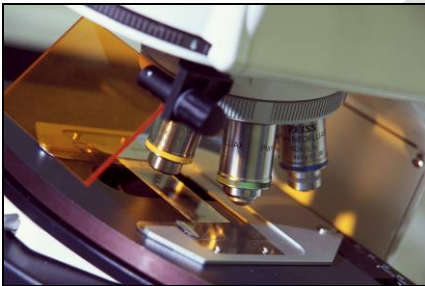
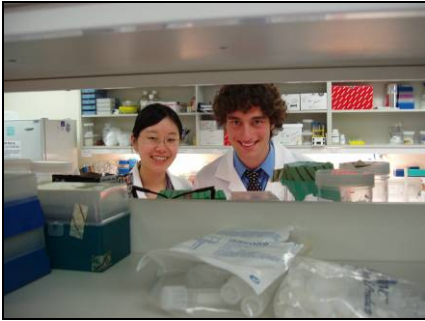




liwa
Lung Institute
of Western Australia Inc



LIWA Scholarships 2010

Project book

Applications for PhD Top Up and
Honours Scholarships close
Friday 30 October 2009 at 5pm

For information about LIWA,
Application conditions &
Award and application forms visit

www.liwa.uwa.edu.au

Phone 9346 3198

or email admin@liwa.uwa.edu.au

Institute Background

The Lung Institute of Western Australia (LIWA) this year celebrates its tenth Anniversary and with that, offers an extended package of student scholarships for 2010.

LIWA is recognised as a Tier One NH&MRC Medical Research Institute, has been accredited as an Independent Medical Research Institute by the Western Australian Government and is the recipient of state medical and health research infrastructure funding.

The Institute is based at Sir Charles Gairdner Hospital in Perth. LIWA is formally affiliated with the University of Western Australia and Curtin University. LIWA is also a registered charity and has been endorsed by the Australian Taxation Office as a deductible gift recipient.

The primary goal of LIWA is to support high quality research into better understanding the cell and molecular biology of respiratory disease and thereby improve the treatment and management of patients with lung conditions. These conditions include emphysema, lung cancer, vascular diseases, asthma and other allergic diseases. This is done through studying disease processes, existing and potential treatment modalities and the impact of disease on the individual and the community at large. Although many groups are committed to improving the welfare of these patients, LIWA is the only integrated scientific and clinical research institute in Australia dedicated specifically to research into lung health and respiratory conditions.

LIWA has two broad areas of research, clinical sciences and biological sciences. Although there is often overlap between these two groups, research projects are directed from units of specialty:

Biological sciences:

- Tissue repair
- Inflammation / immunology
- Molecular genetics
- Pleural disease

Clinical sciences:

- Advanced lung disease and pulmonary vascular unit
- Physiotherapy
- Infectious diseases
- Cardiothoracic surgery
- CF / Bronchiectasis

A total number of 19 research projects have been identified for the year ahead. This booklet provides information on each of these projects.

Education Awards offered in 2010

Once again, LIWA is proud to offer these education opportunities in 2010 to young people with talent in research and a passion to make a difference to lung health.

Honours

In its tenth anniversary year LIWA is offering three scholarships for students undertaking an Honours year or a BMedSci year with value of the scholarship being \$5,000.

PhD Top Up Scholarships

Students with outstanding undergraduate results are encouraged to apply for supplementary awards valued at \$10,000 per annum to top up their income for the duration of their research studies with LIWA. Up to four scholarships are available. The awards are open to applicants across Australia who intend to enrol at the University of Western Australia or Curtin University of Technology.

We now welcome applications for 2010 scholarships.



Phil Thompson
Director

List of research projects

1. Biological Role of Novel Growth Factors in the Pathogenesis of Malignant Mesothelioma
2. What causes Pleurisy (Pleural Infection)?
3. Breathlessness and Pleural Effusion
4. Hedgehog signalling in mesothelial regeneration
5. Suppressor of cytokine signalling proteins in the control of pulmonary fibrosis
6. The interaction between hedgehog and transforming growth factor beta signalling pathways in malignant mesothelioma growth
7. MicroRNA in Malignant Mesothelioma
8. Investigation and assessment of the importance of histone deacetylation and acetylation in the expression of the *KLK1*, *KLKB1*, *KNG1*, *B₁R* and *B₂R* genes in mesothelioma cell lines derived from malignant pleural fluid and in non-cancerous mesothelial cells
9. Capillary vessels formed by lung endothelial cells are functionally altered when co-cultured with lung cancer cells: the newly formed vessels differ in the expression of the kallikrein-kinin cascade proteins and progenitor/stem cell markers.
10. The effect of kinin peptides and kinin receptor antagonists on proliferation of cultured lung carcinoma cells
11. Alternative gene splicing and asthma: is it all the RAGE?
12. Antisense oligomers as a strategy to modify therapeutic targets in asthma
13. Role of EP receptors in epithelial cell function in inflammation
14. Characterisation of β 2 Adrenergic Receptor (ADR β 2) Expression, Function and Regulation in different ADR β 2 polymorphisms
15. Characterising the function of the SNP in the Bradykinin B1 Receptor (BDKR B1) promoter
16. Dendritic cells susceptibility to α -synuclein induced apoptosis
17. Enhancing the efficacy of mannitol in treating bronchiectasis and exploration of the mechanisms involved
18. Effects of air pollution on airway cell biology
19. Exhaled breath biomarkers in asthma, COPD and lung cancer

1. Biological Role of Novel Growth Factors in the Pathogenesis of Malignant Mesothelioma

Supervisor	Winthrop Professor Y C Gary Lee
Research Unit	Pleural Diseases Unit
Essential qualifications	For PhD applicants, a Bachelor of Science with Honours or Masters in Science, or a medical degree (or equivalent)
Essential skills	Cell culture, PCR
Additional skills	Western blot, ELISA
This project is suitable for Funding	X <input type="checkbox"/> Honours/BMedSci X <input type="checkbox"/> Masters <input checked="" type="checkbox"/> PhD <ul style="list-style-type: none">• PhD Top-Up scholarships (the Applicant should apply for APA or UPA)• Honours/Masters/BMedSci, scholarships available.
Contact	Winthrop Professor Y C Gary Lee: glee@meddent.uwa.edu.au

Project Outline

Malignant mesothelioma is an aggressive and incurable cancer that kills 800 patients every year in Australia. In Britain, one patient dies from mesothelioma every four hours. Identification of new therapeutic targets is desperately needed.

Using global gene profiling, our group has examined the gene expression of thoracoscopic biopsy of human mesothelioma tissues. Significant up-regulation of several novel genes in mesothelioma over other cancers and benign diseases was uncovered. These findings have been verified in a second patient cohort.

Work in the host laboratory has confirmed the presence of these target genes in human pleural fluids, and *in vitro* studies have shown the sufficiency of these genes in key biological steps of tumorigenesis.

The proposed PhD project aims to establish the i) necessity of these proteins in mesothelioma pathogenesis using RNA gene silencing technology *in vitro* and in established murine models; ii) factors governing their up-regulation in mesothelioma; and iii) relevance of FGF-9 expression (in blood, pleural fluid, and tumor tissues) in clinical diagnosis, prognosis and predicting treatment response in mesothelioma patients.

This project examines exciting novel targets with great translational importance, employing a wide range of molecular and *in vivo* techniques and human samples – already established in Professor Lee's group which has a strong track record in translational pleural research – to ensure successful delivery of a high quality doctoral thesis.

2. What causes Pleurisy (Pleural Infection)?

Supervisor	Winthrop Professor Y C Gary Lee
Research Unit	Pleural Diseases Unit
Essential qualifications	For PhD applicants, a Bachelor of Science with Honours or Masters in Science, or a medical degree or equivalent
Essential skills	Cell culture, PCR
Additional skills	Western blot, ELISA
This project is suitable for Funding	X <input type="checkbox"/> Honours/BMedSci X <input type="checkbox"/> Masters X <input checked="" type="checkbox"/> PhD <ul style="list-style-type: none">• PhD Top-Up scholarships (the Applicant should apply for APA or UPA)• Honours/Masters/BMedSci, scholarships available.
Contact	Winthrop Professor Y C Gary Lee: glee@meddent.uwa.edu.au

Project Outline

Bacterial infection of the pleural space is a common disease affecting 65,000 in the USA and UK each year and is a major cause of morbidity and mortality in developing countries.

The interaction between bacteria and the pleura has seldom been studied. Our group has developed in vivo models and in vitro techniques of studying bacterial migration into the pleural cavity, and the biological responses of pleural mesothelium upon exposure to bacteria. This is a clinically important subject but rarely studied. Data from this project will therefore be highly publishable and will add valuable knowledge to existing literature.

The proposed PhD project aims to establish the biological effects of different types of common respiratory pathogens on mesothelial cells and in animal models. The results will also be confirmed and compared with pleural and blood samples of a large cohort of patients with pleural infection already collected.

3. Breathlessness and Pleural Effusion

Supervisor	Winthrop Professor Y C Gary Lee
Research Unit	Pleural Diseases Unit
Essential qualifications	For PhD applicants, a Bachelor of Science with Honours or Masters in Science, or a medical degree or equivalent
Essential skills	Cell culture, PCR
Additional skills	Western blot, ELISA
This project is suitable for Funding	X <input type="checkbox"/> Honours/BMedSci X <input type="checkbox"/> Masters <input checked="" type="checkbox"/> PhD <ul style="list-style-type: none">• PhD Top-Up scholarships (the Applicant should apply for APA or UPA)• Honours/Masters/BMedSci, scholarships available.
Contact	Winthrop Professor Y C Gary Lee: glee@meddent.uwa.edu.au

Project Outline

Malignant pleural effusion is common, affecting 1 in 3 patients with breast, 1 in 4 of lung cancer and 95% of patients with mesothelioma. Breathlessness is the most common symptom of malignant effusion, but the pathophysiology remains poorly understood.

The Pleural Unit sees a large number of patients with pleural effusions and has an established ultrasound practice, a dedicated clinical research fellow and supported by a laboratory research team. This setting provides an ideal opportunity to investigate the physiology of pleural effusion, especially in relations to breathlessness.

The proposed PhD project will aim to look at factors that predict improvement in breathlessness upon drainage of effusions, including ultrasound and radiological features, pleural fluid biomarkers, etc.

The candidate will learn clinical practical skills, state of the art management of pleural effusions, and laboratory skills.

4. Hedgehog signalling in mesothelial regeneration

Supervisor (s)	A/Prof Steven Mutsaers (Chief Supervisor) Dr Carla Thomas
Research Unit	Tissue Repair Unit/PathWest
Essential qualifications	For Honours or Masters: a BSc in a biological science area. For PhD, Honours or equivalent in a biological science area , or a medical degree
Essential skills	Good laboratory practice and computing skills
This project is suitable for Funding	X <input type="checkbox"/> Honours/BMedSci X <input type="checkbox"/> Masters <input checked="" type="checkbox"/> PhD <input type="checkbox"/> For PhD Top-Ups (applicant should apply for APA or UPA) <input type="checkbox"/> For honours, Masters and BMedSci, full scholarship available
Contact	A/Prof Steven Mutsaers mutsaers@liwa.uwa.edu.au 9346 2312 Dr Carla Thomas cthomas@cyllene.uwa.edu.au 9346 3924

Project Outline

The mesothelium is composed of a monolayer of specialised cells that extends over the entire surface of the serosal cavities (pleural, pericardial and peritoneal) and most internal organs. Injury to the mesothelium normally results in activation of repair processes which are unique as regrowth of cells appears diffusely across the denuded surface whereas in true epithelia, healing occurs solely at the wound edges as sheets of cells. The mechanisms involved in mesothelial regeneration are controversial but in recent studies we showed that mesothelial cells present in the serosal fluid settle on the wound surface, proliferate and repopulate the injured area. These free floating cells may originate from surrounding mesothelium but also may originate from the bone marrow. We have recently shown that mesothelial cells are multipotent and can differentiate into other cell types, consistent with a progenitor or stem cell like role. This study will further examine the concept of a mesothelial stem cell by examining expression of the developmental hedgehog (Hh) signalling pathway in regenerating mesothelial cells. The Hh pathway is a highly conserved signalling pathway responsible for the regulation of cell proliferation, differentiation and patterning during mammalian embryonic development of the neural tube, axial skeleton, limbs, lungs, skin, hair and teeth. It controls cell proliferation through stem cell and stem-like progenitor regulation. Expression of this pathway has been associated with adult stem cell activation in regenerating tissues including the lung and aberrant expression of this pathway has been associated with the development of several cancers including non small cell lung cancer.

This study will use cell and molecular techniques including tissue culture, cell transfection, real time PCR, *in situ* hybridisation, western blot analysis, cell proliferation, cell viability and apoptosis, and cell motility assays to examine the following aims:

1. Determine if regenerating mesothelium expresses Hh mediators and if Hh signalling occurs via ligand driven Hh pathway activation.
 2. Assess the effect of blocking the Hh signalling pathway on expression of Hh target genes, cell viability, proliferation and migration of mesothelial cell lines and on mesothelial regeneration *in vivo*.
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5. Suppressor of cytokine signalling proteins in the control of pulmonary fibrosis

Supervisor	Dr Cecilia Prêle (Chief Supervisor) A/Prof Steven Mutsaers
Research Unit	Tissue Repair Group, LIWA and Anatomical Pathology Research, PathWest
Essential qualifications	For Hons - BSc in a biological science discipline For MSc or PhD - BSc (Hons) or equivalent in biological discipline, or a medical degree or equivalent
Essential skills	Good organisational skills, motivation and dedication
This project is suitable for	X <input type="checkbox"/> Honours/BMedSci X <input type="checkbox"/> Masters <input checked="" type="checkbox"/> PhD
Funding	PhD Top-Up scholarships (the Applicant should apply for APA or UPA) Honours/Masters/BMedSci, scholarships available.
Contact	ceciliap@liwa.uwa.edu.au mutsaers@liwa.uwa.edu.au

Project Outline

Excessive deposition of collagen and fibrosis is characteristic of many pulmonary conditions including idiopathic pulmonary fibrosis (IPF), a fatal disease of unknown aetiology which is unresponsive to current therapy. Recent findings by our group and others have implicated the interleukin-6 (IL-6) family of cytokines in lung fibrosis through direct stimulation of fibroblast proliferation and regulation of collagen deposition or induction of secondary pro-fibrotic mediators. IL-6 belongs to a family of cytokines that includes IL-11, IL-31, oncostatin M (OSM), leukemia inhibitory factor, cardiotrophin-1 and ciliary neurotrophic factor. All of these cytokines recruit the co-receptor gp130 to initiate intracellular signalling through the SHP2-ERK1/2 or STAT1/3 pathways. These pathways act as effectors of differentiation, proliferation, apoptosis and migration.

In previous studies using mice with gp130-mediated hyper-activation of ERK1/2 (gp130^{ΔSTAT}) or STAT1/3 (gp130^{757F}) pathways, we observed dramatic changes in the fibrotic response between genotypes following intranasal delivery of bleomycin. Protection from fibrosis was observed in gp130^{ΔSTAT} mice whereas profound fibrosis occurred in gp130^{757F} mice compared to wild type (wt) controls. We have also shown increased fibrosis is mediated via STAT3 signalling and independent of the degree of inflammation and TGFβ-mediated Smad3 activation. More recently, we have identified reduced expression of suppressor of cytokine signalling (SOCS)-1 by IPF fibroblasts. SOCS proteins negatively regulate STAT-induced signal transduction pathways. This study will investigate the possibility that aberrant regulation of gp130-mediated STAT1/3 signalling by SOCS1 contributes to the development of lung fibrosis. Techniques that will be used in this study: animal handling/monitoring and bleomycin treatment; Immunohistochemistry; Flow Cytometry; culture of primary human lung fibroblasts; real time PCR; ELISA.

6. The interaction between hedgehog and transforming growth factor beta signalling pathways in malignant mesothelioma growth

Supervisor	Dr Bahareh Badrian A/Prof Steven Mutsaers Dr Carla Thomas
Research Unit	Tissue Repair Unit/PathWest
Essential qualifications	For PhD applicants, a Bachelor of Science with Honours or Masters in Science or equivalent
Essential skills	Good laboratory practice and computing skills
This project is suitable for	X <input type="checkbox"/> Honours/BMedSci X <input type="checkbox"/> Masters <input checked="" type="checkbox"/> PhD
Funding	<ul style="list-style-type: none">• PhD Top-Up scholarships (the Applicant should apply for APA or UPA)• Honours/Masters/BMedSci, scholarships available.
Contact	A/Prof Steven Mutsaers mutsaers@liwa.uwa.edu.au 9346 2312 Dr Bahareh Badrian bbadrian@cyllene.uwa.edu.au 9346 3924

Project Outline

Malignant Mesothelioma (MM) is an aggressive asbestos-associated tumour predominantly of the pleura, with a very poor prognosis. Current treatments are ineffective, therefore novel therapeutic approaches are required. Increasing evidence is pointing to the reactivation and aberrant expression of developmental signalling pathways, such as the hedgehog (Hh) pathway, as critical to the pathogenesis of certain cancers. The significance of aberrant Hh pathway signalling in the development and growth of MM remains to be determined.

Recent studies have clearly shown an interaction between Hh and transforming growth factor beta (TGF β) signalling pathways in a variety of cell types. TGF β interacts with the Hh pathway downstream of the signalling receptor smoothed (Smo) and acts as a potent inducer of transcription factors Gli1 and Gli2 in some normal and cancer cells. Gli2 induction by TGF β is rapid, independent from Hh receptor signalling and requires a functional Smad pathway, the predominant TGF β signalling pathway. Gli1 expression is subsequently activated in a Gli2-dependent manner. We and others have clearly shown a role for TGF β signalling in MM growth, particularly TGF- β_2 , although its relationship with Hh signalling has not been investigated in these cells. In preliminary studies we have shown upregulation of Gli1 in MM cells following TGF β_1 treatment, supporting interaction between these signalling pathways. Targeting the cooperation of Hh and TGF β signalling may provide new therapeutic opportunities for treating MM. This study will examine the interaction of these two signalling pathways to determine if TGF β can regulate Hh signalling in MM cells and/or Shh induces cellular responses through TGF β -mediated activation of the Smad3 pathway.

This study will use cell and molecular techniques including tissue culture, cell transfection, real time PCR, western blot analysis, cell proliferation, cell viability and apoptosis, and cell motility/invasion assays to examine the following aims:

1. Determine if TGF β can induce expression of Hh mediators
 2. Determine if Hh regulates MM cell responses through TGF β -mediated signalling
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7. MicroRNA in Malignant Mesothelioma

Supervisor	Dr Bahareh Badrian (Chief Supervisor) A/Prof Steven Mutsaers
Research Unit	Tissue Repair Group
Essential qualifications	Degree in Biochemistry and/or Molecular Biology (or similar)
Essential skills	Basic laboratory and computing skills
Additional skills	Knowledge of Real-time PCR and tissue culture techniques highly desirable.
This project is suitable for	X <input type="checkbox"/> Honours/BMedSci X <input type="checkbox"/> Masters X <input type="checkbox"/> PhD
Funding	<ul style="list-style-type: none">• PhD Top-Up scholarships (the Applicant should apply for APA or UPA)• Honours/Masters/BMedSci, scholarships available
Contact	Dr Bahareh Badrian 9346 3924 bbadrian@liwa.uwa.edu.au (preferred)

Project Outline

Malignant Mesothelioma (MM) is an aggressive and fatal cancer that is primarily caused by asbestos exposure, is associated with a poor prognosis and a 5 year survival rate of less than 1%. The current estimate suggests that the incidence of MM will peak in the western world in 2020. Even though use of asbestos is banned in most developed countries, secondary asbestos exposure from asbestos containing building materials is still a concern for the general population and asbestos is still being used in developing countries. This makes MM a concern for many years to come. There is currently no effective treatment for MM. Therefore it is important to understand the biology of this disease for the development of an effective treatment for MM.

The current project aims to determine the role of miRNAs in the development and regulation of MM. miRNAs are short non protein coding RNAs of approximately 22 nucleotides in length that are known to alter gene expression at a post transcriptional level. These molecules contribute to the initiation and progression of cancer and malignant tissues exhibit a unique miRNA expression profile that is different to normal tissue. Therefore, we believe that miRNAs may play an important role in the biology of MM. Current studies in our laboratory have identified a set of miRNA that appear to be important in MM. This project will investigate two of these miRNAs, miRNA-223 (downregulated in MM) and miRNA-222 (upregulated in MM).

Aims:

1. To determine the levels of miRNA-222 and 223 in MM cell lines.
 2. To overexpress and inhibit these miRNA and determine their effect on MM growth and cell death.
 3. To use current prediction databases/literature and determine the potential protein targets for miR-222 and 223.
 4. To select 2 potential protein targets for further study.
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9. Capillary vessels formed by lung endothelial cells are functionally altered when co-cultured with lung cancer cells: the newly formed vessels differ in the expression of the kallikrein-kinin cascade proteins and progenitor/stem cell markers.

Supervisor	Prof Kanti Bhoola (Chief supervisor) Dr Neil Misso Dr Shashi Aggarwal Faang Cheah*
Research Unit	Inflammation and Genetics* Units
Essential qualifications	For PhD applicants, a Bachelor of Science with Honours or Masters in Science or equivalent
Essential skills	Real-time PCR, Western Blotting, Gel electrophoresis, Some training in genetics
Additional skills	Optional-Microscopy but can be trained
This project is suitable for Funding	X <input type="checkbox"/> Honours/BMedSci X <input type="checkbox"/> Masters <input checked="" type="checkbox"/> PhD <ul style="list-style-type: none"> • PhD Top-Up scholarships (the Applicant should apply for APA or UPA) • Honours/Masters/BMedSci, scholarships available.
Contact	Profbhoola@iinet.net.au nmisso@liwa.uwa.edu.au

Project Outline

Tumour progression and metastasis depends on the formation of blood vessels, which ensures the delivery of oxygen, nutrients and growth factors. In normal physiology, as well as in pathological settings, two distinct processes, vasculogenesis and angiogenesis, are involved in the formation of new blood vessels. The term angiogenesis describes the growth of endothelial sprouts from pre-existing blood vessels by migration, proliferation, three-dimensional organization and tube formation. In contrast, vasculogenesis refers to the in situ differentiation of endothelial precursor cells, namely angioblasts. The existence of putative stem cells in the adult lung has been suggested recently. A clear indication of the presence of these cells can be obtained by using a combination of markers, including CD34, VEGF-R2, CD117 and PECAM-1, and by investigating the typical cellular morphological characteristics. Recent reports implicate the serine protease tissue kallikrein (hK1, KLK1) in carcinogenic processes. Tissue kallikrein cleaves kininogen to form kinin peptides, which mediate their cellular actions through the transmembrane receptors, B1 and B2. These kinin receptors are coupled to heterotrimeric G proteins, including Gaq (pathway linked to intracellular mobilization of calcium and phosphoinositide turnover) and Ga12,13 (pathway linked to c-Jun kinases).

Hypotheses: 1) Kallikrein-kinin cascade proteins and progenitor/stem cell markers are expressed in lung endothelial and lung adenocarcinoma cells. 2) Capillary vessel formation by lung endothelial cells is regulated by co-cultured lung adenocarcinoma cells. 3) The expression of kallikrein-kinin cascade proteins and progenitor/stem cell markers differs in the new capillary vessels formed by co-cultured lung adenocarcinoma and lung endothelial cells.

Specific Aims: 1) To determine the expression of the proteins and genes of the kallikrein-kinin cascade (KLK1, KLKB1, KNG1, BDKRB1, BDKRB2) and progenitor (VEGF-R2, CD34)/stem cell markers (CD133) in capillary vessels formed by cultured lung endothelial cells and by co-cultured lung adenocarcinoma and lung endothelial cells, at specified time points during *in vitro* cell culture. 2) To investigate the morphological changes in capillary vessels formed by co-cultured lung adenocarcinoma and lung endothelial cells at specified time points during *in vitro* cell culture.

11. Alternative gene splicing and asthma: is it all the RAGE?

Supervisor	Winthrop Prof Philip J Thompson (Chief Supervisor) Dr Cecilia Prêle, Tissue Repair Group Dr Brad Shelton, Molecular Genetic Unit
Research Unit	Molecular Genetics Unit
Essential qualifications	For PhD applicants, a Bachelor of Science with Honours or Masters in Science, BMedSci or equivalent
Essential skills	
Additional skills	
This project is suitable for Funding	<input type="checkbox"/> Honours/BMedSci <input type="checkbox"/> Masters <input checked="" type="checkbox"/> PhD <ul style="list-style-type: none">• PhD Top-Up scholarships (the Applicant should apply for APA or UPA)
Contact	Dr Brad Shelton, Molecular Genetic Unit, 1 st Floor, B Block, SCGH Tel: 9346-7947

Project Outline

The Receptor for Advanced Glycation End-products (RAGE) is a cell-surface receptor implicated in a wide array of inflammatory conditions. Activation of the receptor by ligand binding can initiate a positive feedback-loop of pro-inflammatory signalling that leads to chronic and sustained inflammation. However, despite high levels of RAGE expression in the lung, little is known about the role of RAGE in airway inflammation, particularly in asthma.

One important mechanism of RAGE regulation that may contribute to asthma development is the process of alternative mRNA splicing. RAGE exists as several alternatively spliced variants, including a soluble variant (sRAGE) that is capable of binding ligand, but lacks the intracellular signalling domains necessary for activating the pro-inflammatory signalling cascade. As such, sRAGE is thought to act as a protective mechanism against the pro-inflammatory effects of RAGE. Changes in the level of sRAGE expression have been demonstrated in several disease states, but have not yet been examined in asthma.

The aims of this project would be to:

- 1) Examine differences in RAGE and sRAGE expression in peripheral blood cells (PBMCs) and serum of asthmatic patients and non-asthmatic controls.
- 2) Examine the effect of stimulation with pro-inflammatory mediators on the expression of RAGE and sRAGE in PBMCs isolated from asthmatic and non-asthmatic patients.
- 3) Examine differences in RAGE-mediated pro-inflammatory signalling in PBMCs from asthmatic and non-asthmatic patients
- 4) Confirm the effects of increased sRAGE concentrations in decreasing intracellular pro-inflammatory signalling in PBMCs.

Use state-of-the-art genetic techniques to modulate the splicing of RAGE to favour the soluble splice variant.

12. Antisense oligomers as a strategy to modify therapeutic targets in asthma

Supervisor	Winthrop Prof Philip J Thompson (Chief Supervisor) Dr Chalermchai Mitrpant, Molecular Genetic Unit Dr Svetlana Baltic, Molecular Genetic Unit
Research Unit	Molecular Genetics Unit
Essential qualifications	For PhD applicants, a Bachelor of Science with Honours or Masters in Science or equivalent.
Essential skills	
This project is suitable for Funding	X <input type="checkbox"/> Honours/BMedSci X <input type="checkbox"/> Masters <input checked="" type="checkbox"/> PhD <ul style="list-style-type: none">• PhD Top-Up scholarships (the Applicant should apply for APA or UPA)• Honours/Masters/BMedSci, scholarships available.
Contact	Dr. Chalermchai Mitrpant, Molecular Genetic Unit, 1 st Floor, B Block, SCGH Tel: 9346-7949

Project Outline

Allergic asthma is a chronic immunologic inflammatory disease of airway characterised by hyperreactive airway responsive to various stimuli, termed airway hyperresponsiveness (AHR). Interplays between activated immune cells and epithelium mesenchymal tissue unit (EMTU) produce proinflammatory cytokines and contribute to pathophysiology of asthma. When antigens are chronically exposed to asthmatics, activated resident mast cells degranulate and secrete cytokines, chemokines, proteases, histamine and phospholipid metabolites, which lead to vasodilation, an increase in vascular permeability and recruitment of innate immune cells. These immune cells constantly induce injury to EMTU and activate tissue factor, which aggravates inflammation and eventually leads to airway remodeling.

One way to attenuate the symptoms in asthmatics is to prevent the action of proinflammatory cytokine released from both immune cell and epithelium mesenchymal unit. Gene knockout study in mouse demonstrated that ablation of certain cytokines can attenuate AHR and mucous production and some have been put forward to clinical studies. Antisense Oligomer (AO) approach is a strategy, which allows researcher to modify gene expression either knockdown or alteration the isoform of RNA transcript via different mechanisms. Induction of non-functional protein, creating non-productive transcript or suppressing mRNA translation are the proposed mechanism for gene knockdown.

The project is to use AO to interfere gene expression of protein involving in pathophysiology of asthma. The target gene could be cytokines, cytokine receptor or tissue factor released from either immune cell or EMTU. AO optimisation will be undertaken in stimulated cultured airway epithelium or immune cells. RT-PCR and protein readout, enzyme linked immunosorbent (ELISA) or western blotting, will be used to determine efficiency of the AO *in vitro*.

13. Role of EP receptors in epithelial cell function in inflammation

Supervisor	Winthrop Prof Philip J. Thompson (Chief Supervisor) Dr Svetlana Baltic Dr Chalermchai Mitrpant
Research Unit	Molecular Genetic Unit
Essential qualifications	For PhD applicants, a Bachelor of Science with Honours or Masters in Science or equivalent
Essential skills	
This project is suitable for Funding	X <input type="checkbox"/> Honours/BMedSci X <input type="checkbox"/> Masters <input checked="" type="checkbox"/> PhD <ul style="list-style-type: none">• PhD Top-Up scholarships (the Applicant should apply for APA or UPA)• Honours/Masters/BMedSci, scholarships available.
Contact	Dr Svetlana Baltic, Molecular Genetic Unit, 1 st Floor, B Block, SCGH Tel: 9346-7949

Project Outline

Epithelial cells represent a vital component of the innate immune system. In addition to providing the first physical barrier against environmental insult, they produce a wide range of cytokines, chemokines and growth factors transducing pro-inflammatory signals in response to inhaled antigen or allergens. The close interaction between airway epithelium and cells of the innate and adaptive immune response allows epithelial cells to play a key role in the pathogenesis of both chronic airway inflammation and lung remodelling.

Prostaglandin E2 (PGE2), a member of the prostanoid family of inflammatory mediators, acts to limit the immune-inflammatory response, as well as tissue repair processes in the lung, and represents an endogenous protective mechanism of the airways. The biological activity of PGE2 is mediated by four PGE2 (EP) receptors that are all expressed in airway epithelial cells. Activation of each receptor leads to distinct functional responses. Although EP receptors play a prominent role in airway inflammation, very little is known about the expression and function of these receptors in human lung. The existence of four EP receptors and the possible expression of multiple receptors in a single cell may explain the multiplicity of biological responses elicited by PGE2, and suggests an intricate system of regulation controlling PGE2 activity that has not yet been fully elucidated. The potential to manipulate the PGE2 receptor system for therapeutic purposes is significant.

This project will test the hypothesis that the nature of the anti-inflammatory effects mediated by PGE2 is dependent upon which EP receptor is activated. The role of each EP receptor in terms of epithelial cell function - regulation and differentiation of the production of pro-inflammatory cytokines and chemokines in human airway epithelial cells will be assessed. Cutting edge molecular genetic techniques will also be employed to knock out specific EP receptor subtypes and determine functional outcomes with respect to key cytokine and chemokine production by airway epithelium.

16. Dendritic cells susceptibility to α -synuclein induced apoptosis

Supervisor	Dr Mirjana Fogel (Chief Supervisors) Winthrop Prof Philip J Thompson Dr Svetlana Baltic
Research Unit	Inflammation and Immunology Unit
Essential qualifications	A Bachelor of Science or equivalent
Essential skills	
This project is suitable for Funding	X <input type="checkbox"/> Honours/BMedSci X <input type="checkbox"/> Masters PhD <ul style="list-style-type: none">• Honours/Masters/BMedSci, scholarships available.
Contact	mirjanaf@liwa.uwa.edu.au

Project Outline

Background –Dendritic cells (DC) are major antigen-presenting cells which play a central role in the initiation and regulation of the immune response. Apoptosis (programmed cells death) is carefully regulated by diverse signals that influence the decision of a cell between life and death. Apoptosis is triggered by a variety of stimuli, including neuropeptides and neuroproteins released from nerve terminals¹.

Forerunner data -Little is known about the signals that contribute to apoptosis or survival of DC. Recently, we identified one such signaling molecule that may possess both pro-apoptotic and anti-apoptotic activities on DC. This novel molecule is neurotoxin α -synuclein, which is synthesized and released by both, neuronal and immune cells, including human DC. Over-expression α -synuclein is associated with a number of inflammatory neurological diseases, such as Alzheimer's disease, Parkinson's disease, multiple system atrophy (MSA) and multiple sclerosis. Our findings also suggest that increased expression of α -synuclein in inflammation may be responsible for enhanced apoptosis of DC.

Based on our forerunner data, we proposed to further examine a role of α -synuclein in apoptosis of *in-vitro* cultured human DC. Since it has been shown that (in neuronal cells) α -synuclein may have a dual role in cells survival and that, depending on cell type and α -synuclein concentrations, it may mediate apoptosis or may have a protective role², we **hypothesised** that:

Dendritic cells susceptibility to α -synuclein induced apoptosis depends on DC maturation status and α -synuclein concentration.

Aim 1 - To determine concentration of α -synuclein that cause apoptosis of immature and mature DC.

Aim 2 – To investigate effects of α -synuclein on expression of Bcl-2 apoptotic/survival family members in immature/mature DC

Methods to be used - DC preparation and culture, RNA isolation, Reverse Transcriptase PCR (RT-PCR), MTT test (cell-survival assay), annexin-V Apoptosis Detection assay and FACS analysis.

17. Enhancing the efficacy of mannitol in treating bronchiectasis and exploration of the mechanisms involved

Supervisor	Mr Jamie Woods (Chief Supervisor) Winthrop Prof Philip J Thompson Dr Neil Misso
Research Unit	CF and Bronchiectasis
Essential qualifications	For PhD applicants, a Bachelor of Science with Honours or Masters in Science or equivalent
Essential skills	
This project is suitable for	X <input type="checkbox"/> Honours/BMedSci X <input type="checkbox"/> Masters X <input type="checkbox"/> PhD
Funding	<ul style="list-style-type: none">• Honours/Masters/BMedSci, scholarships available.
Contact	pjthomps@liwa.uwa.edu.au Jamie.Wood@health.wa.gov.au

Project Outline

Sputum clearance is a key part of treating patients with bronchiectasis. Inhaled mannitol is a proven method for enhancing clearance of airway secretions particularly in CF and to some extent in Bronchiectasis. However mannitol also causes bronchospasm in patients with increased bronchial reactivity. Patients with Bronchiectasis often have increased bronchial reactivity. Inhaled cromoglycate inhibits some forms of bronchial reactivity.

Hypothesis: cromoglycate and salbutamol will inhibit airway reactivity induced by mannitol in patients with Bronchiectasis and will do so by different mechanisms and will facilitate mannitol being used in a wider spectrum of patients.

Aims

- 1) To undertake a four way parallel group trial to evaluate the role of cromoglycate and salbutamol on mannitol therapy in bronchiectasis;
 - 2) To evaluate the mediator release in patients treated with mannitol and the modulating role of cromoglycate and salbutamol.
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18. Effects of air pollution on airway cell biology

Supervisor	Dr Neil Misso Prof Philip Thompson
Research Unit	Inflammation Unit
Essential qualifications	For PhD applicants, a Bachelor of Science with Honours or Masters in Science or equivalent. A Bachelor of Science or equivalent
Essential skills	
This project is suitable for Funding	<input type="checkbox"/> Honours/BMedSci <input checked="" type="checkbox"/> Masters <input checked="" type="checkbox"/> PhD <ul style="list-style-type: none">• Honours/Masters/BMedSci, scholarships available.
Contact	nmisso@liwa.uwa.edu.au pjthomps@liwa.uwa.edu.au

Project Outline

Particulate matter (PM) of varying size and composition is a major air pollutant in both urban and rural settings. Inhalation of PM may cause the activation of lung cells such as epithelial cells, fibroblasts, dendritic cells and macrophages, with adverse consequences, particularly for patients with lung diseases such as asthma and COPD.

Aims

- 1) To investigate the physicochemical characteristics (size, composition) of PM in different air pollution settings (urban, rural, mining, industrial).
 - 2) To investigate the pro-inflammatory, genotoxic and cytotoxic effects of different subfractions of PM on human respiratory cells.
 - 3) To assess the molecular mechanisms (signal transduction, apoptosis, transcription factors, DNA methylation) involved in the toxic effects of PM on human respiratory cells.
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19. Exhaled breath biomarkers in asthma, COPD and lung cancer

Supervisor	Dr Neil Misso Winthrop Prof Philip J Thompson
Research Unit	Inflammation
Essential qualifications	A Bachelor of Science or equivalent
Essential skills This project is suitable for Funding	<input type="checkbox"/> Honours/BMedSci <input checked="" type="checkbox"/> Masters <input checked="" type="checkbox"/> PhD <ul style="list-style-type: none">• Honours/Masters/BMedSci, scholarships available.
Contact	nmisso@liwa.uwa.edu.au pjthomps@liwa.uwa.edu.au

Project Outline

Patients with lung diseases, including asthma, COPD and lung cancer, exhale a variety of volatile organic compounds (VOC) in their breath.

Aims

- 1) To measure the pattern of VOC in the exhaled breath of patients with asthma, COPD and lung cancer.
- 2) To compare the pattern of exhaled breath VOC in patients with asthma, COPD or lung cancer with that of healthy control subjects without lung disease.

Exhaled breath samples will be collected in Bio-VOC sorbent tubes and analysed for the pattern of VOCs by gas chromatography-mass spectrometry.
