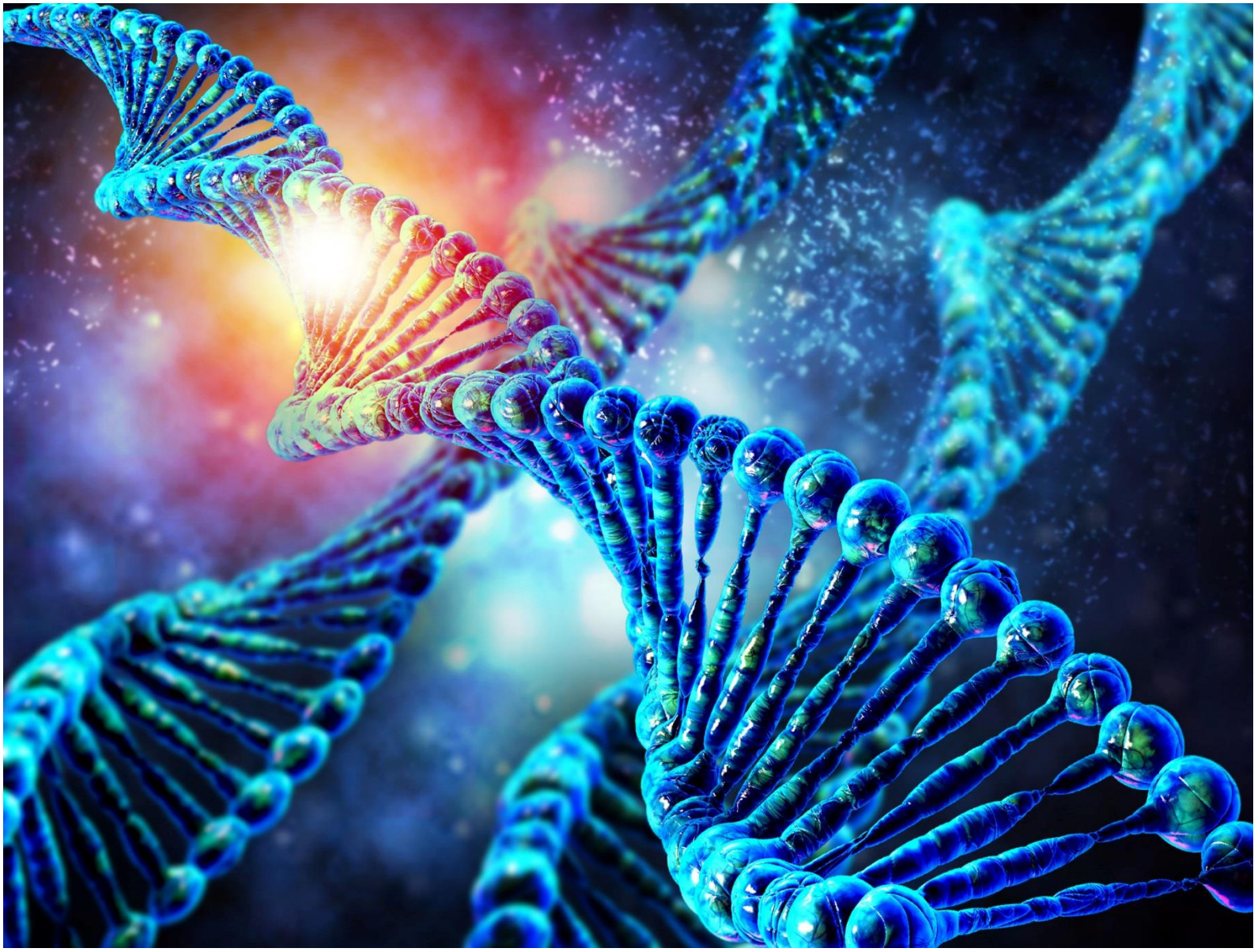
2020 | Projects

PhD | Masters | Honours

SCHOOL OF MEDICAL SCIENCE | GRIFFITH UNIVERSITY



FURTHER INFORMATION

This Information booklet outlines program prerequisites, study requirements and areas of research currently available for Research Program Candidates. The research projects listed are outlines, and subject to negotiation. Students are also welcome to discuss projects in areas that may be of interest to them, but are not included here.

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CONTENTS

WELCOME FROM THE SCHOOL OF MEDICAL SCIENCES EXECUTIVE TEAM

Welcome to the MSC 2020 HDR, Honours and Masters Project book. We support promising students by providing outstanding research training opportunities in a dynamic and stimulation research environment with access to cutting-edge facilities. As an Honours, Masters or PhD student in MSC, you join a team with a wide variety of expertise in the medical sciences from cancer to critical care and bench to bedside. Our unique cross-disciplinary capability is recognised nationally and internationally for its quality and output, and for its success in attracting research funding. Our research addresses a range of key challenges in health care you can be a part of this endeavor.

In MSC we host a large and diverse group of young HDR researchers from around the world. Our internationally-renowned research leaders have supported and inspired many students through to successful completion of their research higher degree. Your research training in MSC will help you discover where your future direction might lie, will equip you with the professional skills to give you excellent choices, and will provide you with a strong foundation on which to build your chosen career.

PREFACE

The Bachelor of Health Science Honours program was first established in 1996, and has been very successful. Students from the first year have won national competitive scholarships and enrolled in PhD research programs in the School of Medical Science.

The Bachelor of Biomedical Science Honours became available in 2001 to join the Bachelor of Health Science Honours program and in 2009 Bachelor of Medical Science students also entered the Honours program. As of 2015, the Bachelor of Medical Laboratory Science Honours program is available.
The Master of Medical Research programs provide research opportunities for international or domestic students who want to enter postgraduate research programs.

These programs provide training in a variety of medical science fields, encouraging innovative research and preparing students for lifelong learning in medical research. Graduates are suitable for employment in universities, government research organisations, hospitals and medical related industries.

The School of Medical Science is focused on developing expertise in specialist research facilities in genetics, molecular biology and cardiovascular science, with growing interests in biochemical science.

Candidates will find that the Honours or Masters Programs requires dedicated effort and initiative, but research at this level is exciting. For those who grasp the opportunity, the work done will often lead to that first conference paper, or scientific publication.

This guide highlights potential Honours, Masters and PhD/HDR projects. It is important to note that many projects are flexible. That is an Honours project could be extended for a PhD, and similarly, a component of a PhD project could be extracted for Honours. Furthermore, if you find a project that you're interested in, but it's 'not quite right', it may be able to be modified. All that's often required is a discussion with the supervisor.

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In general, graduates will be well placed to continue in research as employees or in post-graduate study; having gained a deeper understanding of analytical rigour and the nature of scientific truth - but more than this, graduates will leave with important lifelong skills, able to think critically, to ask more meaningful questions, and to view the workings of the world with more rational eyes.

HOW TO SUCCEED IN A RESEARCH PROGRAM

Firstly, the research project is heavily weighted and much effort must be directed toward it. Skills are needed in planning, in experimental design and implementation, and in data collection and analysis. Clear writing in both the literature review and thesis discussion is also required.

The often heard statement that “I know what I mean, but don’t know how to say it” mostly means that “I have a vague idea of what I mean, and when I understand what I mean, I will be able to write it down clearly!” Clear, crisp, unambiguous writing is very important. Take heed of your supervisor’s early comments. A good basic rule is that each sentence must stand on its own and very long sentences are to be avoided. There are Style Guides available in the library, but most lessons can be learnt from articles published in good journals.

Determining just what is relevant in the sea of information, and synthesising information, are difficult tasks. Be prepared to spend a lot of time on these.

Access to, and analysis of, relevant information is crucially important - make sure you can find your way about Medline and other databases. The earlier you start your literature search the better.

Few candidates will have much experience in the planning of experiments, and supervisors can be expected to have a major role here. However, the collection and analysis of data will be primarily the candidate’s responsibility - the semester I courses are specifically designed to assist here.

Moreover, one of the key roles of the entire supervision team (associate as well as principle supervisors), is to provide assistance and guidance through their considerable experience. As such, your supervision team is integral to your success in a research program. HDR are additionally required to have a 'thesis committee'. The thesis committee is comprised of experts outside of the supervision team. The thesis committee is an addition point of help, advice and guidance.

Undertaking a research program is potentially very rewarding. However, it is also very intensive and high achievement will require dedicated effort.

THE ROLE OF THE SCHOOL AND SUPERVISOR

The supervisor is responsible for ensuring that the laboratory requirements for the project can be met, and that any requirement for ethical permission to conduct the project is arranged.

The supervisor is also responsible for ensuring that the projected costs of the research can be met. A provisional budget is allocated to each project, which may be partly used to fund general laboratory requirements, at the supervisor's request. All spending from this budget must be ratified by the supervisor.

The School will ensure access to a desk, shared access to a computer and printing facilities, and will supply reasonable needs to stationery supplies.

With regard to supervisory assistance, candidates can reasonably expect to discuss their project and general progress with supervisors at least once a week, and with some projects, contact will need to be far more frequent.

Supervisors are required to provide reasonably comprehensive and written feedback on drafts of written work, and one (less) comprehensive criticism of final drafts, if necessary.

Supervisors are required to make special arrangements if they are to be absent at crucial periods (e.g. prior to student seminar presentations). If they are to be away for longer than a week at any time during the student's candidature, a temporary supervisor acceptable to the student will be arranged.

ROLE OF PROGRAM DIRECTOR

Students can approach the Program Directors about any issues that are troubling them at any time - it is part of the Directors role, and confidentiality is ensured. Failing this, or if the Program Director is also a supervisor, students may arrange to see the Head of School.

The Program Director will also assist with general advice on academic and research matters, whenever required, and is responsible for ensuring that seminar rooms are booked and suitably equipped.

The Program Director is also responsible for collating marks awarded to items assessed during the year, and following discussions with the academic staff involved, is responsible for notifying students of final grades awarded.

School Of Medical Science

PHD I HONOURS I MASTERS RESEARCH PROJECTS

2020

GRIFFITH UNIVERSITY
GOLD COAST CAMPUS

Bio and Gene Therapies for Cancer

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Kick and Kill: a novel two-step oncolytic therapy for cancer

PhD | Masters | Honours project

Our laboratory is at the fore front of developing novel cancer therapies, especially for those advanced cancers that causes most modalities. Thinking outside of the square, we have developed a novel strategy of adapting and selecting clostridial bacteria and explored the use of their spores for targeted cancer oncolysis from within. This is due to the fact that late stage cancers always have unique hypoxic microenvironment. Strict anaerobic clostridial bacteria could find the hypoxic microenvironment as a heaven to live, thus causing destruction of the cancer microenvironment, which is resist to current cancer therapy approaches. An international patent has been gained and a clinical trial is imminent.

Immune therapy for cancer: the development of a novel cancer vaccine for patients after cancer surgery

PhD | Masters | Honours project

Our laboratory is exploring several strategies to enhance immune cells' ability to eliminate cancer cells or prevent cancer from reoccurring in clinical settings, such as after surgical remove. We are developing novel approaches to provide the immune system with ability to mount a strong response against cancer cells by using patients' own cancer infiltrating lymphocytes or CAR-T cells or using low molecular weight protein mediators involved in cell growth, inflammation, immunity, differentiation and repair.

Bone Biology

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Chemokine regulation of bone remodeling and repair

PhD | Masters | Honours project

Bone remodelling is a normal skeletal function to renew bone tissue, but is also directed to heal stress fractures and can become imbalanced leading to bone loss in osteoporosis or skeletal cancer. How do the bone cells know which skeletal sites to target? We will use an innovative model of stress fracture *in vivo* to investigate chemokine expression during activated remodelling of early SFx healing and to test the hypothesis using in vivo models of human menopause. We will also use a highly innovative gene therapy approach to deliver a dominant negative mutant to MCP1 (7ND) to inhibit its action in bone *in vivo,* following oestrogen withdrawal. This knowledge will be important to develop approaches to facilitate healing in cases of non-union or slow SFx repair and many conditions that increase fracture risk such as osteoporosis, inflammatory bone loss and loosening of orthopaedic implants.

Optimising sterilisation of allograft tissues for orthopaedic surgery

PhD | Masters | Honours project

Despite advances in biomaterials, allograft bone remains a necessary graft material in orthopaedics. To eliminate *bacterial* infection, gamma irradiation at 25 KGy is used for terminal sterilisation. We have been working to reduce the dose of radiation because it weakens the bone tissue and destroys many bio-active factors. One approach is to protect the bone using free radical scavengers. So, cortical bone will be irradiated at 0, 10, 25 and 50 kGy in the presence or absence of vitamin E (alpha tocopherol) or tocopherol acetate. Specimens will be subjected to microbiological assays to determine the sterility assurance level (SAL); mechanical tests; assessment of collagen structure and its cross-links; and cell culture for bone cell activity. Finally, tocopheral treated bone will be implanted in Cr:NIH-rnu nude rats to test efficacy of incorporation. We will also determine if growth factors such as the bone morphogenetic proteins (BMPs) are maintained.

Cancer

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Using CRIPSR gene editing to reactivate p53

PhD | Masters

In cancer, p53 is the most commonly mutated gene [1] indicating that inhibition or loss of its function is highly critical to cancer formation and maintenance. However, all HPV-positive tumours have wildtype p53, as E6 is highly efficient in forcing its rapid destruction, via E6AP and the proteasome. This offers us a unique opportunity to look at activating CRISPR (or CRISPRa) as an approach to therapy. Reactivation of p53 does occur when we use E6 siRNA resulting in apoptosis of cells. Indeed, the concept of restoration of p53 activity as a therapeutic approach has been investigated previously using nutlin-3a, which reactivates p53 by inhibiting MDM2 [2] and results in apoptosis. This has also been shown to overcome local immune suppression and enhance antitumour responses *in vivo* [3]. Activating CRISPR uses the same technology as CRISPR/Cas but uses a dead Cas 9 fused to transcription activation proteins such as VP64. This forced higher expression of p53 which should overcome the E6 and allowing restoration of p53 function. This would result in senescence or apoptosis as shown by us using E6-directed siRNA [4].

1. Kalu, N.N., et al., *Genomic characterization of human papillomavirus-positive and -negative human squamous cell cancer cell lines.* Oncotarget, 2017. **8**(49): p. 86369-86383.
2. Saha, M.N., et al., *Pharmacological activation of the p53 pathway in haematological malignancies.* J Clin Pathol, 2010. **63**(3): p. 204-9.
3. Guo, G., et al., *Local Activation of p53 in the Tumor Microenvironment Overcomes Immune Suppression and Enhances Antitumor Immunity.* Cancer Res, 2017. **77**(9): p. 2292-2305.
4. Putral, L.N., et al., *RNA interference against human papillomavirus oncogenes in cervical cancer cells results in increased sensitivity to cisplatin.* Mol Pharmacol, 2005. **68**(5): p. 1311-9.

Cancer Immuno-therapy

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Viral oncogene silencing and innate immune activation – A novel approach for treating human papilloma virus-positive oropharyngeal cancers

PhD | Masters | Honours project

Human papilloma viruses (HPV) are the main culprit in cervical and oropharangeal cancers. HPV positive (+) cancers are regarded as 'oncogene addicted', displaying an absolute requirement for the continued expression of the oncogenes for their viability owing their survival, and thus making these genes salient targets for developing specific therapeutic agents. There is a strong association between HPV and oropharyngeal squamous cell carcinomas (OPSCC), a subset of head and neck cancers (HNCs). Alarmingly, HPV-associated OPSCC are on the rise in Australia, and the number of cases of HPV+ OPSCCs surpasses that of cervical cancer in the USA. Current treatment of locally advanced OPSCCs include chemotherapy, and radiotherapy, or a combination of these, but with unfavourable outcomes. New therapeutic options for OPSCC are therefore warranted. HPV oncogene editing has been shown to be effective at reducing tumour burden in HPV+ cervical cancer models. The pharmacological use of immune activators has recently been explored for cancer immunotherapy. This project aims to determine the feasibility of combining gene editing technology and immune activators for the treatment of OPSCC.

Cancer Molecular Pathology

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Molecular characterization of tissue based genetic markers in colorectal cancers

PhD | Masters | Honours project

Colorectal cancer is amongst the most common malignancy found in the Western world and usually ranks high in incidence and mortality among malignancies in those countries. Globally, colorectal cancers accounted for about 1 million new cases. There is evidence that molecular research contributes directly to improve the care of patients with colorectal cancer by more accurately refining prognosis and selecting the most appropriate adjuvant therapy for individual patients with colorectal carcinoma. In order to do this, our research focuses on studying novel tissue-based prognostic indicators at the molecular level. The objective of this project is to detect and validate of various novel genetic markers with significant clinical implications in predicting patient prognosis, tumor recurrence and metastasis in colorectal cancers. This project will use different technologies for candidate biomarker identification, and subsequently, study the biological function of these markers, and their expression in patient derived colorectal cancer tissues.

Molecular and biological implications of red/processed meat molecules in colorectal cancers

PhD | Masters | Honours project

Recent reports by researchers from the World Health Organisation have found a potential link between the consumption of processed meat and increased risk of developing colorectal cancers. Previous studies have indicated that a diet resulting in high exposure to heme and N-Nitroso compounds increase the risk of cancer pathogenesis in bowel tissues. Therefore, it is anticipated that a diet that contains red/processed meat will increase an individual's risk of developing colon cancer. This project specifically aims to investigate the following. (1) Investigate the link between processed meat molecules and colon cancer cell proliferation; (2) Establish whether heme molecules and N-Nitroso compounds involve in the molecular pathogenesis colorectal carcinomas in-vitro and in-vivo; (3) Quantify or measure the amount of these molecules or compounds in cancer tissue or blood samples from patients diagnosed with colorectal carcinomas.

Cardiovascular Disease

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Effect of QueRcEtin Supplementation On pLatelet function and markers for OxidatiVe strEss and inflammation: RESOLVE study

PhD | Masters

Platelets play an important role in the development of cardiovascular disease and the formation of arterial thrombosis (clot). Antithrombotic agents are regularly used for the prevention of cardiovascular events in high risk individuals. Furthermore, antiplatelet therapy is the standard treatment for patients undergoing cardiovascular procedures. Despite the clinical benefits achieved with antiplatelet therapy, some patients still develop thrombotic episodes, and there is growing data to suggest inadequate cardiovascular protection by these agents. Quercentin is one of the most abundant flavonols. It has been shown to exert antioxidant and cardiovascular beneficial properties as well as anti-inflammatory and antiplatelet. There have been limited clinical studies studying the effect of quercetin supplementation on healthy volunteers and in those people at risk of CVD. This study will examine the effect of quercetin supplement consumption for 28 days on platelet function and markers for oxidative stress and inflammation in healthy human volunteers.

Cardiovascular Research

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The effects of obesity and the metabolic syndrome on myocardial mitochondrial dynamics and function

PhD | Masters | Honours project

Myocardial mechanical function and tolerance to an ischaemic event is compromised in obese individuals with metabolic syndrome (obesity, dyslipidaemia and insulin resistance). Maintaining normal myocardial function and the hearts ability to withstand the adverse effects of ischaemia is dependent on normal mitochondrial morphology and function. Mitochondria are dynamic organelles that continuously undergo fission, fusion and mitophagy in response to changes in their metabolic demands and substrate availability. Metabolic dysregulation (dyslipidaemia, insulin resistance and increased oxidative stress) associated with metabolic syndrome possibly has profound effects on mitochondrial dynamics, morphology and function. The aim of our work is to investigate and understand how obesity and metabolic syndrome alter mitochondrial turnover/dynamics and morphology and how these changes influence mitochondrial function. We utilize a rodent model of obesity and metabolic syndrome to investigate these mitochondrial changes in obesity and metabolic syndrome.

The effects of obesity and depression on myocardial pro-survival signaling, mitochondrial turnover and tolerance to ischaemia

PhD | Masters | Honours project

There is a strong link between obesity and depression with patients with both these conditions suffering from poorer post-myocardial infarction outcomes. Current estimates are that depression increases a persons risk of cardiovascular disease associated death four-fold. Myocardial mechanical function and tolerance to ischaemia event is compromised in obese individuals with metabolic syndrome. The impact of obesity/metabolic syndrome together with depression on myocardial function and stress (ischaemia/reperfusion) tolerance is not known. Although early evidence suggests that the myocardium of obese patients suffering from depression is more prone to ischaemia/reperfusion injury, the mechanisms for these changes are not known. Our studies aim to establish how these two conditions influence myocardial function and tolerance to an ischaemic event and the mechanisms for these changes. We are currently developing a rodent model of depression and will add a model of obesity with depression to the suite of models at our disposal to answer these questions.

Cardiovascular Research

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Novel Cardioprotection by Opioids

PhD | Masters | Honours project

Opioid receptors are one of several potentially protective G-protein coupled receptor (GPCR) systems expressed within the heart. It is emerging that endogenous opioid peptides possess autocrine/paracrine regulatory functions in heart, and may play roles in improving the hearts ability to withstand the damaging effects of heart attack/myocardial infarction. Our group has recently identified a unique and powerful cardioprotective phenotype resulting from chronic exposure to morphine exposure. The degree of protection exceeds that for ischaemic preconditioning (often touted as the most protective strategy known to man), and persists for 48 hours or more following morphine withdrawal. Furthermore, the protective response is evident in young and aged hearts whereas most other strategies lose efficacy in older hearts. Thus, this response, when understood at a mechanistic level, offers considerable therapeutic promise. However, the mechanistic basis of this unique protective phenotype remains elusive.

Novel methods of conditioning the transplant recipient

PhD | Masters | Honours project

In conjunction with the Critical Care Research Group (CCRG)
The CCRG is dedicated to improving heart transplant success, and aims to do so by assessing various aspects of the transplant process. In order to further improve transplant success via an avenue currently unstudied by the CCRG, we hypothesise that protection harnessed by novel sustained preconditioning and/or mitochondrial transplant can improve post-transplant outcomes in the recipient, manifested as a reduction in I-R injury. This proposed project broadly aims to *condition the recipient* (or relevant cardiac surgery patient) using protection harnessed from opioid-induced SLP and/or mitochondrial transplant. Specifically, this project aims to;
1. Demonstrate efficacy of transferred cardioprotection with SLP by:
A) Generating SLP cardioprotection in a deliverable form (powder)
B) Assessing the effects of SLP powder against ischemia-reperfusion injury (I-R injury)
2. Demonstrate efficacy of mitochondrial transplant by:
A) Characterising the specific activity of mitochondria to be used for transplant
B) Assessing the effects of mitochondrial transplant against I-R injury.

Vascular Dysfunction in Chronic Stress and Protection by Adenosine and Opioid Receptors

PhD | Masters | Honours project

In conjunction with Prof John Headrick.
This project will test for involvement of specific kinase signaling pathways (PKC, PI3-kinase, Erk1/2) in the vasoprotection provided by A_1 and A_3 adenosine receptors in post-ischaemic coronary vessels. Specifically, the abilities of A_1 and A_3 receptors to selectively modify endothelial dysfunction will be compared in untreated hearts and in hearts treated with pharmacological inhibitors or activators of PKC, PI3-kinase, and Erk1/2. If warranted, this may be coupled with analysis of the effects of A_1 and A_3 agonism on activation of these proteins in cultured endothelial and smooth muscle cells. A parallel study will identify whether opioid receptors also mediate a similar

vasoprotection, characterised by enhanced vascular function and reduced vascular death, and whether similar signaling pathways are involved. Additionally, given that little is known about coronary vascular function in the setting of chronic stress, this project will be repeated in hearts from mouse models of chronic stress.

Cardiovascular Research/Public Health

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Characterization of lower limb vasculature and cardiovascular disease risk factors in transport workers

PhD | Masters | Honours project

Queensland Transport workers have a high incidence of metabolic risk factors consistent with metabolic syndrome (dyslipidaemia, insulin resistance, hypertension, obesity). Traditionally, transport workers are subject to prolonged periods of sitting and inactivity, teamed with a poor diet, which heightens the risk for cardiovascular disease and diabetes. Lower limb blood flow and endothelial shear stress decreases during periods of prolonged sitting, increasing the risk of microvascular dysfunction. This project will investigate lower limb vasculature and blood flow in transport workers using a doppler ultrasound (basic training will be provided). This project will also address whether endothelial dysfunction can be prevented with intermittent periods of activity that break excessive periods of sitting.

Chronic Pain

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Effect of low impact activity on chronic pain of aged care residents: Evaluation of intervention promoting exercise and functional mobility

PhD | Masters project

In Australia one in three people aged over 65 suffer from chronic pain, draining the quality of life among the elderly. Consequences of pain include impaired mobility, risk of falls and depression. Alternative therapies such as low impact exercise (Taichi and meditation) are gaining popularity as non-pharmacological therapies that could complement or even replace pharmacotherapy in relieving chronic pain in elderly, however, more evidence is needed to support that claim.

This study will compare the effect of low level supervised activity level in residents of NSW and Gold Coast. Outcome of the study will help us understand variations between perception of pain and its management in different aged care centres and assessment of daily activity, risk of falls and rate of anxiety and depression in elderly performing slow motion exercises compared to those with minimal activity in their daily routine with the aim to help improve the quality of life among the elderly by long-term implementation nationwide.

Effect of sedentary lifestyle and nutrition on activity level, chronic pain and blood clotting in aged care residents and seniors living at home

Honours project

Chronic pain in elderly has been suggested to have a relationship with nutrition and lack of movement. Many factors impact the quality and quantity of dietary intake in aged care residents. These seniors show nutritional deficiency due to a decline in energy requirement (physical inactivity, loss of lean muscle mass and increased adiposity) that gradually reduces food intake.

This study aims to compare baseline data to post intervention data collected by interviews with residents to complete pain assessment, general health, and diet and activity questionnaires. The effect of different diets and activity level in residents of different aged care centres will be assessed. Intervention will include non-strenuous low impact daily activities with or without wearable devices to aid repetitive movement to alleviate the impact of chronic pain. Simple blood tests, anthropometric measurements and quality of life outcomes will be analysed and presented to seniors to encourage physical activity within their limited capacity.

Immunology of Cancer

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Blog page: www.cancure.com

An immune system trained to recognize the first signs of new or recurrent growth can begin to attack cancers long before the best scans detect them. The latest vaccines incorporate clever new ways that malignant cells can be tagged, exposed and destroyed. Understanding how the immune system works is very important in our treatment of cancer going forward. The immune system is good at battling most diseases, but cancer is equally good at eluding our defense systems. New therapies being designed will deliver a one-two punch: using drugs to kill the cancer cells and then helping the immune system better to detect cancer, promoting the immune cells to attack and kill the remaining cancer cells.

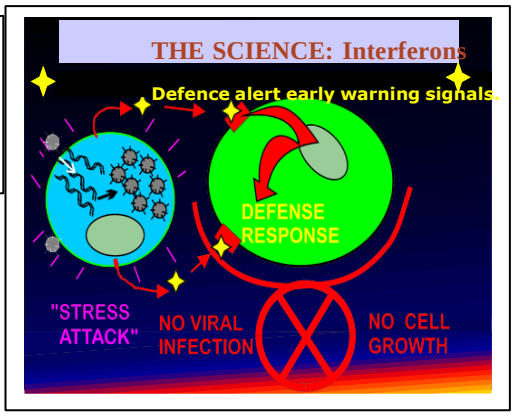


Fig. 1 Role of interferons in cell to cell signalling during defence responses to infection.

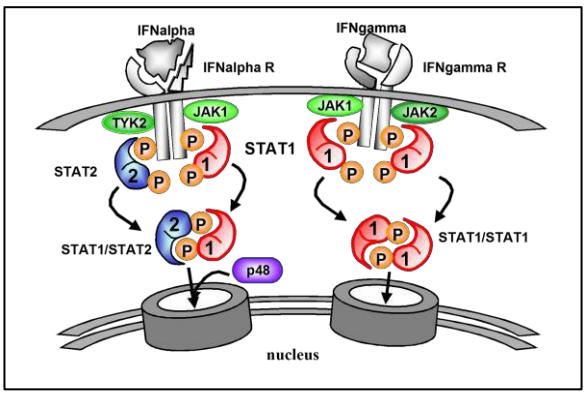
Cytokines are important biological factors that form a major part of therapy for cancers like leukaemia and melanoma and anti-viral therapy. Our goal is to improve the drug and immune therapy for preventing disease such as viral infections and cancer by increasing understanding of the actions of immune enhancing agents, like the cytokines, interferons.

Our laboratory has recently discovered a protein produced at high levels by cancer cells called Galectin-1 that kills the immune cells, thereby providing protection to the cancer. We have found that we can block this protein (Galectin-1) such that the host mounts a stronger immune attack against the cancer, slowing down the progression of the tumours. These drug molecules blocking Galectin will help the immune response to overcome the cancer and the aim of this study is to combine such anticancer drugs with vaccines to promote the elimination of cancers in animal models.

Cytokines form part of the early warning signaling systems that activate defense mechanisms in our cells against invading organisms. They also alert our immune cells to respond to infection and to eliminate any infected cells or aberrant cells that might cause lethal diseases like cancer. We are studying novel drugs that either directly kill cancer cells or promote cytokine responses via the immune system to kill the cancers.

One of the cytokines we study is the Interferons, which bind on the cell surface to receptors that transfer the signal inside the cell and activate enzymes known as JAK family tyrosine kinases (see Fig.2). These enzymes in turn pass on the signal inside the cell by modifying proteins (STATs and IRFs), placing phosphate (P) groups onto key tyrosine residues. The next step in interferon signaling involves STAT and IRF proteins forming complexes and relaying the signal to the nucleus where they act as transcription factors turning on the expression of several hundred different genes in our cells, including many genes encoding proteins inhibiting cell growth. As a result of their anti-cell growth, defense activating and immune enhancing properties, the interferons have become approved drugs for treating cancers such as melanoma and leukemia and viral diseases including hepatitis and multiple sclerosis.

Fig. 2 Interferon signalling pathway from the cell surface to the nucleus.



Unfortunately, during the progression of many diseases, whether viral infection or cancer, the signaling pathways used by the interferons often become disrupted, resulting in loss of cell response to interferons. Studies have shown that this loss of interferon response in infected cells is caused by genetic changes or by microorganism encoded proteins whose role is to disrupt interferon signaling, providing a survival advantage to the invading organisms. In cancer, we often find a decrease in the strength of the signal induced by interferons inside the tumour cells. The interferon project is to study what controls expression of the proteins activated by interferons inside cells that relay the signal to the nucleus. We are also characterising the function of novel interferon regulated genes that control the cell cycle.

Novel immunotherapies for cancer treatment

Masters | Honours project

Cancer cells avoid or evade the immune surveillance system. They do this by a number of different means. One of these is by producing inhibitors of the immune system such as Galectins which kill activated T cells. Another is the result of the selection of changes resulting in loss of expression of surface markers on the cancer cells. Many of these surface markers act as antigens required for recognition by the killer cells of the immune system that would otherwise eliminate them, preventing the cancer cells from developing into a tumour. Recent progress in the immunotherapy of cancer has resulted in new clinically approved products called the immune checkpoint inhibitors that help to restore the ability of the immune system to attack and remove cancers very effectively, helping patients to overcome and eradicate their disease

Despite production of the Galectins or the reduction in surface antigen expression on cancer cells, our studies and those of other groups have shown that by treating cancer cells with Galectin inhibitors or using the cytokines, interferons, the antigen presenting function of cancer cells can be restored and in fact, can be greatly enhanced such that the good guys or CD8+ cytotoxic T cells can then kill and eliminate cancer.

Our vaccines use a process mediated by the action of interferon signalling to increase expression of many of the different genes involved in the pathways of antigen processing and presentation in mammalian cells. Using different cancer models and cytokines, we are studying ways of making cancer vaccines more effective when used to immunise mice. The aim is to protect them from challenge by injection with live cancer cells. The immunity to cancer corresponds with a significantly increased level of cytotoxic T lymphocytes (CTLs) in vaccinated mice that targeted and killed the cancer cells. It is proposed that our vaccine strategy of treatment will provide an excellent basis for developing regimens to treat and prevent human cancers and we currently have a cancer vaccine in clinical trial being used to treat melanoma patients.

Techniques involved include immunoassays, cell culture, transfection of cell lines with expression vectors, other recombinant DNA techniques, immunodiagnostic assays (cytotoxic T cell assays), fluorescence activated cell analysis, vaccination/immunisation of mice in cancer models.

The aim of this project is to extend the observations to other cancer models in mice such as melanoma, breast cancer, colon cancer and more. To this end, we have obtained transgenic mouse strains in which the females develop breast cancer very similar to human breast cancer. Cell lines have been established in culture from these cancers and these lines will be used to develop better anti-breast cancer vaccines to test in the transgenic mouse strain for its ability to promote CTL production and prevent the onset of breast cancer in these mice. The long term goal is to use the vaccine as a therapy to treat human breast cancer as one immunotherapy and combine it with other existing immunotherapies as well as to block Galectin function.

Identify small drug molecules that can kill cancer cells and promote a stronger immune response against the cancers

Masters | Honours project

We have been collaborating with Prof. Jiri Neuzil's laboratory and other laboratories overseas to determine the role of novel anticancer drugs targeting mitochondria and related drugs in promoting immune responses against cancer cells. Projects based around the study of the killing actions of these drugs, called "MITOCANS" are aimed at finding improved new cancer therapies. We have also screened many already approved drugs for human use and found several of these act as Mitocans and have very high anticancer activity. The aims of this project are to identify precisely the drug target inside the cells and further define how they selectively can kill cancer cells.

We use ultrasound imaging analysis and luciferase light based systems to follow the growth of cancers in animal models and to study the effects of these small drug molecules for their actions on killing cancer cells in culture or growing as tumours in animals.

Study of gene regulation and loss of cellular responsiveness to interferons: either caused by viruses or as a result of genetic mutation in cancers

Masters | Honours project

We have shown that cancer cells are often resistant to interferons because these cells are deficient in the expression of the transcription factors (STATs and IRFs) required for interferon signaling. Other groups have also established that viruses disrupt the interferon response systems when they infect. In particular, our evidence from studies of human melanoma points to an important role for the interferon activated transcription factors, STAT1 as well as another member, STAT5 in regulating cellular responsiveness to interferons. In order to understand the mechanism for the changes in STAT expression in cancer cells, we have characterized the promoter region of these genes in humans and are aiming to improve our understanding of their regulation.

The aim of this project is to further determine how expression of the cytokine regulated signalling proteins, such as STATs, become suppressed inside virally infected cells and human cancer cells. One possible mechanism whereby these genes could be suppressed is via changes occurring in the regulation of their promoter regions.

Methods based on identifying immune cells, their function in animal models of cancer will be used including cell culture and immunobiochemical analyses, cytokine multiplexing, flow cytometry, tumour growth assays, animal handling, ultrasound and other techniques.

Hence, one of the aims of this project is to increase our understanding of the promoter regions of those genes encoding cytokine regulated signaling factors. Other explanations that could account for the reduced expression of interferon regulated signaling factors are possible. These alternative mechanisms include alterations in the levels of expression of other transcriptional repressors or activators.
A number of candidate proteins regulating STAT gene expression have been identified and the relative contribution of these regulatory factors, some which are transcription factors themselves, in controlling STAT gene expression will be studied as part of this project. Different cellular systems will be examined, including virally transformed cells particularly focusing on Epstein Barr viral (EBV) infected and transformed human B cell lines (lymphomas) as well as other human cancer cells derived from melanoma skin cancer or breast cancer in an effort to delineate the reasons why these cells lose their responsiveness to interferon as a therapy.

Natural product based treatments for cancer

Masters | Honours project

This project is examining the identification of drugs derived from natural products that have potent anticancer activities as well as immune enhancing properties. A number of recent compounds have been derived from Australian flora and fauna that show potent anticancer activities and we aim to define what these compounds are and how they work in promoting the elimination of cancers. One such study involves derivatives from Malaleuca Alternafolia (commonly known as Tea Tree Oil). We have found that such drugs have very powerful immune modulating properties, can selectively inhibit viral replication and are able to promote production of

cytokines and immune cells that attack cancers. The antiviral mechanisms of action and the mechanism of cancer cell killing will be studied. Also, the nature of the immune enhancing properties of these compounds will be examined as part of this study.

A range of recombinant DNA methods will be used including production of gene reporter constructs containing gene regulatory elements, human cell culture and transfection, luciferase assays, immunobiochemical analyses, expression vectors, PCR based cloning techniques, ShRNA knockdown of gene expression.

Identification of cancer stem cells and the role of tumor microenvironmental drivers such as hypoxia in their progression

Masters | Honours project

The tumour microenvironment is one of significant stress for cancer cells with intense competition and selection pressures for survival. We propose that these stresses select cancer cells that are more efficient at evading the immune defences and at invading into surrounding tissues. The mechanisms for the selection of the emerging cancer stem cells in these environments and markers that will allow their ready identification inside tumours based on GFP expression are the focus of this study.

We have found that it is possible to selectively modify primary cancer cells to produce more highly metastatic variants using hypoxic conditions. These cell lines are the focus of our studies in order to identify novel inhibitors that will kill and prevent the spread of cancer.

A range of molecular biological techniques and immunofluorescence, cell sorting and other methods are used to identify where in tumours the cancer stem cell populations reside when within tumours growing in animals. Once we identify these stem cells and study their behaviour, we can determine more precise mechanisms for targeting and killing these cells to eradicate the source of the cancer and eliminate metastases.

Immunology/Microbiology, Host Immune Responses

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Host responses to Vibrio cholerae

PhD | Masters | Honours project

Cholera is a devastating infection that can spread epidemically, caused by the bacterium *Vibrio cholerae*. This bacterium colonises the gut and secretes toxins, causing diarrhea that is fatal in vulnerable people. The bacterium also secretes signaling molecules into the gut lumen allowing the bacteria to signal to each other, and co-ordinate expression of the toxin and other virulence factors. This project aims to understand more about the interplay between bacteria and host immune signaling using purified or synthetic molecules and cell culture models of infection and will give further insight into the pathogenesis of this globally significant pathogen.

Medicinal Chemistry

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Development of novel phthalic acid diesters as potential human Parainfluenza virus therapeutics

PhD | Masters | Honours project

Infectious diseases, such as Dengue (DENV), Chikungunya (CHIKV) and Human parainfluenza virus (hPiV3), are a major cause of avoidable mortality and morbidity, particularly for children in developing countries. However, due to the rapidly mutating nature of viruses, resistance to conventional drug therapies occurs. The proposed research project is ongoing and follows on from our previous work where we isolated a chemical compound from a Bangladeshi mangrove fern *Acrostichum aureum* that showed potent activity particularly against hPiV3, but also moderate activity against DENV2 and CHIKV. This project aims to synthesise the isolated compound and also synthesise analogues where chemical groups have been varied, then test these compounds for potency as potential anti-viral agents against hPiV3, DENV2 and CHIKV. It is hoped that this work will lead to the identification of a new agent with potent antiviral.

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Degradation of Galectin-3 using proteolysis targeted chimeras (PROTACs)

PhD | Masters | Honours project

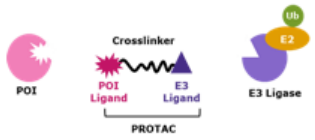
From previous studies[1,2], it is clear that the use of Proteolysis-targeting chimera (PROTAC) molecules can result in the effective degradation of target-proteins. PROTAC techniques involve the exploitation of normal protein degradation

essential for cellular maintenance and hijacking the system to specifically target proteins of interest (POI) for degradation.

Work is underway within the Institute for Glycomics to synthesise novel PROTAC molecules to achieve the successful proteolysis of the Galectin-3 protein, which is known to be intimately involved in cancer progression.

To achieve an effective PROTAC design the molecule must provide high affinity binding to both Galectin-3 and a suitable ubiquitin ligase, and maintain these interactions whilst not inhibiting the overall ubiquitination (or tagging for destruction) process.

The project will involve synthetic organic/carbohydrate chemistry, along with NMR spectroscopy, mass spectrometry and other associated techniques for structural characterisation of the synthesised PROTACs. These would then be assessed for their biologically activity.



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Medicinal Chemistry, Molecular Microbiology

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Analysis of surface carbohydrate structures from Gram-negative Moraxellacae bacteria

PhD | Masters | Honours project

The aim of this project is to isolate surface carbohydrate components from bacteria in the *Moraxellaceae* family, then determine the structures and biological significance of these carbohydrate molecules. Obtaining structural carbohydrate information will enable us to determine the role of these carbohydrates in disease and develop potential new therapeutic strategies.

The project will require the development of knowledge and skills in the areas of cell culture, chemical and biochemical extraction and manipulation strategies, nuclear magnetic resonance (NMR) and mass spectrometry (MS) of isolated carbohydrate materials.

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Microbiology (Bacteriology)

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Make a difference! Quality assurance for medicinal maggots and maggot therapy in compromised healthcare settings, such as during war and disaster or in remote communities and poverty.

Honours

Maggot therapy is the treatment of wounds with living fly maggots to remove dead tissue (debridement), to control infection and to stimulate wound healing. We are a team of Griffith researchers developing medicinal maggot production solutions for war, conflict, disasters, and other compromised healthcare settings, so that better wound care can be provided to communities that are hard-to-reach. Our innovative solutions include 1) a shipping container laboratory for field hospital deployment, and 2) do-it-yourself (DIY) medicinal maggot production laboratories which can be built and run by hard-to-reach communities during war time. We are looking for an Honours student to undertake a program of microbial quality assurance research. Preparation of medicinal maggots for therapy involves the harvesting of fly eggs, disinfection of these eggs with a variety of chemicals, and the testing of their sterility. You will i) explore what types of microbes are found on medicinal flies that are produced in our shipping container- and DIY labs, ii) develop a protocol for sterility testing of fly eggs and maggots prepared for maggot therapy, and iii) monitor the sterility of medicinal maggots produced with our container laboratory and various prototype DIY labs. This is an applied medical science project where you have the opportunity to contribute to cutting-edge R&D that will save many limbs and lives in communities affected by war, disasters and poverty.

Microbiology and Immunology

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Disseminated infection and immune defense against pathogenic bacteria

PhD | Masters | Honours project

A microbiology and immunology research project is available in the field of infectious diseases, host defense and bacterial pathogenesis. The project will focus on disseminated infections and the progression of disease following exposure to different type of bacteria; this will include elements of bacterial virulence and host immune responses that influence infection progression and the control of infection in the host. The project will study *Streptococcus agalactiae* isolated from cases of human disease and will take place within the Level 9 Laboratories of the G40 Griffith Health Centre, Gold Coast. The project will use a range of techniques comprising in vivo models, in vitro cell culture, high-end microscopy, functional genetic approaches and molecular methods such as nucleic acids and protein quantitation to gain insight into how microbes colonize the host. Particular areas for study include antimicrobial immune responses, microbial evasion of immunity, and bacterial virulence factor repertoires.

Microbiology, Pathogenesis of Camplylobacter Jejuni

Background

Bacteria of species *Campylobacter* are widespread in the environment, they are commensals, and sometimes pathogens, of animals and birds; they are found in soil and waterways as faecal contamination and most importantly, are now recognised as one of the major causes of enteric disease in humans. Indeed *Campylobacter* species, in particular *C. jejuni,* are the most common cause of food borne disease in the world and have surpassed *Salmonella* and *Shigella* spp as causes of lost productivity in the workplace. The mechanisms of pathogenicity in humans, colonisation in animals and survival in the environment of *Campylobacter* spp are poorly understood. However, motility and chemotaxis have been shown to be essential for colonisation and infection by campylobacters and the closely related helicobacters.

The ongoing genomic analysis of the sequenced *Campylobacter jejuni* strain NCTC11168 has provided data on the genetic framework for chemotaxis in campylobacters, but it is not yet possible to provide a model for how campylobacters detect chemotactic signals from this information. Although 11 putative chemoreceptor genes have been identified, their role, signal specificity, cellular organisation and function are unknown, and it is not clear if the chemoreceptor gene content varies between strains. Chemoreceptors detect environmental clues important in colonisation and pathogenicity, and it is possible that chemoreceptor signal transduction is linked to other regulatory networks in the bacterial cell.

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Identification of specific amino acid residues responsible for interactions of chemosensory receptor Tlp1 with chemotaxis proteins CheW and CheV of Campylobacter jejuni.

PhD | Masters | Graduate Diploma | Honours project

The natural habitat of campylobacters is the intestine of warm-blooded animals, and therefore chemotactic motility is an important mechanism involved in the colonisation and pathogenicity of this microorganism. Bacterial motility is subject to sensory control mechanisms that introduce a bias into the swimming direction of the organism towards beneficial environments and away from unfavourable conditions. Although chemotaxis has been demonstrated for *Campylobacter* the chemical substrates, mechanisms involved in the sensory control of motility and the role of chemotaxis in disease, are poorly understood. We, therefore hypothesise that the chemosensory receptor proteins play a key role in chemotaxis and are involved in the pathogenicity of this organism as the first line of bacterial – host interaction and thus provide rational targets for the design of novel antimicrobial agents.

This project involves characterisation of interactions of the signaling domain of one of the chemoreceptors of *C. jejuni,* named Tlp1 with CheW and CheV chemotaxis proteins. The major aim of this project is to identify which amino acids in the signaling domain of Tlp1 are responsible for binding with CheW and CheV though systematic site-specific mutagenesis followed by analysis of the mutated proteins using yeast 2-hybrid protein-protein interaction system.

This project will further the studies to elucidate the role of Tlp1 chemoreceptor in chemotaxis and pathogenicity of *C. jejuni*, which can potentially provide a tremendous insight into the mechanisms of chemotaxis of this organism.

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Characterisation of the role of the Campylobacter jejuni chemosensory receptor Tlp7 in the chemosensory signal transduction.

PhD | Masters | Graduate Diploma | Honours project

The natural habitat of campylobacters is the intestine of warm-blooded animals, and therefore chemotactic motility is an important mechanism involved in the colonisation and pathogenicity of this microorganism. Bacterial motility is subject to sensory control mechanisms that introduce a bias into the swimming direction of the organism towards beneficial environments and away from unfavourable conditions. Although chemotaxis has been demonstrated for *Campylobacter* the chemical substrates, mechanisms involved in the sensory control of motility and the role of chemotaxis in disease, are poorly understood. We, therefore hypothesise that the chemosensory receptor proteins play a key role in chemotaxis and are involved in the pathogenicity of this organism as the first line of bacterial – host interaction and thus provide rational targets for the design of novel antimicrobial agents.

The primary aim of this research project is to characterise Tlp7, one of 7 receptors of the *C. jejuni* 11168. In order to characterise the function of the Tlp7 receptor in *C. jejuni* 11168, the gene, which encodes for Tlp7 in *C. jejuni* had been cloned and expressed in *E. col*i host. The aim of this project is to understand the role of Tlp7 in chemotaxis. To date we have identified 3 specific ligands that interact with Tlp7. To further characterise this interaction, recombinant Tlp7 protein will be produced and specific ligands, that bind to this protein, will be investigated using surface plasmon resonance (SPR). An extension of the project will involve construction of a mutant and a complemented mutant of Tlp7 in an *E. coli* host. This will be followed by construction of an isogenic mutant and complemented mutant *C. jejuni* 11168 strain. *C. jejuni* 11168 mutant strain will be compared to wild type strain for its ability to sense Tlp7 specific mutants using chemotaxis assays, cell culture and animal models.

This project will further the studies to elucidate the role of Tlp1 chemoreceptor in chemotaxis and pathogenicity of *C. jejuni*, which can potentially provide a tremendous insight into the mechanisms of chemotaxis of this organism.

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Identification of Campylobacter jejuni lectins involved in bacteria-host interactions

PhD | Masters | Graduate Diploma | Honours project

Carbohydrates (or glycans) that modify proteins and lipids play a key role in numerous cell recognition events, including those involved in the regulation of the immune system, and in the attachment of pathogenic organisms to host tissue. Protein-carbohydrate interactions have been identified as adherence factors for numerous commensal and pathogenic bacteria. These interactions between carbohydrates and pathogens are dependent on carbohydrate binding proteins known as lectins.

Campylobacter jejuni, the most prevalent cause of gastroenteritis in developed countries, is a highly motile, Gram-negative spiral rod that requires microaerobic conditions for growth. *C. jejuni* is a zoonotic pathogen, being a commensal organism in poultry and other wildlife. *C. jejuni* does not ferment or oxidise carbohydrates as a carbon source, instead relying on amino acids such as aspartate and serine. All carbohydrate binding is attributed to interactions important for adherence and/or colonisation of the host rather than for energy acquisition. *C. jejuni* has recently been shown to recognise a range of carbohydrate structures including Fucose and Sialic acid containing glycans.

C. jejuni lectins are yet to be identified or characterised, however, two putative lectins have been identified through homology to known lectins of other pathogenic organisms. These two putative lectins are the *C. jejuni* genes *Cj1534c* (putative Sialic acid binding lectin) and *Cj1677* (putative fucose binding lectin).

This project will be involve screening for additional lectins expressed by *C. jejuni* which will be performed using additional bioinformatic analysis and affinity chromatography to find glycan binding proteins from *C. jejuni* cell lysates. The putative lectins identified will be characterised using isogenic mutation of the genes and glycan binding analysis of the mutant bacteria and purified protein expressed using an *E. coli* expression system.

The identification and characterisation of *C. jejuni* lectins may provide new targets for the development of novel therapeutics for *C. jejuni* infection.

Microbiology, Vaccines Against Gonorrhea

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Vaccine development for Neisseria gonorrhoeae

PhD | Masters | Honours project

Gonorrhoea is a significant health problem worldwide, leading to infertility and increased transmission of HIV. Cases in Australia have more than doubled in the last five years. This is partly because of rising antibiotic resistance. The World Health Organisation and CDC count *Neisseria gonorrheae* as an urgent theat. With some strains almost untreatable by antibiotics, the control of gonorrhoea depends on the development of a vaccine. This project aims to discover novel virulence factors based on identification of genes that are required for interaction with human cervical epithelial cells and that are upregulated during interactions with human cervical epithelial cells. The distribution of the identified vaccine candidates will be investigated in a diverse range of *N. gonorrhoeae* strains and the functions of proteins will be examined using a panel of antimicrobial stress assays. The vaccine potential of these candidates will also be assessed in a protection model to determine if antibodies raised against these proteins can inhibit association and invasion of cervical epithelia and as such offer protection against gonococcal colonization.

Mitochondrial Physiology

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Mitochondrial adaptions and transformation in the human placenta

Masters | Honours project

The placenta has unique physiological characteristics, consisting of an underlying layer of cells called cytotrophoblasts (CT) that fuse to form the syncytiotrophoblast (ST).During the transformation from CT to ST, associated mitochondria undergo morphologic and functional alterations. Mitochondria within the ST are crucial to maintaining a healthy pregnancy, and have therefore been hypothesised to be central in the pathophysiology of placental dysfunction and development of gestational disorders including gestational diabetes mellitus (GDM). However, the molecular mechanism behind the functional and morphological adaptions observed in mitochondria between the two cell lineages remains inconclusive. The objective of this project is to examine previously established differences in proteomic profiles from the mitochondrial populations to determine the pathway/s involved in transformation and adaptations in the human placenta. Through identification of the pathway/s we aim to lay the foundation for targeted treatments preventing mitochondrial dysfunction and ultimately, gestational disorders.

Molecular Basis of Disease

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Understanding the cellular machinery used by the AIDS virus to spread infection.

PhD | Masters | Honours project

Once a virus has grown up in an infected cell the newly assembled virus particles need to escape and spread the infection. Different viruses have evolved different strategies to escape from cells. Some viruses, known as cytolytic viruses, simply burst the host cell membrane and are released. Other viruses (non-cytolytic) escape by budding off from the membrane of the infected cell and the infected cell lives on to serve as a virus factory. Non-cytolytic viruses include the human immunodeficiency virus (HIV) responsible for Acquired Immune Deficiency Syndrome (AIDS), hepatitis B Virus (HBV), hepatitis C virus (HCV), and herpes simplex virus (HSV). This project investigates the key protein that mediates the process of virus budding. Our goal is to develop new antiviral drugs active against HIV, HBV, HCV and HSV. You will be trained in molecular biology, recombinant protein expression, analysis of protein-protein interactions in the living cell and electron microscopy.

Understanding the molecular basis of Wiskott-Aldrich Syndrome (WAS)

PhD | Masters | Honours project

Wiskott-Aldrich Syndrome (WAS) is an inherited immunodeficiency and blood clotting disorder caused by dysfunction of the WAS Protein (WASP). WASP is specifically expressed in haematopoietic cells (platelets, lymphocytes, neutrophils, macrophages). A protein of similar structure and function (N-WASP) is expressed in all cells, but is most highly expressed in neurons. There is a homolog of WASP/N-WASP in yeast. Intriguingly, human WASP functions in place of yeast WASP when expressed in yeast. In humans and yeast, proteins of the WASP family function in assembly of the actin cytoskeleton. This project investigates the physical interaction of yeast WASP with actin and other partner proteins in the living cell. Our goal is to test a hypothesis for how interaction with proteins of the WASP family protects cells from protein aggregation and disease. You will be trained in molecular biology, recombinant protein expression, analysis of protein-protein interactions in the living cell and fluorescence microscopy.

Molecular Cell Biology

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Wine, killer yeast and ion channels

PhD | Masters | Honours project

Commercial strains of wine yeast are sometimes killed off by contaminant yeast known as “killer yeast” during wine fermentation, resulting in a failed ferment. To combat this issue, killer yeast capable of wine fermentation are now commercially available and being used in wine making. Killer yeast differ from other yeast in that they secrete a factor known as “killer” that kills other yeast. Other yeast express a potassium channel known as Target Of Killer (Tok1). Killer causes Tok1 to pump all the potassium out of the yeast cells so they die. Intriguingly, mammalian cells express potassium channels so similar to Tok1 that they functionally substitute for Tok1 when expressed in yeast. Here we test whether yeast cells expressing the human potassium channel in place of Tok1 are sensitive to killer. Killer is now present in wine - is this a potential health concern? You will be trained in molecular biology.

Neurodegeneration Research

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Small Ubiquitin-like modifier (SUMO) pathway in Parkinson's disease

PhD | Masters | Honours project

The Small Ubiquitin-like Modifier (SUMO) conjugates to target proteins to alter their function and/or interactions. This makes SUMOylation a critical regulator of protein handling and SUMOylation plays key roles in receptor endocytosis, nucleocytoplasmic translocation and autophagy. Pathological protein aggregates in Parkinson's disease contain high levels of SUMO conjugates, indicating a link to neurodegeneration. SUMOylation is a highly dynamic process and modified substrate proteins are subsequently deSUMOylated by a member of the SENP family of SUMO proteases. Of these, SENP3 which cleaves SUMO-2/3 isoforms from SUMOylated substrates is of particular interest because it regulates cell fate in response to stress. We found that expression of SENP3 in PD was significantly increased in both brain tissue and patient-derived cell lines compared to controls, indicating systemic upregulation. The project is to assay SENP3 as a potential biomarker in PD and control tissue and cell lines obtained from PD cases and age-matched controls.

Copper metallothionein as a potential biomarker in Parkinson's Disease

PhD | Masters | Honours project

Copper is increased in Parkinson's disease serum and cerebrospinal fluid and is decreased in brain tissue as is expression of the copper transporter, CTR-1, indicating copper dysregulation. The primary pathological feature of PD is aggregation of the pre-synaptic protein, alpha-synuclein. Copper can bind to alpha-synuclein and induces aggregation. Copper is buffered by copper-binding proteins, such as metallothionein (MT). Recently, we found that MT induction could block copper-dependent alpha-synuclein aggregation and was increased in astrocytes, but reduced in neurons. MT may cross the blood-brain-barrier and any free copper in the brain will bind to endogenous MT. Copper-MT may then be transferred out of the brain, ultimately to the kidney and excreted in the urine. We found increased protein-bound copper in PD compared to control urine and increased MT in urine of animal models. The project is to determine MT levels and copper status in PD urine samples as a potential biomarker.

Effects of extracellular alpha-synuclein on neuronal and non-neuronal cell types

PhD | Masters | Honours project

Parkinson's disease and atypical Parkinson's diseases, result from CNS cell loss and dysfunction linked to aggregates of the pre-synaptic alpha-synuclein protein. Cytoplasmic pathological alpha-synuclein inclusion bodies occur predominantly in affected brain regions and there is evidence that alpha-synuclein is released by neurons and taken up by both neuronal and glial cells. However, extracellular α-synuclein has also been shown to interact with neural cell types, including astrocytes and microglia, mediating neuroinflammation, cell-to-cell spread and other aspects of pathogenesis, including compromised glymphatic flow. A more detailed understanding of the important extracellular interactions of α-synuclein with neuronal and non-neuronal cell types may provide new targets for therapies that modulate the disease process. Building on previous studies and publications in this area, the project(s) will investigate how extracellular alpha-synuclein interacts at the cell surface to drive components of disease progression, such as calcium channel activity, astrocyte activation, microglial phagocytosis and expression/distribution of aquaporin.

Neuroscience

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The role of neuroinflammation in the development of alcoholic brain damage

PhD | Masters | Honours project

Neuroinflammation is mediated via activation of microglia, the innate immune cells in the brain. In a healthy adult brain, these cells are in a resting or quiescent state and become activated in response to environmental triggers. Activation of microglia occurs along a spectrum with the highest level of activation associated with release of proinflammatory, cytotoxic factors and partial activation has been associated with the release of neuroprotective factors. Recent studies have suggested that activated microglia play a key role in the development and progression of neurodegenerative diseases including Alzheimer disease and Parkinson disease as well as in normal aging. Activated microglia have also been implicated in the pathogenesis of alcohol-related neurodegeneration. This project will investigate the role of miR-155 on mediating the expression of neuroinflammatory genes in susceptible and spared regions in the brain of human alcoholics.

Understanding the neuroprotective effects of natural phytochemicals in alcohol-induced neuroinflammation

PhD | Masters | Honours project

Natural phytochemicals, such as resveratrol, have garnered attention in recent years due to their potent anti-inflammatory, immunomodulatory and neuroprotective properties. Resveretrol has also been shown to confer protection against the oxidative stress, DNA damage and neurotoxicity due to alcohol exposure. There is emerging evidence that alcohol consumption results in changes in the expression levels of specific miRNAs as well as miRNA-regulated systems. This project will investigate the direct effects of alcohol on microglia-like cells as well as the indirect effects on neurons using a cell-based model of neuroinflammation as well as the potential for natural compounds such as Resveretrol to attenuate these effects This project will involve the development of a cell based model of neuroinflammation that will be used to screen natural phytochemicals for their anti-inflammatory properties.

Understanding the role of miRNAs in mediating alcohol-induced neurodegeneration

PhD | Masters | Honours project

MiRNAs play key roles in neuronal function and are often dysregulated in neurodegenerative diseases. As such, targeting miRNAs for manipulation is emerging as a promising avenue for the development of novel therapeutics with the potential to protect the brain from damage and reverse cognitive deficits. One way of manipulating miRNA levels is through the delivery of antagomirs directed against specific miRNAs. These antagomirs have been shown to induce neuroprotection in models of Alzheimer disease and ischaemic stroke, and can restore brain function. Alternatively, miRNA levels can be manipulated using natural compounds, such as Resveretrol, which have been shown to bind to and lower the levels of specific miRNAs. Here, we propose to develop and deliver antagomirs directed to silence miRNAs and investigate their function in neuronal cells.

Pharmacology

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Evaluation of heart rate variability and exhaled breath condensate from atrial fibrillation and heart failure patients

PhD | Masters | Honours project

AF affects one in four people over the age of 40. Atrial enlargement and fibrosis are predisposing factors for the development of AF. Intrinsic structural changes involve the proliferation and differentiation of fibroblasts into myofibroblasts resulting in atrial fibrosis. Atrial fibrillation is associated with increased rates of stroke, systemic embolism and HF. The development of HF is associated with significant morbidity and mortality due to remodelling of cardiac tissues with associated fibrotic changes. Abnormalities in heart rate variability, a measure of autonomic imbalance, and has been shown to be significantly associated with the degree of left ventricular dysfunction, progression and prognosis of the patients with HF. When oxygen supplies are inadequate to meet oxygen demands, cells release purine intermediates such as adenosine and the purine catabolic uric acid. Consequently, elevated levels of ATP degradation products in body fluids have been suggested to be a good index of tissue hypoxaemia. This project will investigate uric acid levels, heart rate variability and metabolomic evaluation of exhaled breath condensate in AF and HF patients.

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Platelet TGF-beta-1 and serotonin levels in patients with atrial fibrillation and heart failure

PhD | Masters | Honours project

The development of HF is associated with significant morbidity and mortality due to remodelling of cardiac tissues with associated fibrotic changes. Myofibroblasts are key effector cells of tissue remodelling. While myofibroblasts appear only transiently in physiological tissue during responses such as normal wound healing, they accumulate in

fibrotic diseases. Transforming growth factor β1 (TGFβ1) is a master regulator of both physiological wound healing and pathological fibrogenesis. Serotonin also induces fibroblast to myofibroblast transition and stimulates the release of collagen and fibronectin-1 via the 5-HT_{2B} receptor. Serotonin also contributes to cardiac valve degeneration, a known risk factor for AF and HF. There are many potential sources of serotonin including cardiac fibroblast and myofibroblast cells, the pancreas, where serotonin is co-released with insulin and from platelets. Upon activation, platelets can release large amounts of serotonin stored in dense granules, as well as inflammatory cytokines including TGFβ1 from the alpha granules. This project will evaluate platelet activation and function in AF and HF patients as well as measure cytokine release from the activated platelet.

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The effects of proton pump inhibitors and pneumonia in COPD patients

PhD | Masters | Honours project

The prevalence of chronic obstructive pulmonary disease (COPD, emphysema and/or bronchitis) in Australians aged 45 and over was 5.1% in the 2014-2015 National Health Survey, an estimated 460,400 people. The prevalence of this condition does not differ significantly between males and females (5.2% and 4.9% respectively). Proton pump inhibitors (PPIs) are used to reduce acid secretion in the stomach may be associated with a risk of COPD patients developing pneumonia. The aim of this study is to determine whether the use of gastric acid-suppressive agents increases the risk of pneumonia in COPD patients that results in hospitalization at the Gold Coast University Hospital. This project will involve the collection of clinical data from hospital patients, the implementation of COPD disease severity surveys and analysis of spirometer results from COPD patients who have been de-prescribed PPIs.

Physiology

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The pathophysiology of chronic stress

PhD | Masters | Honours project

Major chronic diseases, including coronary heart disease, major depressive disorder (MDD), type II diabetes, and breast, prostate and colorectal cancers are predominantly environmental and lifestyle driven, with gene factors playing a lesser (albeit important) role. Chronic stress may be a critical link across 'diseases of modernity', disrupting immuno-inflammatory, endocrine and metabolic processes. We have developed animal models of chronic stress and commenced interrogating systemic/molecular outcomes. Projects may examine:

- Sexual dimorphism in stress responses (sex is a modifier of MDD, CVD and stress responses. The basis of these effects remains to be detailed.)
- Physical activity and stress (exercise prevents/improves CVD and MDD, yet induces some molecular stress. How activity/inactivity modify stress responses and MDD will be studied)
- Dietary factors are important in MDD and CVD (polyunsaturated fatty acids may be beneficial, suppressing inflammation for example. Studies will assess effects of dietary fats on stress responses and MDD development).

Teaching & Learning

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Evaluation of the Virtual Techniques Centre to enhance student learning

PhD | Masters | Honours project

Laboratory classes are a key component of student learning in scientific disciplines and are designed to teach concepts and practical skills to students through experiential learning. The aim of the project is to evaluate the effectiveness of the Virtual Techniques Centre which consists of a video library and associated supporting materials in enhancing the student's laboratory experience. The videos are designed to explain and demonstrate a variety of laboratory techniques and to provide pre-laboratory instruction and review for students. The videos have been used as a teaching resource in the lab class itself as well as in training of laboratory demonstrators to ensure that students receive consistent information across multisession lab classes. Some data has already been collected in the form of evaluations. The project aims to analyse the collected data to determine the impact these videos have had on student engagement through facilitating and promoting deeper understanding of laboratory practicals.

Vascular Biology, Biochemistry and Imaging (VaBBi)

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Revealing new interactions between the liver and heart/blood vessels that could prevent and treat cardiovascular disease

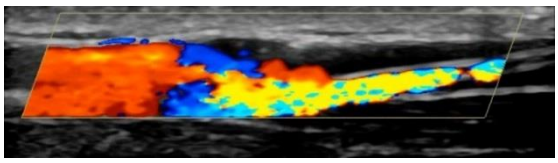
PhD | Masters | Honours project

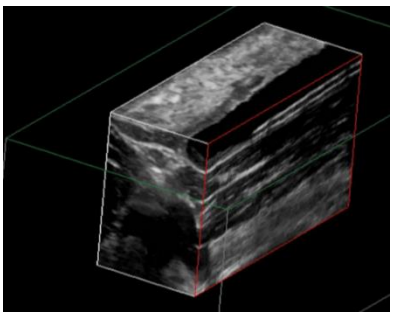
Dr Bulmer's research indicates that a liver compound called bilirubin inhibits multiple processes responsible for the progression of cardiovascular disease (i.e. atherosclerosis) and protects the heart from heart attack. Honours and PhD projects are available to explore the effects of mildly elevated bilirubin (investigated in cell culture, small animal experiments/human trials) on lipid metabolism, alteration of hormone synthesis/endocrinology, platelet function and protecting from free radical induced damage in heart attack models. Students will be research/medicine focussed, interested in pathophysiology and lateral thinkers, to explore what is a very open field ready for new discoveries. Students will work in laboratory environments (principally involved in completing clinical biochemistry assays, heart and vascular imaging [state-of-the-art echocardiography/venography] and potentially surgeries), may undertake clinical activities (patient recruitment, blood collection etc.) and will enjoy writing and communicating their outstanding discoveries.

Understanding the impact of venous cannulation on vascular inflammation, blood flow and coagulation

PhD | Masters | Honours project

Dr Bulmer's group recently developed a unique collaboration with the Alliance for Vascular Access Teaching and Research (AVATAR) at Griffith University (http://www.avatargroup.org.au/our-team.html). The AVATAR group aim to improve outcomes in patients requiring the placement of vascular access devices (ie. venous and arterial cannulas). The aim of our group is to measure the impact of various cannulation practices (ie. insertion, flushing, infusion) on vascular function in humans. We use state-of-the-art ultrasound (see below) to assess venous structure and blood flow in cannulated veins, developing very high resolution images and videos while cannulas are maintained (usually over 6-24 hours). Our imaging techniques are so sensitive that we can detect endothelial injury and thrombi within veins and cannulas, which represent early markers of cannula failure. We also collect blood from inserted cannulas and assess various haematological (platelet function/activation using FACS) and biochemical (e.g. tissue factor, nitric oxide) parameters, which contribute to understanding why cannulas fail. Our research is also **supported by external grant income,** a postdoctoral fellow and an experienced research assistant, who supervise the project and student training. **Honours/Masters/PhD top-up scholarships may be available** to students who demonstrate an excellent academic record and commitment to research.





Dr Bulmer's lab is well supported by multiple research assistants and PhD students to assist in training new recruits and has an excellent track record of publication, which can students benefit from (as co-authors). Prospective students should be highly motivated, demonstrate a strong academic record, have a passion for and commitment to research. Students wishing to transition into medical studies would also benefit greatly and are encouraged to apply.

www.griffith.edu.au/health/school-medical-science