular Radiation Biology Laboratory

Evaluation of DNA strand breakage by ^{125}I -labelled DNA Ligands

Supervisors: Dr.Pavel Lobachevsky & Assoc. Professor Roger Martin

This project is part of a programme of research aimed at developing of ^{124}I -labelled DNA ligands for use in cancer radio immunotherapy and PET imaging. The combination of both positron and Auger electron emission in the decay scheme of ^{124}I presents very special opportunities. The general requirement to position an Auger-emitter very close to DNA to fully exploit the cytotoxic potential of Auger emission is well-established, but a more recent development is the integration of this requirement into a general tumour targeting strategy. The focus of this strategy is a conjugate of the radioactive DNA ligand linked to a tumour targeting protein specific for an appropriate cell surface receptor. After internalisation, the conjugate-receptor complex is degraded, with release of the labelled ligand and its translocation and binding to nuclear DNA. As well as targeting the radioisotope to DNA for maximal cytotoxic damage, the DNA acts as a “sink” to accumulate labelled ligand during multiple cycles of receptor-mediated endocytosis. The positron-emission feature of ^{124}I enables this “sink” effect to be exploited in the context of PET imaging generally, as well as in conjunction with Auger therapy. Adoption of the general strategy for imaging-only applications requires re-design of the DNA ligands so that the iodine atom is positioned away from the DNA helix so as to *minimise* DNA damage (as distinct from *maximising* DNA damage for combined therapy/PET imaging objective). Since experimental work with ^{124}I raises radiation safety challenges due to the high energy of the gamma emissions (the most abundant is 0.6MeV; other components about 2 MeV), the BSc Hons project will focus on the prototype Auger-emitter ^{125}I , for which the energy of the photons is around 35KeV. Since the DNA breakage from decay of DNA-associated isotope is a consequence of the Auger emissions (rather than gamma-emissions), the distance-damage relationship is expected to be similar for the two isotopes. Ultimately however, similar experiments with ^{124}I will need to be done.

In collaboration with Dr Jonathan White at the University of Melbourne’s School of Chemistry, new iodinated DNA ligands have been designed and synthesised. These ligands have the iodine atom positioned at varying distances from the axis of the DNA helix. The overall aim of the program of which this project part, is to establish the relationship between distance of the iodine atom from DNA and the extent of DNA breakage, particularly DNA double-strand breaks (DNAdsbs). This particular project will focus on a new ligand designed to exhibit minimal DNA damage. The experimental work will involve:

- preparation of ^{125}I -labelled DNA ligands, by iododestannylation of the trialkyl-tin precursors synthesised by collaborators in Associate-professor Jonathan White’s lab at Bio21
- purification of the radioactive ligands by preparative HPLC
- incubation of the labelled ligands with plasmid DNA
- agarose gel electrophoresis of the plasmid DNA samples, and quantitation of the relative amounts of intact, linear and nicked plasmid species, and
- computation of the DNA breakage efficiency (DNSdsbs per decay) for each labelled ligand.

For more information about this project contact:

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Peter MacCallum Cancer Centre, Molecular Radiation Biology Laboratory

Preferred background: science, biomedical sciences

Project start time: February or July 2008

B.Sc. Honours 2008

Molecular Radiation Biology Laboratory

Protection of radiation-induced apoptosis and g-H2AX by methylproamine analogues

Supervisors: Dr. Tom Karagiannis & Assoc. Professor Roger Martin

As indicated in the introduction to Project 1, incubation of cells with methylproamine analogues reduces radiation induced cell-death. Following exposure to ionizing radiation cell-death occurs either by necrosis or by programmed cell-death (apoptosis), depending on the cell type and the radiation dose. The aim of this project will be to determine whether the DNA minor groove binding ligands protect cells from radiation-induced apoptosis.

Our preliminary studies using pulsed-field gel electrophoresis suggest that methylproamine protects cells by inhibiting the formation of ionizing radiation-induced DNA double-strand breaks (DSBs), which are the most severe with respect to cell survival and preservation of genomic integrity. In this project levels of g-H2AX will be used as marker for DSBs instead of DNA fragmentation. The rationale for using this histone variant as a marker for DSBs is that an early cellular response to DSB induction is phosphorylation of the serine 139 residue of H2AX forming g-H2AX. This phosphorylation event occurs rapidly following the induction of DSBs and spreads over large chromatin domains (megabase-sized regions) surrounding the DNA lesions. For example, within minutes following ionizing radiation g-H2AX forms discrete nuclear foci, containing DNA repair factors which are easily detectable by immunofluorescence-based assays.

Therefore, the specific aims of this project are to determine whether methylproamine and structurally related analogues protect cells from radiation-induced apoptosis and g-H2AX formation. Fluorescence-based microtitre plate (96-well) assays will be used to detect markers of apoptosis and immunofluorescence (fluorescence microscopy and flow cytometry) will be used to monitor levels of g-H2AX.

For more information about this project contact:

Dr. Tom Karagiannis, Tel: +61 3 9656 1292, Email: tom.karagiannis@petermac.org

Peter MacCallum Cancer Centre, Molecular Radiation Biology Laboratory

B.Sc. Honours 2008

Molecular Radiation Biology Laboratory

Assessment of the radioprotective activity of methylproamine in radiosensitive cell lines deficient in DNA break repair.

Supervisors: Dr. Tom Karagiannis & Assoc. Professor Roger Martin

Ionising radiation causes cell-death by inducing DNA damage, predominantly single and double DNA strand breaks and base damage. Cells have evolved complex molecular pathways to respond to DNA damage. Single strand breaks are usually repaired rapidly and efficiently by one of the excision repair pathways. In contrast, double strand breaks are repaired by either non homologous end joining or homologous recombination, which involve more elaborate signal transduction cascades. Mutation of DNA repair genes results in a marked increase in the radiation sensitivity of cells.

Methylproamine protects cells from radiation-induced cytotoxic DNA damage, but it is unknown as to whether the radioprotective effect pertains to a particular subclass of DNA lesion(s), or whether it is more global. Thus the aim of this project is to investigate the effect of methylproamine analogues on the radiation sensitivity of a variety of mutant cell-lines, each deficient in radiation a particular facet of DNA repair. The experiments will involve treating wild type and mutant cell-lines with radioprotector compounds prior to irradiation and examining the effects of the radioprotectors on radiation-induced cell death and apoptosis.

The techniques will include mammalian cell culture and clonogenic survival. Fluorescence-based microtitre plate assays will be used to assess apoptosis and fluorescence microscopy will be used to evaluate nuclear uptake of compounds.

For more information about this project contact:

Dr. Tom Karagiannis, Tel: +61 3 9656 1292, Email: tom.karagiannis@petermac.org

Peter MacCallum Cancer Centre, Molecular Radiation Biology Laboratory

Preferred background: science, biomedical sciences

Project start time: February or July 2008

**Pregnancy Research Centre
The Royal Women's Hospital**

B.Sc. Honours 2008

PROJECT TITLE: THE ROLE OF HOMEBOX GENE *TGIF* IN PLACENTAL ENDOTHELIAL CELLS

PROJECT DESCRIPTION

The placenta plays a crucial role in the development of the embryo and growth of the fetus. Impaired placental development and function is a significant contributing factor to clinically significant obstetric pathologies such as fetal growth restriction and pre-eclampsia. A common feature of placental pathologies is abnormal development of the placental vasculature.

Endothelial cells that line the blood vessel walls are metabolically active and carry out a wide range of functions that are essential for maintaining vascular function. The formation of blood vessels (angiogenesis) requires coordinated changes in endothelial cell morphology, cell-extracellular matrix interactions and gene expression. Homeobox genes have been shown to regulate such processes in the vascular system in the fetus and adult. Homeobox genes are targets for therapeutics in the cardiovascular system so their importance and potential are well established. In the placenta, the role of homeobox genes in endothelial cell development and differentiation is not known, but is highly likely to be important.

Our previous honours student discovered new homeobox genes, including several that have not been previously reported in endothelial cell types. In this project we will investigate the role that homeobox gene *TGIF* plays in endothelial cells in the placenta by the following methods.

- 1) Determining the level of *TGIF* in the placental pathologies, fetal growth restriction and pre-eclampsia. We will isolate and culture endothelial cells directly from normal and pathological placentae. We will use reverse transcriptase-PCR (polymerase chain reaction) and Northern analysis to measure *TGIF* mRNA levels and Western analysis to protein levels. We expect to show that *TGIF* expression is altered in endothelial cells of pathologies compared to the normal placenta.
- 2) We will artificially alter the expression level of *TGIF* in placental endothelial cells. We will do this in a well-characterised placental endothelial cell line (HPEC-A2). We will use antisense RNAi techniques to decrease the levels of *TGIF*. We will use real-time PCR to measure *TGIF* mRNA levels and Western analysis to *TGIF* protein levels to confirm the levels of homeobox genes have been altered. We will then use Superarray to identify down-stream target genes of *TGIF*. We will verify the candidate target gene mRNA and protein analysis for evidence of altered expression. In addition we will assess cell morphology, proliferation and apoptosis to determine whether they are affected when *TGIF* expression levels are reduced. In this project you will gain experience in a wide variety of molecular biology methods, immunohistochemical techniques and cell culture, methods.

PREFERRED BACKGROUND OF STUDENT: A background in biology, molecular biology or genetics is preferred

NAME OF SUPERVISOR(S): Dr. Padma Murthi, Dr. Bill Kalionis

DEPARTMENT & INSTITUTION: Pregnancy Research Centre, Department of Perinatal Medicine, Royal Women's, Hospital and Department of Pathology, University of Melbourne

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B.Sc. Honours 2008

PROJECT TITLE: HOMEBOX GENES IN PLACENTAL STEM CELLS

PROJECT DESCRIPTION

Stem cells are immature cells that can be coaxed in the laboratory to mature into specific types of tissue such as bone, cartilage and muscle. Stem cells from umbilical cord blood have been used for many years as a safe and acceptable alternative to bone marrow transplantation for many leukaemia patients. Stem cells have been isolated from a variety of adult and embryonic sources. Adult stem cells are being used in clinical trials to repair injuries of the bone and cartilage, regenerate cells and organs, and treat cancers. Recently, the placenta has been shown to be a plentiful source of stem cells. The placenta has numerous advantages over traditional methods of preparing stem cells and provides a safe, non-controversial alternative to embryonic or fetal stem cells. You will use a variety of methods to harvest placental stem cells.

In stem cells, one of the crucial markers is the homeobox gene Oct-4. Homeobox genes are important regulators of transcription and control processes such as cell differentiation. Stem cells express Oct-4 and must switch off this gene to differentiate. We have identified homeobox genes expressed in stem cells from the placenta. In this project you will use RNA interference methods to inactivate one of these homeobox genes. You will use PCR and Western analysis to confirm mRNA and protein reduction respectively. Following successful gene inactivation, you will use functional assays (e.g. proliferation, migration) to determine the role of the homeobox gene in stem cells.

To further characterise the homeobox gene, you will determine its expression pattern in the normal placenta. Finally, you will measure the homeobox gene mRNA and protein levels in placental pathologies and compare them with control placentae to determine if the homeobox gene plays any potential role.

Methods: RT-PCR, real-time PCR, cell culturing, siRNA gene inactivation, plasmid-based overexpression

PREFERRED BACKGROUND OF STUDENT: A background in biology, molecular biology or genetics is preferred

NAME OF SUPERVISOR(S): Dr. Bill Kalionis, Dr. Padma Murthi

DEPARTMENT & INSTITUTION: Pregnancy Research Centre, Department of Perinatal Medicine, Royal Women's, Hospital and Department of Pathology, University of Melbourne

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B.Sc. Honours 2008

INVESTIGATING BIOCHEMICAL DIFFERENCES BETWEEN PREGNANT WOMEN WITH HIGH BMI (BODY MASS INDEX) AND THOSE WITH NORMAL BMI

Project Description

Obesity continues to increase at alarming rates in the developed world. Obesity in pregnant women is an independent risk factor for the complications of hypertension and caesarean section. Although many people think of adipose tissue as merely a repository for energy storage, adipose tissue contains multiple enzymes capable of metabolising various steroids and produces circulating hormones of its own, known as adipokines. Steroid concentrations are much higher in pregnancy as the placenta and reproductive tract tissues produce steroids in increasing amounts as the pregnancy progresses. Steroid hormones such as progesterone and oestrogen have been shown to be involved in the control of labour. Other steroid hormones such as cortisol have effects on blood pressure and sugar metabolism. Adipose tissue possesses multiple enzymes capable of activating or inactivating all of these circulating steroid hormones. Adipose tissue also produces its own hormone, leptin which is known to be associated with growth regulation. Alterations in steroid metabolism in women with high Body Mass Index (BMI) may be responsible for some of the complications known to be more common in these women.

In this study we aim to use molecular biology techniques real-time RT-PCR and Western blot to investigate expression of steroid metabolising enzymes in adipose tissue samples taken from women with high BMI and women with normal BMI at term. We also aim using the same techniques, to investigate the effects of increases adipose tissue on circulating leptin concentrations and production of leptin by reproductive tract tissues.

Background: A background in biology or molecular biology is preferred.

Name of Supervisor: Dr Penelope Sheehan

Department and Institution: Pregnancy Research Centre, Department of Perinatal Medicine, Royal Women's Hospital, University of Melbourne

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It is likely that in the following weeks additional B. Sc. Honours projects will become available for 2008.

If this does occur, I will produce a supplement to this project booklet which will be available prior the application deadline.

John R. Underwood
B.Sc. Honours Co-ordinator.
