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HONOURS 2014

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INTRODUCTION

Brisbane's Translational Research Institute (TRI) is Australia's most innovative biomedical research facility. Combining the research intellect of five leading research institutes with a co-located biopharmaceutical manufacturer, TRI has the capacity to discover, produce, test and manufacture new treatments and vaccines in one location.

TRI is comprised of a number of partner organisations including The University of Queensland's Diamantina Institute, Mater Research, and School of Medicine; Queensland University of Technology's Institute of Health and Biomedical Innovation; and the Princess Alexandra Hospital's Centres for Health Research.

The research conducted by these partners encompass common and serious disease such as cancers, diabetes, inflammatory diseases, HIV, malaria, bone and joint diseases and obesity. TRI is part of Diamantina Health Partners, a leading academic health sciences alliance that delivers innovative patient care and improved health outcomes.

With 650 researchers amongst the best in their field located at TRI and the adjacent biopharmaceutical manufacturer, Patheon Biologics (formerly known as DSM Biologics), we are accelerating the development of vaccines and new therapies for serious and common diseases and illnesses.

Located at the Princess Alexandra Hospital campus, the seven-story TRI building incorporates four floors of state-of-the-art laboratories, facilities for research support, administration and teaching, while its Clinical Research Facility, located at the hospital, enables human trials of new drugs and therapies.

A key advantage of TRI is that it brings together researchers from different research fields and facilitates interaction and collaboration regardless of academic affiliation. This generates an ideal environment for students to study in any research group at TRI or even across different groups spanning university affiliations. UQ students are welcome to undertake Honours projects with QUT-based groups and vice-versa. Similarly, students from universities other than QUT and UQ are also welcome to undertake their studies at TRI.

Some of the TRI partners also offer scholarships to Honours students and more information concerning these opportunities can be found on the individual partner websites:

www.di.uq.edu.au/
www.som.uq.edu.au/
www.ihbi.qut.edu.au/
www.research.mater.org.au/



BONE AND JOINT HEALTH

BONE REGENERATION IN CRANIOFACIAL APPLICATIONS: BILAYERED PATIENT SPECIFIC BONE INDUCING SCAFFOLDS

PRIMARY RESEARCHER

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ASSOCIATES

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PROF SASO IVANOVSK

BACKGROUND

Bone loss in the maxillary and mandibular jaw bones is an inevitable consequence of tooth loss, and can also occur due to trauma or the surgical treatment of pathology (eg. Cancer).

In addition, tooth loss affects a large portion of the population and results in significant negative impact in terms of function, esthetics, quality of life and general wellbeing. As tooth loss becomes cumulative with age, it is more commonly found in the elderly and is likely to increase with the aging population.

Dental reconstruction, especially that involving dental implants, often requires the regeneration of bone. Currently available methods are not able to predictably reconstitute large vertical bone deficiencies commonly found following edentulousness in the posterior regions. Similarly, regeneration of large jaw bone defects is required to restore function, aesthetics and quality of life to patients who suffer craniofacial trauma or resective surgery of oro-facial tumors.

This is principally achieved with autogenous bone grafting, which has significant morbidity due to the need for a second surgical site, and hence alternative methods would provide a significant advancement in managing these patients.

HYPOTHESIS/AIMS

This proposal advocates an innovative and trans-disciplinary approach aimed at producing personalised tissue engineered constructs for oro-facial bone regeneration.

Our hypothesis is that the current inability to predictably regenerate large vertical bone defects in the jaws can be addressed by utilising CAD/CAM and 3-D printing technology combined with surface biofunctionalisation to

produce personalised bone inducing scaffold for oro-facial application.

This project proposes the development of a bioactive bilayered bone scaffold composed of an outer 'shell' made of a rapid prototyped scaffold, with high structural integrity that will mimic native bone and provide mechanical and space maintenance properties similar to those imparted by cortical bone.

Within this shell there will be a 95% porous electrospun microfibrinous mesh that will permit bone formation and the establishment of a newly formed functional vasculature ingrowth mimicking the structure of cancellous bone.

APPROACHES

Fused deposition modelling and melt electrospinning writing will be utilised for the fabrication of the biphasic scaffold and subsequently in vitro characterised (cell proliferation, cell differentiation using qRT-PCR, calcium assay, alkaline phosphatase assay and immune-chemistry).

The scaffold will be tested in vivo, using an extra-skeletal rabbit model for assessing vertical bone formation, which our group has already established.

BONES AND IMMUNOLOGY LABORATORY

PRIMARY RESEARCHER

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BACKGROUND

Bone fracture is an under-recognized and increasing burden on health systems and society and new therapeutic approaches are required. The emerging field of osteoimmunology has exposed the immune system as a viable target for bone therapeutic approaches.

We offer Honours/Masters research projects aiming to develop therapies to accelerate healthy fracture healing and projects investigating if deficits in the immune response underlie compromised fracture repair in disease settings. Projects include but are not limited to:

1. Identification of the specific macrophage subsets required for normal fracture repair mechanisms.
2. Determine if fracture repair can be accelerated via targeting immune cells.
3. Are alterations in immune mechanisms during fracture repair the cause of compromised healing in osteoporosis.

HYPOTHESIS

1. Macrophages are a regulatory conduit during bone repair, able to influence inflammation and granulation tissue formation as well as bone-explicit anabolic and catabolic repair mechanisms.
2. Inappropriate biasing of fracture-associated macrophage activation leads to deregulated fracture repair mechanisms and is an underlying cause of compromised fracture healing.
3. Therapeutic manipulation of macrophages can boost appropriate and balanced functionality of chondrocytes, osteoblast and osteoclast during repair in healthy or osteoporotic bone.

AIMS

Further characterise the temporo-spatial involvement of resident tissue and inflammatory macrophages during the multiple phases of fracture repair.

APPROACHES

Use an innovated internally fixed pre-clinical fracture model to generate fracture tissues samples across a healing time course. Subsequently use immunohistology techniques to characterize the in situ phenotype and distribution pattern of macrophages within fracture associated tissues.

REFERENCES

Pettit AR, Chang MK, Hume DA and Raggatt LR. Osteal Macrophages: A new twist on coupling during bone dynamics. *Bone*, 2008: 43(6), 976-82.



TRIO



CANCER RESEARCH

3D MORPHOMETRIC ANALYSIS OF A NOVEL IN VITRO BIOENGINEERED PROSTATE CANCER MODEL

PRIMARY RESEARCHER

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ASSOCIATES

PROF DIETMAR W. HUTMACHER
PROFESSOR, CHAIR REGENERATIVE
MEDICINE, APCRC-Q, IHBI

BACKGROUND

Prostate cancer (PCa) is the second most frequently diagnosed malignancy in men, with 1.1 million cases worldwide annually. Progression of PCa is slow. Most men are diagnosed with localised disease; however, a percentage of cases will progress to advanced disease.

There are no relevant in vitro models to study the mechanisms underpinning tumour progression of localised PCa. Cell lines such as LNCaP and PC3 are not suitable as they represent advanced metastatic PCa. The tumour microenvironment (e.g. stromal-epithelial interactions, immune and hormonal influences) plays a critical role in PCa progression, but is not routinely incorporated in conventional models.

A 3D in vitro co-culture model has been developed to study in a systematic and quantifiable way the synergistic effects of the tumour microenvironment on localised PCa progression. Cancer-associated fibroblasts (CAFs) and non-malignant prostate fibroblasts (NPFs) derived from human patient tissue have been incorporated into plasma-treated melt-electrospun poly(ϵ -caprolactone) (PCL) scaffolds, which mimics the tumour microenvironment.

Within the meshes, the cells proliferate, deposit extracellular matrix and form a 3D stromal network that, when co-cultured with benign prostatic epithelial cells (BPH-1), induces epithelial transformation.

HYPOTHESIS

We hypothesise that our in vitro system is able to categorise patients into low- and high-risk groups for PCa progression based on the morphometric changes of BPH-1 cells. The obtained results will be key to understanding the interactions between malignant cells and the tumour microenvironment in PCa progression. This work will help to further develop in vitro diagnostic platforms for patient-specific cancer therapies.

AIMS

We propose to thoroughly quantify 3D cellular morphometric features (sphericity, volume, orientation), as well as 3D live cell migration, of the different cells included in our in vitro model under different biological conditions.

APPROACHES

Confocal microscopy, software analysis (Amira, Imaris, ImageJ, Metamorph, NIS Elements), 3D live cell microscopy, cell culture.

CELL-SCAFFOLD INTERACTIONS IN A NOVEL IN VITRO BIOENGINEERED PROSTATE CANCER MODEL

PRIMARY RESEARCHER

DR ELENA M. DE-JUAN-PARDO
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BACKGROUND

Prostate cancer (PCa) is the second most frequently diagnosed malignancy in men, with 1.1 million cases worldwide annually. Progression of PCa is slow. Most men are diagnosed with localised disease; however, a percentage of cases will progress to advanced disease. Currently, there are no relevant in vitro models to study the mechanisms underpinning tumour progression of localised PCa.

Cell lines such as LNCaP and PC3 are not suitable as they represent advanced metastatic PCa. Furthermore, the tumour microenvironment (e.g. stromal-epithelial interactions, immune and hormonal influences) plays a critical role in PCa progression, but is not routinely incorporated in conventional models.

We have developed a 3D in vitro co-culture model to study in a systematic and quantifiable way the synergistic effects of the tumour microenvironment on localised PCa progression. Cancer-associated fibroblasts (CAFs) and non-malignant prostate fibroblasts (NPFs) derived from human patient tissue have been incorporated into plasma-treated melt-electrospun poly(ϵ -caprolactone) (PCL) scaffolds, which mimics the tumour microenvironment.

Within the meshes, the cells proliferate, deposit extracellular matrix and form a 3D stromal network that, when co-cultured with benign prostatic epithelial cells (BPH-1), induces epithelial transformation.

ASSOCIATES

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MEDICINE, APCRC-Q, IHBI

HYPOTHESIS

We hypothesise that our in vitro system is able to categorise patients into low- and high-risk groups for PCa progression based on the morphometric changes of BPH-1 cells. The obtained results will be key to understanding the interactions between malignant cells and the tumour microenvironment in PCa progression. This work will help to further develop in vitro diagnostic platforms for patient-specific cancer therapies.

AIMS

We propose to thoroughly quantify surface properties of the scaffolds after plasma treatment vs NaOH treatment. We also propose to quantify scaffold-cell interactions in terms of cell viability, adhesion and proliferation for each one of the different cells included in our in vitro model under different biological conditions.

APPROACHES

Scanning Electron Microscopy (SEM), X-Ray Photoelectron Spectroscopy (XPS), sessile drop (contact angle), tensile stress tests, cell culture, immunohistochemistry, PicoGreen and/or MTT cell proliferation assays.

THE ROLE OF KALLIKREINS IN OVARIAN CANCER METASTASIS

PRIMARY RESEARCHER

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BACKGROUND

Epithelial ovarian cancer (EOC) is the leading cause of death in gynaecological tumours. Most of the patients are diagnosed when tumours have spread in the abdominal cavity (metastasis), half of them with a pool of fluid in their abdominal cavities (ascites). At this stage, patients have not only the cancers embedded in solid stroma in primary and metastatic sites but also cancer cells floating in ascites fluid (Fig 1). Current treatment includes surgery followed by cytotoxic chemotherapy, but most patients will develop resistance leading to a 30% 5-year overall survival rate. Thus, we need to better understand the molecular pathways in these environments for efficient treatment.

We reported that kallikrein (KLK)4 and KLK7 proteases are highly expressed in ascitic EOC cells compared to primary tumours (1, 2). Our recent studies revealed these proteases regulate a network of molecular pathways associated with less cellular response to chemotherapy, and cell survival using transcriptome sequencing analysis (RNAseq). We have established a 3-dimensional (3D) suspension model to mimic the ascites microenvironment while a published 3D-Matrigel model can mimic the solid stroma seen in EOC patients. These models will be used to further investigation of functions of KLKs involved in this microenvironments.

HYPOTHESIS

KLK proteases regulate molecular pathways to enhance chemoresistance and cell survival in EOC cells.

ASSOCIATES

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AIMS

1. To validate the expression profile of genes regulated by KLK7; and
2. To determine the relevance in the ovarian cancer cells with/without KLK7.

APPROACHES

Cell cultures: 2D monolayer, 3D-suspension and 3D-matrices and chemosensitivity assays
RT-PCR, Western blot analysis,
immunohistochemistry and microscopy

REFERENCES

Dong Y, Clements JA. Cancer Res. 70: 2624-33. 2010.

Dong Y, Clements JA. PlosOne 8(2): e570569: 2013.

IDENTIFYING NOVEL DNA REPAIR PROTEINS AS DRUG-TARGETS FOR TRIPLE NEGATIVE BREAST CANCERS

PRIMARY RESEARCHER

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BACKGROUND

One in eight woman worldwide (12%) develops invasive breast cancer during their lifetime. While the overall outcome for patients has dramatically improved recently, breast cancer remains a killer among the female population. Aside from non-melanoma skin cancer, breast cancer is the most common cancer among women in the United States and in Australia. For the US only, the 2013 American Cancer Society's estimates for breast cancer predict that about 232,340 new cases of invasive breast cancer will be diagnosed and about 39,620 women will die from breast cancer.

Despite decades of research, breast cancer remains the leading cause of death in women after lung cancer. Still today, very little is known about the genetic background of non-BRCA1, non-BRCA2 breast cancer predisposed families, and we still poorly understand whole categories of patients such as the triple negatives, who are lacking 3 essential cell receptors and thus don't benefit much from commonly-used hormone therapy. Interestingly, most breast cancer predisposition genes are also involved in DNA-damage repair mechanisms. These genes constitute excellent therapeutics targets, as they specifically sensitize breast tumours and metastases to chemotherapies.

AIMS

Through a whole-genome screen, we identified a broad list of genes potentially deregulated in triple negative cancer patients. We are now in the process of applying a second-layer screen (see figure: flow cytometry assay), to:

1. establish whether the protein they encode for plays a role in DNA repair; and
2. decipher their function in vitro, in normal breast tissue and breast cancer cell lines.

One project is available for an Honours student to conduct the DNA repair screen and identify novel DNA repair genes, of interest for breast cancer therapy. One candidate gene will be cloned after analysis of the results for later functional analysis. In parallel, the student will inactivate this same gene in mammalian cells, and establish stable cell lines knocked-down for the gene. This will allow us to investigate the effect of the gene's depletion in cells, and mimic what may happen in a breast tumour.

APPROACHES

This project involves a lot of cell handling and cell culture. In parallel, the student will be trained in molecular biology but a good understanding of the basic concept of PCR, pipetting, cloning, and basic biochemistry is required. The student will become familiar with high-end equipment, such as but not only RTqPCR, flow-cytometry, microscopy.

CHROMOSOMAL INSTABILITY IN CANCER

PRIMARY RESEARCHER

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BACKGROUND

Cells frequently missegregate their chromosomes during cell division. This phenomenon, termed chromosome instability, leads to the formation of aneuploid cells, i.e., cells with abnormal chromosome numbers. Chromosome instability is one of the most malignant features of cancer cells, because it can cause cancer, it accelerates cancer progression and it is an important mechanism for cancer cells to become resistant to cancer therapies.

AIMS

The Duijf laboratory uses in vivo mouse models and in vitro cell models in order to:

1. study how chromosome instability contributes to cancer progression and
2. identify novel mechanisms that cause chromosome instability.

Chromosome missegregation has a variety of known and unknown causes and effects. Therefore, in addition to identifying new mechanisms, the group studies a range of phenomena that are known to be associated with chromosome instability, including DNA damage, mitotic checkpoint defects, sister-chromatid cohesion defects, centrosome overduplication and cytokinesis failure.

With an interest in breast and other cancers, the Duijf group's research goals are translational in nature: to develop new approaches or enhance existing ones in order to improve the diagnosis and treatment of cancer.

RESEARCH PROJECTS

- The cancer biology of chromosome instability in a transgenic mouse model.
- Identification of signal transduction pathways that cause chromosome instability
- Transcriptional regulation of cell cycle genes.
- Development of strategies to specifically target cancer cells with abnormal chromosome numbers.

IMMUNOTHERAPIES FOR HPV-ASSOCIATED CANCERS

PRIMARY RESEARCHER

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BACKGROUND

As a child, Professor Ian Frazer liked to take things apart in order to see how they worked. "I liked the practical aspect of testing ideas with your hands," he says, "and I was curious about how the world worked." It wasn't long before Frazer knew he wanted to pursue a career in research.

In 1985 Frazer moved to the University of Queensland to become a lecturer and Director of Immunology at the Princess Alexandra Hospital, where he went on to develop and direct the Centre for Immunology and Cancer Research (CICR). During this time, he established one of the first research groups in the world focussing on papilloma virus immunology. At the time it was thought HPV was rare and aggressive, but Frazer showed that it is extremely common, often latent, and that a subset of people develop detrimental chronic infections.

There are more than 20 million women already infected with HPV, for whom the existing vaccine cannot prevent cervical cancer. Moreover, cervical cancer is just one aspect of the total cancer burden caused by papilloma viruses, which include other genital cancers as well as throat cancers. Frazer believes these viruses are also responsible for certain types of skin cancer and is searching for evidence of the association.

Prof Frazer continues to lead his research group in the Epithelial Cancer Division at UQDI, focusing on the development of a therapeutic vaccine to treat those already infected with HPV. To this end, he wants to understand why the success of immunotherapy is extensively determined by the local environment around either the infection or the tumour. This microenvironment seems to have the ability to turn off the immune response, which presents a challenge to the development of immunotherapeutics. Overcoming that hurdle will have profound implications across a range of diseases.

Thus far Frazer and his colleagues have developed two promising new immunotherapies for HPV-associated cancers, which are currently in early stage trials. In his search for the immune on/off-switch, Frazer adds, "we have observed that local factors, particularly inflammation, determine whether vaccine-induced immune responses are locally effective against chronic virus infection and skin cancer."

RESEARCH PROJECTS

- Regulation of effector T cells by the innate immune response.
- Immunotherapy for virus associated skin cancer.
- Cervical cancer control in Vanuatu.

CELL-CYCLE DEFECTS IN MELANOMA

PRIMARY RESEARCHER

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BACKGROUND

Over time, cells collect mutations that slip through the normal DNA repair mechanisms, yet melanoma cells collect far more than expected, even compared to other cancers. This is curious, considering the primary DNA repair mechanism is intact in most melanomas. Associate Professor Brian Gabrielli is searching for cell cycle defects responsible for this, and believes it is the key to developing improved melanoma diagnostics and selective cancer treatments with long term benefits.

Because melanomas are extremely difficult to completely eliminate, he believes the best strategy will be to integrate specific anti-tumour treatments with immunotherapies that enable long term cancer surveillance, essentially using the body's own immune system to keep melanoma in check.

Already his group has identified a defect most likely responsible for the increased mutation load in melanoma. They found that, in normal skin cells, UV radiation causes the cell cycle to pause at the 'G2 phase-checkpoint', just before mitosis begins. This checkpoint arrest then triggers a secondary DNA repair mechanism that fixes any damage missed by the primary repair mechanism. Gabrielli found that this coupled checkpoint-repair mechanism is defective in a substantial number of melanoma cell lines, allowing UV-induced genetic damage to accumulate.

Gabrielli believes there are numerous advantages in carrying out his melanoma research at UQDI. "The combination of Professor Matt Brown's ability to look at coding regions of the genome together with our ability for functional assessment places us in a very unique position," he says. Taken together with the clinical collaborations with the PA Hospital, he believes only a few places in the world can boast such a combined advantage, particularly in melanoma research.

RESEARCH PROJECTS

- Identifying the molecular basis for defective checkpoints in melanoma.
- Targeting defective cell cycle responses to ultraviolet radiation and TopoII inhibitors in melanoma.
- Defining the molecular changes in moles underpinning morphological changes detectable by non-invasive imaging techniques to improve their diagnostic and prognostic ability for early stage melanoma.

CHARACTERISING THE EFFECTS OF INSULIN IN PROSTATE CANCER PROGRESSION

PRIMARY RESEARCHER

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BACKGROUND

Prostate cancer is the most commonly diagnosed lethal cancer in men and the second-leading cause of cancer death. Androgen-dependant gene pathways regulate the growth and maintenance of both normal and malignant prostate tissue.

Androgen-deprivation therapy (ADT) in patients exploits this dependence when used to treat recurrent and metastatic prostate cancer (PCa) resulting in tumour regression. However, this response initially seen with ADT eventually gives way to regrowth of prostate tumour cells no longer reliant on testicular androgens. This advanced disease state, referred to as castrate resistant prostate cancer (CRPC), is currently incurable.

Our research aims to identify the molecular mechanisms which drive progression to CRPC. While ADT provides anti-cancer response in these advanced patients, the side effects include key features of metabolic syndrome including hyperinsulinaemia. Hyperinsulinaemia appears to precede other metabolic changes and increases in adiposity, and may be a direct result of androgen deprivation and is associated with poor outcomes including more rapid progression to CRPC and increased cancer mortality. Determining the mechanisms by which high plasma insulin levels contribute to prostate cancer progression may also open up existing diabetes treatments as potential co-therapies.

We have identified a number of transcriptional networks by which insulin may promote cell survival in androgen deprived conditions. This project will aim to determine the efficacy of current insulin-lowering therapies on these networks as part of a wider project investigating biological pathways by which ADT-induced hyperinsulinaemia have the potential to drive PCa progression.

HYPOTHESIS

In a model of androgen deprivation, insulin can alter cell metabolism and promote cell survival and resistance to apoptosis in prostate cancer cell lines, contributing to disease progression.

AIMS

- Characterise the mechanisms by which insulin drives PCa progression via a program of epithelial to mesenchymal transition.
- Confirm insulin increases resistance to apoptosis in PCa cells using QRT-PCR and western blotting, immunofluorescent microscopy and functional assays of apoptosis resistance.
- Characterise the effects of insulin-sensitising agents' metformin and thiazolidinediones in insulin-driven survival pathways.

APPROACHES

Cell culture, western blotting and QRT-PCR expression analysis, gene knockdown (shRNA), functional assays for cell survival including FACS, live cell microscopy and metabolomics, confocal microscopy.

NOVEL THERAPEUTIC TARGETS IN MELANOMA

PRIMARY RESEARCHER

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BACKGROUND

Nikolas Haass is an Associate Professor at The University of Queensland Diamantina Institute/ Translational Research Institute, Honorary Associate Professor at The University of Sydney and Adjunct Associate Faculty member at the Centenary Institute.

After obtaining his PhD at the German Cancer Research Center/University of Heidelberg, he trained as a dermatologist (focus: cutaneous oncology) at the University Hospital Hamburg-Eppendorf, Germany. He then spent five years at the Wistar Institute/University of Pennsylvania, Philadelphia, as a post-doctoral fellow funded by the German Research Foundation.

As a Cameron Melanoma Research Fellow from October 2007 to February 2013, he headed the group, 'Experimental Melanoma Therapy' at the Centenary Institute. In March 2013 he commenced his current position at UQDI.

Using cutting-edge technology, such as real-time imaging of melanoma cells in 3D culture and in vivo, he and his team investigate the biology of tumour heterogeneity and the role of differential subpopulations of melanoma cells in melanomagenesis with the goal to develop novel therapeutic approaches by simultaneously targeting these differential subpopulations.

RESEARCH PROJECTS

- Targeting the actin cytoskeleton as a strategy for melanoma therapy.
- Disarming Tumor Escape Mechanisms in Human Melanoma With Epigenetic Modifiers.
- Real-time cell cycle imaging of melanoma cells in vitro and in vivo.
- Defining the role of Microphthalmia-associated Transcription Factor (MITF) in melanoma growth by real-time cell cycle imaging.

PROTEOMICS AND SYSTEMS BIOLOGY APPROACHES IN CANCER

PRIMARY RESEARCHER

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BACKGROUND

Dr Michelle Hill wants to know how cancer cells hijack normal cell signaling in order to hide from the immune system, evade cell death, and spread to other organs. Her work is leading the way toward the identification of new targets for anti-cancer therapeutics and the development of early diagnostics.

Changes in protein expression, modification, localisation and thereby function are characteristic, and indeed the cause of diseases including cancer. We are utilising proteomics and systems biology approaches on both cell models and clinical samples to understand the molecular mechanisms of cancer development and progression.

AIMS

The aims of our research are twofold:

1. to develop proteomics techniques for biomarker discovery, and to translate these into diagnostic tests and
2. to utilise systems biology approaches to understand cholesterol-dependent lipid raft and caveolae function in cancer progression in order to discover novel therapeutic targets for drug development. Inter-disciplinary collaboration is crucial to our research program.

Our group receives project funding from the Prostate Cancer Foundation of Australia, Association for International Cancer Research, University of Queensland Collaborative Industry Engagement Fund.

We also acknowledge the support of our industry partners, Agilent Technologies, Brisbane Veterinary Specialist Centre and the Australian Animal Cancer Foundation.

RESEARCH PROJECTS

- Cancer microvesicles as a source of biomarkers and novel target of anti-cancer therapy.
- Systems biology approach to understand lipid raft and caveolin function in health and disease.
- Discovery and validation of novel salivary and blood biomarkers for head and neck cancers using lectin magnetic bead array-mass spectrometry, LeMBA-MS (with Dr Chamindie Punyadeera).
- NPM functions associated with acute myeloid leukemia (with Dr Kerry Inder).



**DIAMANTINA
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AN INVESTIGATION INTO THE ROLE OF EPITHELIAL-MESENCHYMAL PLASTICITY IN PROSTATE CANCER METASTASIS AND THERAPY RESISTANCE.

PRIMARY RESEARCHER

DR BRETT HOLLIER

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BACKGROUND

Prostate cancer associated mortality is due to metastatic tumour burden. Tumours localised to the prostate typically express epithelial adhesion molecules and the majority of patients have a good prognosis with current surgical and/or radiation based therapies. However, once tumour cells have spread outside the prostate (metastasized) the prognosis is far worse. To metastasize, a subset of cells can reactivate a latent, embryonic program, known as epithelial-mesenchymal transition (EMT).

Through EMT, tumour cells acquire mesenchymal-like traits including increased motility, invasiveness and more recently cancer stem cell-like properties to facilitate metastatic dissemination and therapy resistance. To endow full metastatic competency to cells, it is hypothesised that EMT is a transient and reversible phenotypic change, whereby cells can undergo the reverse mesenchymal-epithelial transition (or MET) to regain epithelial characteristics.

Recent reports provide evidence that disseminated tumour cells need to acquire epithelial characteristics (via MET) to complete the cycle of metastasis and establish overt metastasis.

HYPOTHESIS/AIMS

We hypothesise that tumour cells with the capacity to switch between epithelial and mesenchymal states (termed epithelial-mesenchymal plasticity or EMP) are the founders of metastasis. As such, we believe EMP is an attractive target for anti-cancer therapies as it may be possible to inhibit both early (anti-EMT) and late (anti-MET) stages in the metastatic cascade. Our group seeks to better understand the role EMP plays in metastasis and therapy resistance in order to develop novel treatment options for men with aggressive forms of prostate cancer.

APPROACHES

Our group has developed a number of unique cellular models for the study of EMP in vitro and in vivo to allow us to perform detailed studies into this dynamic cellular plasticity. We utilize a broad range of genomic, cellular and molecular biology techniques, including next generation sequencing, microarray gene expression profiling, lentiviral-mediated gene overexpression/knockdown, qRT-PCR and western blotting in combination with functional assays of cell migration, invasion (2D & 3D models), proliferation and therapy resistance to identify therapeutic candidates.

DEVELOPMENT OF AN ANIMAL MODEL TO BETTER STUDY BREAST CANCER BONE METASTASIS

PRIMARY RESEARCHER

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ASSOCIATES

PROF DIETMAR HUTMACHER

BACKGROUND

Breast cancer (BC) tends to metastasize to bone leading to terrible clinical consequences and a high mortality rate with more than 2500 women dying from the disease in Australia every year. This highlights the urgent need to develop new approaches for the clinical management of BC bone metastasis.

Unfortunately, efforts towards this have been hampered by the lack of suitable animal models that recapitulate human bone metastasis.

As a consequence, we have developed a unique in-vivo model, in which a viable bone organ consisting of human bone cells is engineered and grown within a mouse. We have demonstrated that human cancer cells injected via the left cardiac ventricle reproducibly metastasize to the engineered human bone making it possible to recapitulate the human disease.

Expanding on these promising results that are motivating a paradigm shift in the field we hypothesize that after transplantation of human haematopoietic stem cells, the humanized bone organ can support human haematopoiesis and the development of a humanized immune system within the murine host.

Leveraging the research team's world-leading expertise in tissue engineering and cancer research, we furthermore propose to engineer not only a functional humanized bone organ but also an orthotopic humanized breast tissue construct within the mouse to recapitulate all hallmarks of breast cancer: primary tumour growth, cancer cell migration to the circulatory system, homing and extravasation, and finally, interactions of the metastatic cancer cells with the bone microenvironment.

If successful, the proposed animal model will represent a readily translatable platform to study the mutual interactions between human cancer cells and their microenvironment. Using this platform we will be in a unique position to develop and evaluate novel therapeutic strategies against breast cancer bone metastasis at multiple intervention points of the metastatic cascade from the primary tumor to the overt metastasis.

UNDERSTANDING MOLECULAR MECHANISMS DRIVING METASTASIS OF PROSTATE, COLON AND OVARIAN CANCER

PRIMARY RESEARCHER

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BACKGROUND

The mechanisms by which cancer spreads (or metastasises) are unique to each malignancy. For example, while prostate cancer primarily spreads to bone, ovarian cancer disseminates throughout the peritoneal cavity and colon cancer largely metastasises to the liver and lung. My research group, which is located at the state of the art laboratories of the Translational Research Institute, uses molecular, cell biology and protein analysis techniques, mouse models and human cancer samples to understand metastasis of prostate, colon and ovarian cancer. We work closely with clinical teams at the Mater hospital and with local, national and international collaborators. Students attend clinical team meetings and have opportunities to visit collaborating labs to learn new techniques.

AIMS

We have Honours projects aimed at:

- Isolating, expanding and performing genome analysis of cancer stem cells.
- Understanding novel mechanisms required for prostate cancer bone metastasis.
- Targeting a novel glycoprotein in metastasis.

interests of students and they can select from a range of techniques in which they will become proficient including:

- Molecular biology (PCR, cloning, sequencing);
- Cell biology (in vitro growth of cells, microscopy and flow cytometry analysis);
- Protein analysis techniques (Western blot, immunoprecipitation, fractionation);
- Mouse models of cancer (subcutaneous, intravenous, orthotopic, knockouts);
- Genome analysis (bioinformatics approaches).

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APPROACHES

Projects can be tailored to suit the specific



MESENCHYMAL-EPIDERMAL INTERACTIONS IN STEM CELL MAINTENANCE AND CANCER

PRIMARY RESEARCHER

ASSOC PROF KIARASH KHOSROTEHRANI

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BACKGROUND

Associate Professor Khosrotehrani is a clinical scientist interested in skin biology, regenerative medicine and skin cancer. He was recently appointed at the University of Queensland Centre for Clinical Research (UQCCR) and the newly established Translational Research Institute in Brisbane, Australia. Dr Khosrotehrani obtained his MD from the Cochin-Port Royal School of Medicine at René Descartes University, Paris, France, specialized in Dermatology and a fellow of the Australasian College of Dermatologists.

He is also a former graduate of the Ecole Normale Supérieure and the Institut Pasteur of Paris (Université Paris VI, Pierre et Marie Curie) where he obtained a PhD in Physiology and Physiopathology. During his post-doctoral training at Tufts-New England Medical Center, Boston, USA, Dr. Khosrotehrani helped establish the contribution of pregnancy-associated stem cells to tissue repair by demonstrating their multipotent capacity with a specific potency towards the endothelial lineage. The originality of this work was recently acknowledged by the NHMRC through an achievement award (2011) and he is currently an NHMRC Career Development Fellow.

The main focus of his laboratory, the Experimental Dermatology Group, is on mesenchymal-epidermal interactions in stem cell maintenance and cancer. His research has broad applications in skin wound healing, regenerative medicine and cancer initiation and progression.

BACKGROUND

- Understanding the role of the underlying dermis in the genesis and progression of basal cell carcinoma.
- Study of epidermal clonal progression towards cancer.
- Tumour heterogeneity towards metastasis.
- To understand differences between basal cell carcinoma subtypes at the genomic, transcriptomic and proteomic level.

EVALUATION OF FUSION TRANSCRIPTS IN PROSTATE CANCER CELLS

PRIMARY RESEARCHER

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BACKGROUND

Recent studies indicate that gene transcription is quite complex and that most loci undergo alternative transcription.

Consequently, most genes have numerous variant transcripts, and this includes fusion transcripts which comprise of exons from two different genes.

This revelation has resulted in a growing interest in the potential of variants as markers of some diseases.

For example, the SLC45A3-ELK4 fusion transcript is more highly expressed in lethal prostate cancers compared to benign prostate cells. We have surveyed prostate cancer cells and identified hundreds of fusion transcripts. Importantly, some of these fusion transcripts appear to be regulated by therapeutic drugs that are used in the clinic to treat lethal prostate cancers.

We propose that some of these fusion transcripts that are regulated by therapeutic drugs might be involved in prostate cancers acquiring resistance to drug treatment. Thus, this project will focus on characterising the regulation of some of these fusion transcripts in prostate cancer cells.

ASSOCIATES

PROF. JUDITH CLEMENTS
DR JYOTSNA BATRA
PROF. COLLEEN NELSON

HYPOTHESIS

That some fusion transcripts are regulated by therapeutic drugs and this is important in prostate cancers developing treatment resistance. To address this, we Aim to:
Fully characterise candidate fusion transcripts.
Assess the changes in fusion transcript expression in a panel of prostate cancer cells after treatment with therapeutic drugs.
Assess the transcriptome and proliferative changes in prostate cancer cells after adding candidate fusion transcripts into these cells.

APPROACHES

Cell culture, RNA extraction, quantitative RT-PCR, 5' and 3' RACE, RNAseq, siRNA gene knockdown, gene cloning, DNA Sanger sequencing, UCSC genome browser.

EVALUATION OF SHORT TANDEM REPEATS AS MARKERS OF PROSTATE CANCER RISK

PRIMARY RESEARCHER

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BACKGROUND

There are 77 single nucleotide polymorphisms (SNPs) that increase the risk for men developing prostate cancer. However, these 77 SNPs only account for ~30% of prostate cancers. Thus, the majority (~70%) of prostate cancer risk lie in either other SNPs, or other types of genetic variation. We are interested in short tandem repeats (STRs) as a genetic variation that might account for some of the prostate cancer risk.

STRs have great potential as genetic markers as they are widely distributed in the genome, and are highly variable within populations. This has resulted in their use as genetic fingerprints in forensic science. The difference in STR sizes at specific genes leads to over 20 diseases that include Huntington's disease.

Our STR analysis has resulted in the identification of STRs that are located within genes that might be important in prostate cancers developing resistance to therapeutic treatment, or in regulatory DNA that might mediate the expression of important prostate cancer genes. Thus, this project will focus on better understanding the function of these STRs in prostate cancer cells.

HYPOTHESIS

That some STRs affect prostate cancer biology. To address this, we Aim to:

- Carry out gain of function studies for candidate STRs in prostate cancer cells.
- Carry out functional studies of STRs that are located in regulatory DNA.

APPROACHES

Cell culture, RNA extraction, quantitative RT-PCR, luciferase reporter assay, RNAseq, gene cloning, DNA Sanger sequencing, proliferation and migration assays.

THE ROLE OF THE IMMUNE SYSTEM IN EPITHELIAL CANCERS

PRIMARY RESEARCHER

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BACKGROUND

Dr Graham Leggatt and his colleagues have discovered that something curious happens between the immune system and a tumour during the early stages of cancer development: increased cell production - called hyperplasia - attracts a lot of immune cells.

In 1997, Leggatt met Professor Ian Frazer – co-inventor of the cervical cancer vaccine – while at an immunology conference in New York. The encounter led to an opportunity to work with Frazer at the University of Queensland’s Centre for Immunology and Cancer Research (CICR), so Leggatt returned to Australia to investigate the quality of T-cell responses in Human Papilloma Virus (HPV), the primary cause of cervical cancer.

His research focus soon shifted to immunotherapy. While the cervical cancer vaccine prevents HPV infection and therefore substantially reduces cervical cancer risk, Frazer, Leggatt and their colleagues began searching for ways to use the immune system to treat women already diagnosed with cervical cancer. Leggatt notes that he is grateful he had the opportunity, during his first years in the lab, to collaborate with the late virologist Dr Jian Zhou- co-inventor of the cervical cancer vaccine with Professor Frazer. “I benefited highly from that experience.” he says.

Leggatt is a Senior Research Fellow at the University of Queensland Diamantina Institute (UQDI), where he is researching the immune environment in the skin and how its suppression allows early cancerous lesions to grow. He believes that advances in this area could not only guide the development of cervical cancer immunotherapies, but could also help explain how immunity is controlled in other epithelial cancers, including Squamous Cell Carcinoma.

Leggatt believes UQDI is an ideal place to carry out such research. “I am able to work with people like Ian who have vast knowledge and experience in epithelial cancer. There are also fantastic facilities available to us at the UQDI to do all the work – we can do just about anything we want to do.”

RESEARCH PROJECTS

- Trafficking of T cells to cancerous skin
- Immunotherapy of skin tumours after lymphodepletion.
- T cell function in normal and cancerous skin tissue.



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THE ROLE OF THE IMMUNE SYSTEM AND EFFECTIVENESS OF COMBINATION IMMUNE-BASED THERAPIES IN CANCER

PRIMARY RESEARCHER

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BACKGROUND

During his postgraduate studies at UQ and QIMR, Dr Mattarollo developed a strong interest in tumour immunology, and particularly immunotherapy for cancer.

The outcomes of his studies have led to development of pre-clinical and clinical trials conducted in Brisbane and Japan, investigating combination chemotherapy/immunotherapy in cancer patients. Mattarollo joined the research group led by Professor Ian Frazer at The University of Queensland Diamantina Institute in 2007 to undertake postdoctoral research, investigating immune regulation in animal models of cervical cancer.

Stephen furthered his training in the field of cancer immunotherapy by secondment to the laboratory of Professor Mark Smyth at the Peter MacCallum Cancer Centre in Melbourne (2010-2012).

There, he and his group developed a novel therapeutic cancer vaccine for B cell lymphomas, and through collaboration with international colleagues in France, made significant inroads into understanding how the immune system is required for effective chemotherapy treatment outcomes in cancer patients. Returning to UQDI in May 2012, Mattarollo's vision and goal is to develop the field of cancer immunotherapy at the Translational Research Institute and UQ, and promote cross-disciplinary, multi-centre collaboration in Australia for translational research.

Mattarollo's group will focus on developing and assessing combination immune-based therapies in mouse models of human cancer and investigating how tumours escape control by the immune system. Their objective is to improve treatment quality and outcomes for patients with advanced cancers through translation-directed immunological research.

RESEARCH PROJECTS

- Antibody-drug conjugates in therapy against blood cancers.
- The effect of chronic stress on immune surveillance and immunotherapy of cancer.
- Immunosuppressive myeloid cell populations induced by B cell lymphomas.
- NKT cell and Toll-like receptor-driven therapeutic vaccination against blood cancers.

INVESTIGATION OF EPHRIN-B2 AND TAMOXIFEN COMBINATION THERAPY IN VITRO

PRIMARY RESEARCHER

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ASSOCIATES

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BACKGROUND

In Australia, 12,567 women were diagnosed with breast cancer in 2007 and these numbers are expected to increase in the next decade. Studies have shown that between 58-65 % of breast cancers show moderate to strong expression of EphB4, a receptor tyrosine kinase and the presence of EphB4 predicts poorer overall survival of breast cancer patients.

The expression of the natural ligand for EphB4, ephrin-B2, is lost during tumour progression. We have recently described that in breast cancer EphB4 signalling that is activated by its ligand ephrin-B2 is tumour suppressive, indicating that restoring ephrin-B2 expression or administration of the ligand could be a useful treatment option for EphB4+ breast cancers.

Another very well-known receptor that is overexpressed in breast cancer is oestrogen receptor α (ER) which is targeted by different therapeutics including anti-oestrogens. Tamoxifen is the most widely used selective oestrogen response modifier, but endocrine resistance to this treatment is becoming increasingly problematic.

HYPOTHESIS

This study hypothesises that ER and EphB4 positive breast cancers will respond better to ephrin-B2 and tamoxifen combination treatment than tamoxifen and delay development of tumour resistance.

AIMS

Determine if ER+ breast cancer cell growth and viability is reduced by ephrin-B2 and Tamoxifen combination therapy than tamoxifen alone. Establishment of a tamoxifen-resistant breast cancer cell line that is concurrently treated with ephrin-B2 to delay resistance.

APPROACHES

Cell culture, cell biology assays including growth and cell cycle analyses.

NOVEL THERAPEUTIC APPROACHES IN BONE CANCER

PRIMARY RESEARCHER

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BACKGROUND

Liliana studies osteosarcoma - an aggressive bone cancer that afflicts mainly children and adolescents and which has a very poor prognosis due to its ability to quickly spread (metastasize) to the lungs.

Liliana discovered a novel and key regulator of the spread of osteosarcoma tumour cells to the lungs. This means that we now have a greater understanding of how this cancer spreads and a new therapeutic target that may help us prevent fatal metastatic disease in the future.

Her dream is that we will have defined the mechanisms that mediate the crosstalk between osteosarcoma cancer cells and the newly found regulator of metastasis. We will have identified the pathways and molecules involved, and have found therapeutic drugs to target these in the clinic. This would place us in a position to begin clinical trials in osteosarcoma patients to prevent lung metastasis and improve survival.

RESEARCH PROJECTS

- Exploring the interaction between osteosarcoma tumour cells and lung cells to identify the mechanisms that preferentially drive tumour cells from the bone to the lung.
- Investigation of the interaction between highly- and poorly-metastatic clonal variants of osteosarcoma with osteoclasts.
- Tumour-secreted exosomes are emerging mediators of tumourigenesis and metastasis. This project will initially isolate and characterise exosomes from metastatic and non-metastatic OS tumour cells.

INVESTIGATING MECHANISMS OF ACQUIRED RESISTANCE TO FGFR INHIBITORS

PRIMARY RESEARCHER

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BACKGROUND

Fibroblast Growth Factor Receptors (FGFRs) are transmembrane tyrosine kinase receptors activated by FGF ligands. Hyper-activation of FGFRs occurs through gene mutation (bladder and endometrial cancer), amplification (breast, lung and gastric cancers) and/or translocations (multiple myeloma, glioblastoma).

We were the first to report activating mutations in FGFR2 in endometrial cancer (cancer of the uterus). Turning off hyper-active FGFR by small molecule inhibitors results in cell death and inhibition of tumour growth. FGFR inhibitors (e.g. BGJ38, AZD4547) are currently being tested in patients and while kinase inhibitors have shown remarkable clinical responses, many patients develop resistance overtime and their tumour relapses.

AIMS

We aim to be at the forefront of characterizing resistance to FGFR inhibitors. We have several FGFR2-mutant cancer cell lines that are sensitive to FGFR inhibitors.

Following long-term treatment with FGFR inhibitors, we have isolated cells resistant to FGFR inhibition. Resistance to kinase inhibitors generally occurs through the acquisition of genetic/epigenetic aberrations or by switching on alternate pro-survival signalling pathways.

The original parental lines (sensitive to FGFR inhibition) and the isogenic cell lines (resistant to FGFR inhibition) are being characterized for differences in gene expression, copy number variation and protein phosphorylation to identify potential mechanisms of resistance. We will then perform gene knockdown/over-expression and pharmacological inhibition of the relevant pathway to validate these mechanisms. Validation studies will be performed in vitro and in vivo.

To create in vivo models of resistance to FGFR inhibition, endometrial cancer xenografts will be treated with FGFR inhibitors for 8-12 weeks. Similar molecular characterization of these in vivo resistant cells will be performed to see if similar mechanisms of resistance occur in vivo versus in vitro.

APPROACHES

- Tissue culture;
- Western blotting;
- siRNA/shRNA knockdown (lentiviral);
- Pharmaceutical inhibitors;
- Flow cytometry;
- Translational cancer cell biology;
- in vivo xenografts generation, mouse handling;
- Phosphoproteomics;
- Gene expression profiling;
- SNP chips.

TARGETING HUMAN DENDRITIC CELLS FOR CANCER IMMUNOTHERAPY

PRIMARY RESEARCHER

ASSOCIATE PROFESSOR KRISTEN RADFORD

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BACKGROUND

Dendritic cells (DCs) are the key antigen presenting cells responsible for initiating and directing immune responses. In mice there are distinct dendritic cell subsets that are specialised in the types of immune responses they generate.

However, dendritic cells are poorly understood in humans and translation is complicated by differences in human and mouse immune systems and in particular expression of pattern recognition receptors. We identified a rare human DC subtype, termed CD141+ DC that are now considered as prime vaccine targets. This project will develop and validate novel vaccine for cancer that specifically targets human CD141+ DC.

HYPOTHESIS

That specifically targeting antigen to human CD141+ DC will be an effective approach for cancer vaccines.

AIMS

To evaluate novel CD141+ DC targeting antibodies in a humanised mouse model.

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MOLECULAR BASIS FOR THE CONTROL OF SQUAMOUS DIFFERENTIATION AND ITS ROLE IN ORAL AND SKIN CANCERS

PRIMARY RESEARCHER

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BACKGROUND

“Wonderment in nature.”

That’s how Associate Professor Nick Saunders describes what has driven his interest in science ever since a young age. This sense of wonder at the inner-workings of nature led him to the University of Western Australia (UWA) where he first studied anatomy and human biology, and then trained as a pharmacologist.

In Nick’s lab research interests are focused on translating advances in the biological sciences to improved patient outcomes. In particular, we have interest in the molecular basis for the control of squamous differentiation and how it is perturbed during cutaneous or head and neck squamous cell carcinoma formation.

To date, our research has included basic molecular biology of squamous differentiation through to the completion of a clinical trial on a new anti-cancer strategy in head and neck cancer patients. More recently we have developed an interest in the molecular basis for the development of lung metastases in patients with the primary bone malignancy, osteosarcoma.

We are particularly interested in the molecular basis of lung metastasis and how we may target this therapeutically.

RESEARCH PROJECTS

- Understanding the molecular basis for the control of squamous differentiation.
- Understanding how these processes are dysregulated during the development of oral and skin cancers.
- Exploiting this knowledge in the development of novel treatments for skin cancers and oral cancer.
- Interrogating chemotherapeutic sensitivity
- Identifying novel strategies to treat metastatic osteosarcoma.

MOLECULAR PATHOGENESIS OF HUMAN HEMATOLOGIC MALIGNANCIES

PRIMARY RESEARCHER

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BACKGROUND

Linda's research in the last twenty-two years has focused on various aspects of hematopoiesis, including transcriptional regulation during myelopoiesis, the regulation of hematopoietic stem and progenitor cell trafficking in vivo, and, most recently, the molecular pathogenesis of human hematologic malignancies (in particular, the myeloproliferative neoplasms, or MPNs).

The long-term goal of the Scott laboratory is to advance our understanding of normal and abnormal hematopoietic stem cell (HSC) biology, so that improved therapies can be developed for patients with a variety of different hematologic malignancies.

Currently, our group is particularly interested in the process of disease evolution in the MPNs, whether this is the transformation from a chronic phase (ET or PV) to an accelerated phase (MF) or an acute myeloid leukemia (AML). The identification of the mutation(s) that drive myelofibrotic transformation will assist in the development of more effective, targeted therapies for patients with this disorder, and may also provide insights into the molecular events that drive disease evolution in other hematologic and solid tumors.

In addition to MDS, the Scott group has an interest in the biology of pediatric acute lymphoblastic leukemia (ALL), arising from our involvement in the identification of a third type of activating JAK2 mutation. These JAK2 mutations are found in ~25% of patients with Down syndrome-associated ALL [Bercovich et al., Lancet 2008; Scott, Blood Reviews 2013], as well as in a smaller fraction of high-risk sporadic ALL cases, and provide the rationale for Phase I/II trials of JAK inhibitors in these patient groups.

RESEARCH PROJECTS

- Molecular pathogenesis and clonal evolution of the myeloproliferative neoplasms.
- Role of dysregulated JAK/STAT signalling in hematologic malignancies.
- Epigenetic regulation in normal hematopoietic stem cells and their malignant equivalents.
- Molecular basis of leukemogenesis.

IMPROVING PATIENT RESPONSES TO CHEMOTHERAPY

PRIMARY RESEARCHER

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BACKGROUND

Following a Fellowship at UQ's Institute for Molecular Bioscience, where she identified a novel protein in the skin's UV-induced DNA-damage response, an opportunity arose to start her own research group at the UQ Diamantina Institute (UQDI).

"I began working on EGFR immediately," says Simpson. EGFR is a cell surface receptor known to be integral in regulating numerous cellular functions and is a central molecule in tumourigenesis. In collaboration with oncologists at the Princess Alexandra Hospital (PAH), she demonstrated that both EGFR endocytosis and trafficking within the cell are dysregulated in Squamous Cell Carcinoma (SCC), the most common form of head and neck cancer.

Although anti-EGFR antibodies are used in SCC treatment, patient response varies widely. As such, Simpson's group has developed an assay that determines whether EGFR trafficking dysregulation correlates with individual treatment responses. She explains that anti-EGFR therapy can have harsh side-effects so it's important to know who will benefit and who won't. \\\

Simpson aims to develop a prognostic test for anti-EGFR therapy that will guide clinical decisions. "In the longer term," she adds, "we hope to use our mechanistic information to increase responses to therapy and bypass resistance."

Access to clinicians, patients, and tumour samples are crucial to Simpson's work. She explains that the biochemistry of a tumour changes rapidly once removed from the patient, so analysis within half-an-hour of removal is essential. The collaboration between UQDI and PAH enables this.

Simpson believes her findings will have implications for numerous forms of cancer and is passionate about her work. "I have lost family members, including my mother, to cancer. Seeing the patients down in the clinics is also a driver. I love research and find it stimulating, and I enjoy teaching our next generation of research scientists."

RESEARCH PROJECTS

- Improving patient responses to Cetuximab.
- Improving patient responses to Herceptin.
- The role of Girdin in breast cancer metastasis.

EPIGENETIC REGULATION OF MOBILE GENETIC ELEMENTS IN OVARIAN CANCER

PRIMARY RESEARCHER

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BACKGROUND

Mobile genetic elements in the human genome use a copy and paste mechanism to replicate. In most somatic cells, epigenetic silencing, aids the blockade of mobilisation to prevent potentially catastrophic mutations.

However, this epigenetic repression is lost in some cancers, allowing mobilisation and genomic mutation. Additionally, mobile genetic elements are widely used as a proxy measure of genome wide DNA methylation. It is likely that mobile genetic elements act as a scaffold to allow dynamic epigenetic patterning of the genome throughout development. Aberrations of this regulation in cancer may play a key role in cancer phenotypes.

Currently the interplay between epigenetic regulation of mobile genetic elements and the surrounding genome is poorly understood.

This project seeks to understand the epigenetic regulation of mobile genetic elements, and their effect on genome wide epigenetic regulation.

HYPOTHESIS/AIMS

De-methylation of LINE-1 mobile genetic elements contributes to the cancer phenotype of ovarian cancer.

REFERENCES

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THE ROLE OF THE IMMUNE SYSTEM IN THE SKIN AND SKIN CANCER

PRIMARY RESEARCHER

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BACKGROUND

“As a child I was always interested in how things worked and was constantly asking people questions they couldn’t possibly know the answers to,” says Dr James Wells, Research Fellow in the Epithelial Cancer Group at The University of Queensland Diamantina Institute (UQDI). Wells’ curiosity hasn’t abated, but his questions are now focused on the role the immune system plays in recognising and controlling skin cancer.

My team investigates the role of the immune system in the skin, particularly with respect to maintaining skin homeostasis. My research gives insights into how the dysregulation of immune function may lead to disorders like Squamous cell carcinoma in the skin, in order to give insights into strategies for improving immune-based therapies for patients with extensive disease.

We employ staining protocols in order to elucidate immune cell populations within patient SCC lesions, and laboratory-based cell culture assays, transcriptome profiling and cell adoptive transfer models to study how clinically defined immune populations with relevance to SCC are regulated in the skin.

RESEARCH PROJECTS

- Immunotherapy for the treatment of established skin cancer.
- Requirements for the initiation and treatment of Non-Melanoma skin cancer
- Immunophenotyping squamous skin cancer.
- Investigating the cytokine microenvironment of squamous cell carcinoma and its precursor lesions.
- Uncovering CD8 T-cell control mechanisms in the skin.



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DEFINING THE MOLECULAR PHENOTYPE ASSOCIATED WITH PROSTATE CANCER DORMANCY

PRIMARY RESEARCHER

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BACKGROUND

Human prostate cancer is almost universally responsive to androgen deprivation therapy, which is the first line therapy for the majority of men with recurrent or metastatic prostate cancer. Tumour responses are marked, with tumour and serum prostate specific antigen (PSA) decreasing to undetectable in many cases.

Despite this efficacy, disease progression occurs in the majority of men. Thus these men harbour residual disease that ultimately expands to the lethal disease.

To prevent relapse we need to either maintain tumours in a dormant state or eradicate them, and thus the development of new strategies to target residual disease is essential if we are to improve the outcome for men with advanced prostate cancer.

We have a panel of patient-derived xenograft models which respond to castration with extensive tumour regression and a fall in serum PSA to undetectable levels. Despite tumour regression that is so extensive they are no longer palpable, viable tumour cells are consistently identified at the implantation site upon resection.

These models can be divided into two groups:

1. tumours that spontaneously regrow in the castrate environment; and
2. tumours which fail to regrow in the castrate environment. This panel of xenografts will be used to elucidate the molecular characteristics of the tumour and stromal cells in the castrate environment that distinguish between tumours that will ultimately become recurrent versus those that show an extended dormancy phenotype.

Candidate molecules/pathways will be also examined in clinical prostate cancer specimen with the ultimate goal of identifying targets for novel therapeutic strategies to prevent or delay the development of castrate resistant prostate cancer.

HYPOTHESIS/AIMS

The central goal of this proposal is to identify molecular pathways that are associated with escape from dormancy in the castrate environment.

APPROACHES

Histopathological techniques (including immunohistochemistry), bioinformatics, ex vivo tissue slice culture, imaging.



DERMATOLOGY

DERMATOLOGY RESEARCH

PRIMARY RESEARCHER

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BACKGROUND

The delivery of therapeutic agents (drugs, antibodies, vaccines, dyes, nanoparticles) through the skin is a major focus of the Therapeutics Research Centre. However, overcoming the outer skin barrier is the major obstacle facing nanoparticle-based therapeutic treatments.

The honours research project will involve developing a variety of new formulations (binary vehicles, nano-/micro-emulsions, liposomes, organic penetration enhancers) to enhance the penetration of various therapeutic agents past the outer barrier and into the various layers of human skin.

In combination with formulation development, students will also learn to operate state-of-the-art imaging equipment to assess the effectiveness of their formulations.

An example of ongoing projects:

- Transdermal delivery of nanoparticles (e.g. metal oxides, quantum dots).
- Nanoparticles are an exciting delivery platform as it can be conjugated with other therapeutics for the efficient and targeted delivery of therapeutics agents into and beyond the skin.

Our lab also assesses commercial products containing nanoparticles to assess their safety and potential toxicity in the skin.

Delivery of macromolecules (e.g. insulin, vaccines) through the skin using novel formulations:

- The non-invasive transdermal delivery of macromolecules through the skin is a major research objective of our group.
- Using fluorescently-labelled macromolecules, we can optimise the design and development of new formulations for transdermal delivery.

The successful development of Transdermal Delivery System will be evaluated using our melanoma animal model.



DIABETES, NUTRITION AND METABOLISM

IDENTIFICATION OF NOVEL “PLAYERS” IN THE ASSEMBLY AND SECRETION OF ADIPONECTIN

PRIMARY RESEARCHER

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BACKGROUND

The Metabolic Medicine group aims to identify novel strategies to reduce cardiometabolic disease. The group studies mechanisms that govern metabolic and cardiovascular homeostasis. These processes often become defective in obesity resulting in the development of chronic diseases such as type 2 diabetes and cardiovascular disease.

Adiponectin is a hormone released from fat tissue that has important anti-diabetic and cardioprotective properties through the regulation of lipid and carbohydrate metabolism. Adiponectin is secreted in a number of different forms, and studies have shown that the larger multimeric forms are most beneficial for metabolic health [1, 2]. The mechanism of multimeric adiponectin assembly is not yet completely understood, but remains an excellent potential therapeutic target in the treatment of cardiometabolic diseases.

This is an excellent opportunity to learn sophisticated protein and molecular biology techniques in a supportive and friendly team environment. This project will benefit scientists and the broader community by providing insight into the way adiponectin assembly is regulated to achieve good metabolic health.

HYPOTHESIS/AIMS

This projects aims to employ sophisticated protein chemistry and mass spectrometry to identify candidate factors which interact with adiponectin in cells. The role of these candidate factors will be interrogated using primary adipocyte cell culture, siRNA gene silencing and gene overexpression technology, and functional assays.

REFERENCES

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THE IDENTIFICATION OF NOVEL REGULATORS OF ADIPOSE TISSUE FORMATION AND FUNCTION

PRIMARY RESEARCHER

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BACKGROUND

The Metabolic Medicine group aims to identify novel strategies to reduce cardiometabolic disease. The group studies mechanisms that govern metabolic and cardiovascular homeostasis. These processes often become defective in obesity resulting in the development of chronic diseases such as type 2 diabetes and cardiovascular disease.

The development of functional 'fit' fat tissue (adipose tissue) is essential for good cardiometabolic health, as it acts as both a store of energy and an astute sensor of the body's energy requirements. In the case of energy excess, often resulting in obesity, this process becomes even more important as it protects against the commonly associated cardiometabolic diseases. The process of adipose development (known as adipogenesis) is tightly regulated [1, 2].

We have used cutting-edge high-throughput screening (RNAseq) to identify novel candidate genes involved in the regulation of adipogenesis. This is an excellent opportunity to learn some well-established sophisticated cell and molecular biology techniques in a supportive and friendly team environment.

This project will benefit scientists and the broader community by providing insight into the way adipose tissue is regulated to achieve good metabolic health.

HYPOTHESIS/AIMS

This project aims to validate and characterise candidates identified from our RNAseq screening, using primary adipocyte cell culture, siRNA gene silencing and gene overexpression technology, and functional assays.

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CHARACTERISATION OF ADIPONECTIN RECEPTOR MODIFICATIONS IN SUBJECTS WITH OR WITHOUT METABOLIC DISEASE

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BACKGROUND

The Metabolic Medicine group aims to identify novel strategies to reduce cardiometabolic disease. The group studies mechanisms that govern metabolic and cardiovascular homeostasis. These processes often become defective in obesity resulting in the development of chronic diseases such as type 2 diabetes and cardiovascular disease.

Adiponectin is a hormone released from fat tissue that has important anti-diabetic and cardioprotective properties through regulation of lipid and carbohydrate metabolism. Adiponectin's receptors, named AdipoR1 and AdipoR2 (R1 and R2), are responsible for mediating the beneficial effects of adiponectin. Emerging evidence suggests that cell-surface expression of R1 and R2 may be reduced in cardiometabolic disease [1].

Using a range of molecular and cellular approaches we have identified post-translational modifications that regulate the subcellular localisation and trafficking, hence function, of R1 and R2. Increasing our understanding of the role of these modifications in healthy and disease states may reveal novel therapeutic targets.

This project provides the opportunity to perform clinical/translational research and learn advanced molecular biology techniques in a supportive and friendly environment. The project will benefit scientists and the broader community by providing insight into the way these receptors regulate metabolism. Considering the increasing rate of metabolic disease in the community this is a worthwhile pursuit.

HYPOTHESIS/AIMS

This project aims to extend our preliminary findings in cells from subjects with or without cardiometabolic disease. Specifically, the post translational modifications and cell-surface expression of R1 and R2 will be examined in primary cells from healthy subjects or subjects with metabolic disease.

REFERENCES

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HELPING BABIES BEFORE BIRTH / DEVELOPMENTAL DISORDERS

PRIMARY RESEARCHER

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BACKGROUND

During pregnancy, nutrient sulphate is supplied from mother to baby. Our research has shown the essential roles of sulphate in maintaining healthy growth and development. This project will investigate genes that maintain nutrient sulphate levels in human pregnancy. Outcomes of this project will complement current clinical and biomedical studies that are investigating the consequences of fetal sulphate deficiency in human pregnancy.

HYPOTHESIS

Genetic variants that decrease sulphonation capacity are found in the human population.

AIMS

1. Apply bioinformatic analyses to screen genetic databases for potential loss of function variants;
2. Clone mutant gene sequences into a mammalian expression vector;
3. Determine the consequence of sequence variants on sulphonation capacity.

APPROACHES

Students will apply a range of laboratory methods (i.e. bioinformatics, molecular biology, nucleic acid manipulation, human cell cultures, microscopy) to unravel genetic systems that are critical for maintaining healthy development during pregnancy.

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Dawson PA 2013 Role of sulphate in development. *Reproduction* 87(2):43, 1-9

ADDITIONAL PROJECTS

- Investigating nutrient sulfate supply from mother to baby.



SUGAR MODIFICATIONS IN THE REGULATION OF ENERGY PRODUCTION

PRIMARY RESEARCHER

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BACKGROUND

Our team are internationally recognised leaders in the field of glycation and diabetes. Glycation is a group of chemical reactions which leads to permanent modifications of proteins and the end products of this reaction, advanced glycation end products (AGEs) which have wide ranging implications for a number of cellular processes. AGEs are best understood as contributors to the complication of diabetes including kidney disease, blindness, heart attacks and strokes.

However, more recent data have shown that AGEs can also effect insulin secretion and signalling. We have are interested in better understanding their role in switching fuels for energy production in different organs and cells during homeostasis as well as during diabetes.

Diabetes is a metabolic disease characterised by dysfunction induced by loss of glucose control. Individuals suffering both types one and two may go on to develop complications including kidney disease and blindness. The hyperglycaemia and dyslipidaemia present during diabetes facilitates increased generation of advanced glycation end products (AGEs). AGEs interaction with their receptor (RAGE) have been shown to play a role in the progression of complications.

Mitochondria are the powerhouses of the cells providing energy needs for all cellular process. We have published findings highlighting AGEs induced mitochondrial dysfunction. Our most recent data highlights AGEs playing a role in both glucose control and metabolic function in a number of tissues.

HYPOTHESIS/AIMS

Diabetic insult induces pathological mitochondrial function.

We will aim to develop understanding driving factors for changes in fuel utilisation by mitochondria in diabetes. This project will involve the use of advanced technologies such as the Seahorse XF24 to assess energy production and fuel utilisation in a variety of organs, tissues and cells. A broad range of other techniques will be used including confocal microscopy, flow cytometry and real time Q-PCR. We believe that the role of AGEs in changing uptake of fuels and their effects on mitochondrial function are not only important for organs affected by diabetes but that this occurs to maintain normal cellular function and had implications for many other diseases where ATP depletion and mitochondrial dysfunction is evident.

- Characterizing metabolic capacity of tissues and alterations under AGEs stimulation.
- Molecular investigation of AGEs effects on tissue specific alterations to metabolic pathways.
- Examination of AGEs on protein expression key to metabolic function.

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THE ROLE OF GLUT4 IN THE KIDNEY PROXIMAL TUBULE IN DIABETES

PRIMARY RESEARCHER

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BACKGROUND

More than 1 million Australians are diagnosed with diabetes and 70% of deaths are due to associated kidney or cardiovascular diseases. Complications are generally considered to arise from chronic hyperglycaemia and therefore the primary goal in managing diabetes is to lower blood glucose concentrations. Recently, a new class of therapies that lower blood glucose concentrations have been approved for use in type 2 diabetic patients.

These sodium dependent glucose transporter-2 (SGLT2) inhibitors target the kidney proximal tubule to reduce glucose reabsorption and therefore promote urinary glucose loss. Under normal glucose conditions, SGLT2 is considered to be the only transporter expressed in the early segment of the proximal tubule. However, evidence from our laboratory suggests that the insulin-sensitive glucose transporter, GLUT4, is upregulated in the proximal tubule under diabetic conditions.

The role of GLUT4 in kidney tubules is completely unknown. It is likely that its expression in diabetes contributes to greater glucose reabsorption which would exacerbate hyperglycaemia and contribute to kidney complications through glucotoxicity. This alternate pathway for glucose reabsorption in the kidneys would compromise the effectiveness of novel therapies, such as SGLT2 inhibitors.

HYPOTHESIS

The insulin-sensitive facilitative glucose transporter, GLUT4 is upregulated in the diabetic kidney, contributing to glucose reabsorption independently of SGLT2.

AIMS

1. To localise and quantify the expression of GLUT4 in kidney proximal tubules under normal and diabetic conditions.
2. To determine the effects of proximal-tubule cell specific GLUT4 knock-out on overall glycaemic control and kidney function.

APPROACHES

1. GLUT4 expression and localisation within the kidney will be determined in the db/db mouse model of type 2 diabetes, the Akita mouse model of insulin-deficiency and human proximal tubule cell line.
2. Transgenic mice will also be generated whereby GLUT4 is knocked-out specifically from the kidney proximal tubule and diabetes induced. One group will also be administered with an SGLT2 inhibitor so that GLUT4 and SGLT2 are simultaneously blocked. The following measurements will be made:
 - Glucose tolerance test, blood pressure and renal clearance studies to determine glomerular filtration rate and fractional glucose reabsorption in conscious mice.
 - Degree of pathology (histology imaging) and the expression of key genes and proteins (Western blotting and PCR) important for glucose transport in isolated mouse kidneys.



THE ROLE OF THE IMMUNE SYSTEM, GENETICS AND GUT MICROFLORA IN TYPE 1 DIABETES

PRIMARY RESEARCHER

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BACKGROUND

The research passion of Dr Emma Hamilton-Williams, Research Fellow at The University of Queensland Diamantina Institute (UQDI), is type 1 diabetes (T1D), an autoimmune disease that ultimately leads to the destruction of the insulin producing β -cells.

After completing a postdoctoral position in Germany, and further work in California, the wish to be closer to her family and provide her children with an Australian lifestyle and education prompted Hamilton-Williams to move back to Australia in 2011. Eager to continue her research into the detailed effects of T1D promoting genes on the body's immune system, she joined UQDI for the Institute's close fit with her research goals and the opportunity to collaborate with world leaders in autoimmunity, genetics and dendritic cell biology.

Hamilton-Williams' current research aims are two-fold: on one hand she strives to understand the potential protective effects that dendritic cells can provide at certain stages of T1D progression. On the other hand, she aims to unravel the links between T1D susceptibility genes and environmental factors like the gut flora.

Hamilton-Williams is driven by a passion to understand complex diseases like T1D and to find ways to improve the lives of people who suffer from these diseases. The answers to her research questions certainly have the potential to make the prediction and prevention of T1D a reality, as well as change the way we treat the disease.

RESEARCH PROJECTS

- A novel role for the interleukin-2 pathway in humans and mouse models of type 1 diabetes.
- Genetic control of intestinal microflora in type 1 diabetes susceptibility.
- Impaired Regulatory T cell function in type 1 diabetes.



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GENOMIC MEDICINE

THE ROLE OF MICRORNAS IN FETAL ALCOHOL SYNDROME

PRIMARY RESEARCHER

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BACKGROUND

MicroRNAs are small non-coding RNAs that act as potent regulators of gene expression. Abnormal microRNA expression has been linked to a number of human diseases, including cancer.

We are interested in the role of microRNAs in fetal alcohol syndrome. Fetal alcohol syndrome is associated with excessive maternal alcohol consumption during pregnancy, and is characterised by growth restriction, craniofacial dysmorphology and structural/functional abnormalities of the central nervous system. Diagnosis is difficult and underreporting is suspected.

HYPOTHESIS/AIMS

This project will use a mouse model of prenatal alcohol exposure to explore the effects of alcohol on microRNA expression in various tissues, and the downstream molecular and phenotypic consequences.

It involves a range of methodologies, including animal handling and various cell and molecular biology techniques. Increased knowledge of the molecular basis of alcohol-induced damage in utero is expected to improve diagnosis and treatment, and to impact public health policy.

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UNDERSTANDING THE GENETICS OF PROSTATE CANCER: A STEP FORWARD FROM THE GENOME WIDE ASSOCIATION STUDIES

PRIMARY RESEARCHER
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BACKGROUND

In Australia, one in 9 men will develop prostate cancer by the age of 75 and 20,000 new cases are diagnosed annually, making prostate cancer the second most common cancer in men. Age at diagnosis, family history and ethnicity are the most common predictors of disease risk and there is strong evidence to suggest that up to 44% of prostate cancer is genetic in basis.

Genome-wide association studies (GWAS) have led to the identification of more than 40 common, low-penetrance loci for prostate cancer, which together explain more than 25% of familial risk. GWAS results complemented by functional studies may, however, have more immediate clinical impact by the identification of plausible disease biomarkers and novel targets and pathways to inform the application and development of therapeutic options.

Examples include:

- SNP associations identifying the protein biomarker MSMB for prostate cancer risk
- diagnosis and disease monitoring
- incorporation of SNP risk estimates in "family history" risk prediction models.

Knowledge of functional roles for GWAS-identified variants with respect to disease is in the very early stages, as very few genetics research groups also have functional expertise.

HYPOTHESIS/AIMS

To identify the relevance of the novel genetic polymorphisms in prostate cancer pathology, to map these variants to appropriate gene, and to delineate the mechanism by which these genes might alter prostate cancer risk- these include but not restricted to genetic variants affecting miRNA binding, affecting non-coding RNA and/or within the exonic regions affecting protein structure and stability.

APPROACHES

- Bioinformatic mapping of novel variants on putative genes
- qRT-PCR on RNA from various cell lines and flash frozen tissues of prostate cancer
- Western blot and immuno-histochemistry to compare the differential expression of the novel protein in cancerous and adjacent tissues (or cells as appropriate).
- Gene knockdown and over-expression assays in various normal and cancerous cell lines.

GENETICS OF COMMON DISEASES

PRIMARY RESEARCHER

PROF MATT BROWN

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BACKGROUND

Professor Brown's group researches genetics of common diseases, particularly musculoskeletal diseases. They are the central genetics research centre for the Australo-Anglo-American Spondyloarthritis Consortium, the main international AS genetics group. In addition, the group is performing genomewide association studies in multiple sclerosis, osteoporosis, cervical cancer, rheumatoid arthritis, schizophrenia, asthma and several other diseases.

Professor Brown is a Principal Investigator of the Wellcome Trust Case-Control Consortium which did much of the development work and proof of principle studies for genomewide association studies, and is now involved in developing the approaches required for downstream genetics research (resequencing, fine-mapping, copy number variation studies).

Professor Brown's group also collaborates with researchers at the MRC Mammalian Research Facility Harwell, England, in ENU-mutagenesis approaches to develop new mouse strains with bone and joint disorders. Other major collaborations include with Professor Jon Tobias and Dr Celia Gregson (Bristol, UK) on genetics of high bone mass, Professor Huji Xu (Shanghai, China) on genetics of rheumatoid arthritis and ankylosing spondylitis in Han Chinese, and Professor Jamie Craig and Dr Kathryn Burdon (Adelaide, Aus) on genetics of ocular disorders.

RESEARCH PROJECTS

- Genetics of common bone and joint diseases.
- Osteoporosis.
- Interethnic mapping of common human diseases; ankylosing spondylitis, rheumatoid arthritis, schizophrenia.
- ENU mutagenesis and models of musculoskeletal diseases.
- Gene deserts involved in ankylosing spondylitis.
- Genetics of multiple sclerosis.
- Novel gene-mapping approaches using next-generation sequencing.

ROLE OF THE PROTEIN PHOSPHATASE EYA4 IN DNA REPLICATION FORK MAINTENANCE

PRIMARY RESEARCHER

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BACKGROUND

Our DNA is constantly exposed to DNA damaging agents of external (chemical, UV, therapeutics) and internal (reactive oxygen species, replication errors). The maintenance of genome stability is reliant upon the concerted action of DNA damage repair and DNA damage checkpoint mechanisms.

Homologous recombination (HR) mediates the error-free repair of chromosomes that harbor DNA double-stranded breaks (DSBs) and other forms of DNA damage. As such, defects in any of these mechanisms can destabilize the genome and often leads to a cancer phenotype. Special risks also arise during replication.

We recently identified EYA4 as a novel breast cancer gene. Our preliminary findings indicate that loss of EYA4 significantly reduces HR repair of a DNA Double Strand Break (DSB), and arrest the cells in S-phase.

We will determine the mechanism of EYA4 involvement in these two cellular mechanisms essential for genomic stability, and delineate the cellular consequences of EYA4 deficiency. EYA4 is a protein phosphatase and a transcription factor. EYA4 deficiency causes an adult-onset premature hearing loss, child-onset deafness (DFNA10) and cardiomyopathy but very little is known about its exact function.

AIMS

We propose to investigate a completely novel role of EYA4, in genome maintenance. We hypothesize that EYA4 functions at sites of stalled replication forks to help prevent replication fork collapse in human cells.

The honours student will characterize the biological consequences of EYA4 loss for

- cell-cycle progression, replication fork restart, and cell fate,
- the DNA damage response and genomic instability; and
- will investigate factors controlling EYA4 localisation to critically damaged replication forks (foci formation).

APPROACHES

For this project, we are looking for a highly motivated student with a good theoretical knowledge of basic molecular biology and a good understanding of the basic concept of PCR, pipetting, cloning, and microscopy. This project involves novel techniques, and equipment such as flow cytometry and microscopy.

GENETIC AETIOLOGY OF COMPLEX TRAITS AND DISEASES

PRIMARY RESEARCHER

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BACKGROUND

Professor Evans completed his undergraduate degree and PhD at The University of Queensland and the Queensland Institute of Medical Research (QIMR). He came into statistical genetics quite by accident. The difficulty he had experienced previously was that he enjoyed learning about biology, but didn't like working in wet labs.

Up until that time, Evans says he had no idea that the face of medical research was undergoing a revolution, and that there were amazing new areas of medical science opening up in the area of statistics and genetics, and these areas were available to those with an aptitude for maths and computing. Evans was astounded at the cutting edge research that could be performed without ever having to step into a wet lab again.

In 2007, Evans moved to the University of Bristol to take up a Senior Lecturer and then Reader position. His main task in Bristol was to lead genetic studies within the Avon Longitudinal Study of Parents and Children (ALSPAC) - a local population based cohort of 10,000 mothers and children that has since become one of the world's leading cohorts for genetics research.

Since this time, ALSPAC has contributed to over forty large scale genetic studies spanning a diverse range of medically relevant traits and diseases, including osteoporosis and eczema, and has helped identify hundreds of genes that predispose to disease in the process. Evans remains heavily involved in this research and is hoping to find PhD students who are interested in pursuing closer links between Australia and the UK.

His research focuses on dissecting the genetic aetiology of complex traits and diseases by genome-wide association and next generation sequencing approaches, with a particular interest in osteoporosis, ankylosing spondylitis and eczema, but Evans also performs genetic studies across a wide variety of other complex traits and diseases and is active in the development and refinement of statistical genetics methodologies.

"It's wonderful to discover things that nobody else has before. It's also exciting to think that some of your discoveries may make a difference to peoples' lives," says Evans.

RESEARCH PROJECTS

- Next generation sequencing and genome-wide association studies.
- Genetics of common complex traits and diseases.
- Genetics of osteoporosis, eczema and ankylosing spondylitis.
- Using genetics to test whether environmental risk factors cause disease.
- Development of statistical methods for disease gene mapping.



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COMPARISON OF TRANSPOSABLE ELEMENT DETECTION METHODS FOR WHOLE-GENOME SEQUENCE DATA

PRIMARY RESEARCHER

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Background

Transposable elements (TEs), also referred to as mobile genetic elements, are pieces of genomic DNA that are frequently copied from one location to another. (for review see refs 1-3). As the mobilisation of TEs is an ongoing process in essentially all eukaryotes, individuals within a species differ with respect to their genomic complement of transposable elements. In humans, at least three subfamilies of TEs are currently active: LINE-1, Alu, and SVA.

Over the last five years, quite a few different methods have been developed to determine the locations of transposable element copies given whole genome sequence (WGS) [4-15], including some under development by our group [16]. As transposable element detection is becoming a standard part of analysing WGS data, it would be valuable to know which methods or combinations of methods have the best performance characteristics for detection of these variants, both for characterising normal germline genomic TE variation, and in a cancer genomics context where a tumour is compared to a patient-matched normal genome. As we are involved in other large-scale comparisons of variant detection methods [17], we have appropriate tools and methods available which can readily be extended to transposable element insertion detection methods.

HYPOTHESIS/AIMS

It is likely that some published TE detection methods have more desirable performance than others. To answer this, we will utilise a variant simulator (bamsurgeon) [18] to generate a series of whole genome sequences with many known TE insertion sites. We will simulate both the usual characteristics of germline TE insertional variants and those of somatic mutation in tumours where there are substantial co-occurring rearrangements and subclonal expansions.

We will then apply as many TE detection methods to these data as possible, based in part on which software is readily usable, and the various outputs will be standardised to facilitate comparisons between methods. The methods with the best performance characteristics based on the simulated data will be applied to real data, and validations will be carried out via PCR for a subset of results. Consensus methods often outperform any single method when detecting variants [20], so we will ascertain whether this is the case for TE detection. Results of this cross-comparison will be submitted for peer-review and ultimately published to benefit those interested in comprehensive characterisation of genomes.

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NOVEL THERAPEUTIC APPROACHES IN BONE AND JOINT DISEASE

PRIMARY RESEARCHER

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BACKGROUND

Dr Gethin Thomas believes you can have too much of a good thing when it comes to bone growth. While formation of new bone is essential in development, uncontrolled bone growth can lead to severe disability.

Because of this, Dr Thomas is looking for the trigger that switches inflammation to excessive bone growth in a debilitating condition called Ankylosing Spondylitis (AS) thereby identifying new approaches for treatment.

Since my PhD studies, I have studied the biology of the skeleton, specifically the process of bone formation and the cells controlling that process, the osteoblasts.

My interests focus on the roles of specific genes in skeletal regulation and more recently on the identification and characterisation of novel genes involved in bone disease, in particular ankylosing spondylitis and osteoporosis. We utilise a combination of genome-wide association studies (GWAS), whole-genome expression profiling and large-scale mouse mutagenesis approaches to identify new genes involved in skeletal disease.

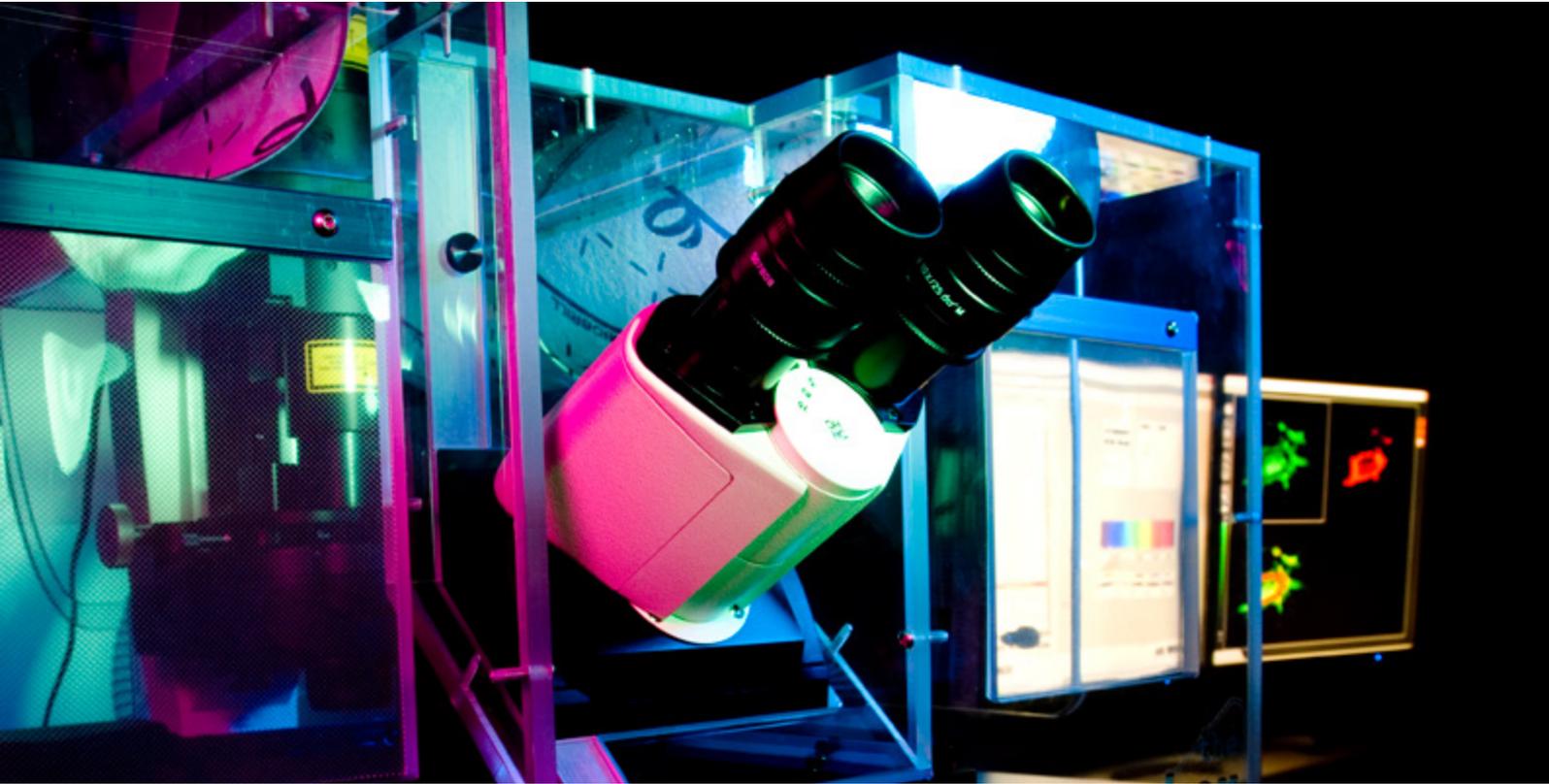
We then undertake functional analysis of these genes to understand their role in disease to aid in the development of new diagnostic and therapeutic approaches. Both the genetic and gene expression profiling studies also allow us to develop diagnostic algorithms for skeletal disease to enable early diagnosis and optimise treatments.

Already Dr Thomas and his colleagues have identified some crucial genetic players in AS-linked bone formation. He explains that the Wnt signalling pathway is essential for normal bone growth. This pathway is usually suppressed in adults, except when bone repair is required, but they have now discovered that two genes known to suppress the Wnt pathway are themselves effectively turned off in a mouse model of AS, thus allowing unregulated bone formation to occur.

Dr Thomas wants to discover what is causing these crucial regulatory genes to shut down, and is searching intently for what he believes is a unique, perhaps genetic, inflammatory signal in AS. "If we can stop that signal," he says, "we can stop AS."

RESEARCH PROJECTS

- Gene expression profiling in ankylosing spondylitis.
- Identification of novel genes in skeletal disease through large-scale ENU mouse mutagenesis.
- Novel treatment approaches to prevent joint fusion in ankylosing spondylitis
- Mechanisms underlying genetic associations in ankylosing spondylitis.



IMMUNOLOGY AND IMMUNE DISORDERS

DEVELOPMENT OF AMINOPEPTIDASE INHIBITORS AS A NOVEL CLASS OF THERAPEUTICS FOR TREATMENT OF IMMUNE-MEDIATED DISEASES

PRIMARY RESEARCHER

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Dr. Nitish Agrawal is an accomplished research leader in the field of molecular biology and biochemistry. He holds degrees in Ph.D Chemistry (Enzymology) from University of Iowa, USA and Honours in Bachelor in Science & Masters in Science from University of Delhi, India.

Dr. Agrawal gained international recognition for his pioneering researches on thymidylate synthase enzyme, design of diagnostic imaging agents, Cystathionine β - Synthase enzyme and HIV1 Envelope glycoprotein-based vaccines during his appointments at the University of Iowa, GE Global Research, University of Michigan and Scripps-USA.

His specialized skills/experience is aligned with Institute's needs in establishing translational research program for treating immune-mediated diseases. Dr. Agrawal is leading contributor of investigational aminopeptidase-targeted drug therapeutics application for treating Ankylosing Spondylitis disease. Dr. Agrawal also holds teaching responsibilities at UQ School of Chemistry & Molecular Biosciences and currently supervises a research assistant-Eugene Lau.

The broad objectives of Dr. Agrawal's research are development and validation of aminopeptidase antagonists for treating immune-mediated diseases such as Psoriasis, Inflammatory Bowel Disease, and Ankylosing Spondylitis (AS).

RESEARCH PROJECTS

- Development of ERAP M1 Aminopeptidase inhibitors as a novel class of therapeutics for treatment of Immune-mediated diseases such as Ankylosing Spondylitis (AS), Psoriasis, Inflammatory Bowel disease (IBD).
- Protein expression and functional studies of ERAP M1 aminopeptidases in Ankylosing Spondylitis (AS), Psoriasis and Inflammatory Bowel disease (IBD).

UNDERSTANDING THE ROLE OF ANTI-MICROBIAL AUTOPHAGY IN INFLAMMATORY BOWEL DISEASE

PRIMARY RESEARCHER

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BACKGROUND

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract characterized by an inappropriate immune response directed towards a dysbiotic gut microbiome leading to significant symptoms frequently requiring surgery to correct.

The causes of IBD remain incompletely understood but the current paradigm is that in a genetically predisposed individual inappropriate immune activation occurs accompanied by an alteration in the resident gut microbial communities. Genetic studies have highlighted multiple pathways implicated in this process including antibacterial autophagy. My lab is focused on understanding the interaction of bacteria with the epithelial cells in the context of IBD using a combination of functional genetics, cell based models, autophagy assays, animal models and patient derived samples. In addition we are exploring the use of small molecules to modulate the cellular response to bacteria with a goal of developing more effective therapeutic agents.

HYPOTHESIS/AIMS

We hypothesize that there is an inherent defect in bacterial handling by the intestinal epithelium underlying disease pathogenesis in inflammatory bowel disease. A medication class used commonly in the treatment of inflammatory bowel disease are thiopurines and these appear to induce autophagy, but it is unknown what impact these medications have on bacterial handling.

1. To determine the effect of thiopurine medications on anti-bacterial autophagy using cell based assays in epithelial cells. This will involve a combination of immunofluorescent microscopy, quantitative PCR, Western blots and quantitative microbiology.
2. To determine the mechanism of autophagy activation by various thiopurine derivatives using a combination of functional genetics (gene knock-out using CRISPR techniques),

small molecule inhibitors, microscopy and Western blotting in multiple epithelial cell lines.

3. To determine the effect of thiopurines on autophagy in vivo using mouse models of inflammatory bowel disease, patient biopsies, and patient derived organoid cultures.

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REGULATORS OF IMMUNE RESPONSES DURING INFECTION AND INFLAMMATION

PRIMARY RESEARCHER

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BACKGROUND

The research interest of Dr Antje Blumenthal lies in the complex interactions between pathogens and the immune system. How are pathogens recognised? How are the appropriate immune responses activated to effectively kill pathogens, but also regulated to prevent tissue damage? Dr Blumenthal is particularly passionate about understanding the immune responses to *Mycobacterium tuberculosis*, the causative agent of tuberculosis (TB). 1.4 million deaths globally every year, the emergence of drug resistant bacteria and the development of an effective vaccine currently pose challenging tasks to researchers, explains Blumenthal.

“If we can understand what is necessary for the body to defeat a pathogen,” she says, “then we can focus potential therapies to help that defence. If we identify processes the pathogen requires to establish and maintain an infection, we can target antimicrobials towards these” Blumenthal says.

Blumenthal is now a Balzan Research Fellow at the UQDI and investigates how the immune system recognises pathogens and how immune responses are initiated. She is also researching how biochemical pathways that regulate embryonic development and cell differentiation contribute to the regulation of immune responses during infection.

These pathways are currently very attractive drug targets, and understanding their immune functions will help inform decisions relating to the development and use of therapeutics in a variety of disease settings. Blumenthal believes that her work on how immune responses are initiated and regulated will provide knowledge applicable not only to infections but to many inflammatory disorders such as rheumatoid arthritis and diabetes.

“That’s really exciting for me,” she says. “It could contribute to the fundamental understanding of how the immune system works.”

RESEARCH PROJECTS

- Innate immune recognition of *Mycobacterium tuberculosis* and other pathogens.
- Molecular mechanisms of macrophage functions.
- Regulators of immune responses during infection and inflammation.
- Discovery of novel anti-microbials.

IMMUNE CELL SUBSETS IN AUTOIMMUNE DISEASE

PRIMARY RESEARCHER

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BACKGROUND

Since his undergraduate degree, Dr Tony Kenna has been interested in the complexity of the immune system; the way the human immune systems protects the body from such a wide variety of 'dangers', ranging from bacteria and viruses, to parasitic worms and tumours.

His particular interest, however, is the process when the immune system becomes faulty. At its core, autoimmunity is a failure of the immune system to recognise the body's own cells and tissues as being harmless and instead attacks. The steps that lead the immune system to this ultimately self-destructive stage are hugely complex, but understanding them is critical for the development of therapeutics to treat autoimmune conditions such as arthritis, inflammatory bowel disease, multiple sclerosis and type 1 diabetes.

Kenna's current research focuses on understanding the role played by particular immune cell subsets in AS and what triggers inappropriate activation of the immune system in autoimmunity. This has led him down some exciting new pathways, including questioning what role the gut immune system has in autoimmune bone diseases.

"We all hear on the TV and radio about healthy digestive systems being important for overall health. One way this is particularly important is in sculpting the immune system." Dr Kenna says, "An unhealthy gut can inappropriately activate the immune system and there's increasing evidence that such immune system activation can cause autoimmune attack of sites far removed from the gut, including bone."

Dr Kenna's team focuses primarily on understanding how the immune system contributes to development of a bone disease called ankylosing spondylitis (AS). Work by Professor Matt Brown has identified 33 genes involved in AS. Many of these genes control immune cell function. One of the major research challenges in this field is to understand the biology underlying these genes and how specific immune cells contribute to disease. This knowledge will inform researchers about novel therapeutic targets and strategies that could be trialled in AS.

RESEARCH PROJECTS

- Transcriptional regulation of inflammation in autoinflammatory diseases.
- Intestinal inflammation in ankylosing spondylitis.
- Innate inflammatory pathways in ankylosing spondylitis.

IMMUNE CELL SUBSETS IN AUTOIMMUNE DISEASE

PRIMARY RESEARCHER
PROF MARK MORRISON
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BACKGROUND

Prof Morrison undertook a PhD and postdoctoral training at the Universities of Illinois and Michigan, respectively, between 1988 and 1992. Following his training he held tenured faculty appointments initially with the University of Nebraska, then The Ohio State University (since 2000). In 2006 he returned to Australia as a CSIRO science leader in metagenomics, serving as the stream leader for Gut Health in CSIRO's Preventative Health National Flagship Research Program.

He also served as one of CSIRO's five "Capability Platform leaders" (in Transformational Biology) between 2007 and 2013; before being appointed as the Chair in Microbial Biology and Metagenomics with the University of Queensland Diamantina Institute in October 2013.

His research interests are to translate genomic and metagenomic datasets into a sound biological framework, producing novel diagnostic, organismal, and enzyme-based technologies. His early training and career activities were in microbial physiology and metabolism, principally with applications in livestock and paediatric nutrition.

Morrison attained international acclaim for his efforts to successfully develop and use genomics and related methods to study anaerobic "commensal" gut bacteria, which includes producing the first genome sequences for *Ruminococcus* and *Prevotella* spp.; both genera now widely acknowledged to play a key role in establishing human gut "enterotypes".

RESEARCH PROJECTS

- Wanted Alive not Dead: Isolation and analyses of "new" human gut bacteria.
- Bacterial mousetraps: the role of serpins in gut bacteria.

T-CELL TOLERANCE AS A THERAPEUTIC APPROACH IN AUTOIMMUNE DISEASE AND IMMUNE MALIGNANCY

PRIMARY RESEARCHER

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BACKGROUND

Associate Professor Ray Steptoe was always interested in science, and began playing with microscopes at age 10. His natural affinity for science eventually led him to study anatomy and human biology at the University of Western Australia (UWA), but he soon realised that learning established knowledge wasn't enough. He wanted to also generate new scientific knowledge. A PhD in immunology presented the perfect challenge. He found the role of Dendritic Cells (DCs) in the eye particularly interesting.

Associate Professor Steptoe and his UQDI colleagues have recently shown that memory T cells are indeed susceptible to tolerance, moreover he has discovered a unique way of shutting off memory T-cell responses. This approach has therapeutic potential and Associate Professor Steptoe believes it can be used to find a universal 'off-switch' in immune memory cells. There are potential applications in numerous inflammatory conditions.

Steptoe looks forward to extending his discoveries into the clinic and believes the collaborations established between UQDI and the Princess Alexandra Hospital are ideal for developing clinical applications of his work.

In the meantime, his awarded Australian Research Council Fellowship and NHMRC grants will enable him valuable access facilities crucial to his research, including a multiphoton microscope. It's arguably more complex than the microscope he received at age 10, but given the new knowledge he will be able to generate, it's also a lot more fun.

RESEARCH PROJECTS

- Cellular and molecular pathways of T-cell tolerance.
- Prevention and reversal of autoimmune diabetes.
- Novel methods of gene delivery for tolerance.
- Immunotherapy of allergies and anaphylaxis.
- Exploring T-cell tolerance in B cell malignancies.



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NOVEL IMMUNOTHERAPEUTIC APPROACHES IN AUTOIMMUNE DISEASE

PRIMARY RESEARCHER

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BACKGROUND

When she was a child, Dr Ranjeny Thomas didn't want to be a scientist. She confesses she was drawn instead to the creative arts. But as it turns out, it is precisely her natural creativity, combined with a love of a good mystery, which has led her to become one of Australia's foremost immunologists. Since my PhD studies, I have studied the biology of the skeleton, specifically the process of bone formation and the cells controlling that process, the osteoblasts.

Ranjeny Thomas, now Professor of Rheumatology at UQ and head of the Autoimmunity Division at the UQ Diamantina Institute, continues to work on dendritic cells and autoimmune diseases. In addition to her progress in RA, her work has advanced understanding of diabetes and ankylosing spondylitis. Already this has led her to develop both a diagnostic test for juvenile diabetes. Research projects span from understanding dendritic cell function through analysis of signaling pathways, in vivo studies of tolerance, through to clinical trials of tolerance in autoimmunity, and clinical studies of risk factors in rheumatoid arthritis and type 1 diabetes.

Her work has given rise to several clinical applications, including:

- An antigen-specific vaccine to treat rheumatoid arthritis, currently in clinical trials
- A therapeutic platform for antigen-specific immunotherapy
- A novel diagnostic test for identification of those at risk of type 1 (juvenile) diabetes
- Novel immunotherapy for type 1 diabetes

Thomas looks forward to finding more creative ways to unlock the mysteries of the immune system and develop new treatments for autoimmune disease. "Immunology research has reached a very exciting stage, where the development of new 'designer therapies' for prevention and treatment of inflammatory diseases that affect the life of millions of people across the world is becoming a real possibility. It's both a privilege and an enormous challenge to be a part of that!"

RESEARCH PROJECTS

- Understanding the molecular control of dendritic cell function in tolerance.
- Initiation of inflammatory arthritis
- Rheumatoid arthritis antigen-specific therapy.
- Type 1 (Juvenile) Diabetes Innate Immunity: mouse models and human longitudinal study.
- Use of statins to reduce atherosclerosis in early rheumatoid arthritis.



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IMMUNOLOGY RESEARCH

PRIMARY RESEARCHER

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ALLERGY/VIRUS INTERACTIONS IN ASTHMA

The Lung and Allergy Research Consortium is focused on undertaking scientific research to understand the pathogenesis of asthma and other chronic lung diseases, with particular interests in allergic inflammation and host defence against respiratory viral infections. Our research has a strong translational focus and is largely performed with samples from healthy volunteers and patients with allergies or respiratory disease.

Why allergens and viruses are common triggers for flare-ups of asthma, but have only modest effects in healthy people, is not well understood. This project will compare and contrast the signalling pathways induced by common allergens and viruses in dendritic cells, and will study the ability of allergens to inhibit anti-viral interferon production.

IMMUNE PROTECTION AGAINST HAEMOPHILUS INFECTIONS IN CHILDREN

Recurrent respiratory infections are common in the Indigenous community, and may lead to chronic lung damage, so there is a need for new vaccination approaches.

We have recently shown that many Indigenous children with recurrent respiratory infections make a weak cell-mediated immune response to non-typeable *Haemophilus influenzae* (NTHi), relative to healthy children. The project will examine the mechanisms involved, focussing on the effects of NTHi isolates on dendritic cell and macrophage functions.

ASSOCIATES

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IMPROVING INFLUENZA VACCINATION FOR PEOPLE WITH CHRONIC LUNG DISEASE

People with chronic lung disease are at increased risk of serious complications following influenza infection.

The project will study important details of the immune response to influenza vaccination in those with chronic lung disease and examine ways to make vaccination more effective.

ALLERGY TO SUBTROPICAL GRASS POLLENS

Grass pollens are a major cause of allergic rhinitis and asthma in Australia but the contribution of the subtropical grasses remains largely undefined. This project will examine patterns of allergic sensitization and pollen exposure in various climatic regions across Australia.

UNDERSTANDING ALLERGEN-SPECIFIC B CELLS

The mechanisms responsible for elevated allergen-specific IgE production in allergic diseases are yet to be fully elucidated. In this project the molecular characteristics of immunoglobulin gene transcripts from peanut and grass pollen allergen-specific B cells will be investigated.

TRIO



KIDNEY AND LIVER HEALTH

OXIDATIVE DAMAGE IN CHRONIC KIDNEY DISEASE

PRIMARY RESEARCHER

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BACKGROUND

The Centre for Kidney Disease Research (CKDR) translational research laboratories are located at the Translational Research Institute at Princess Alexandra Hospital campus.

Researchers of the CKDR are working at the forefront of global trends in kidney research to understand the cellular and molecular basis of kidney disease and to trial innovative new clinical treatments to improve the health and well-being of people with kidney disease.

The CKDR has particular expertise in translating results from laboratory and clinical sciences for application to improve public health outcomes. We are offering several Honours projects in 2015.

Chronic kidney disease (CKD) is increasing in Western societies, particularly in association with other common diseases like hypertension and diabetes, and also with ageing. The epithelial cells of the tubular epithelium are particularly sensitive to oxidative damage, and their death and deletion by apoptosis contributes to the tubular atrophy seen in CKD.

Although oxidative stress/damage is known to occur in CKD, the specific role/s of organelle dysfunction in the kidney tubular epithelial cells in the progression of CKD is not well defined. This information potentially offers a powerful means of managing the disease.

AIMS

The aim of the project is to identify markers of organelle dysfunction (eg. of mitochondria, lysosomes) and to correlate these changes with some key phenotypical/morphological changes in the chronically-diseased kidney (eg. apoptosis, autophagy, cell senescence). This information will then be used to test some key therapies that may modulate the changes that cause CKD.



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HOW DOES KIDNEY CANCER DEVELOP RESISTANCE TO TARGETED THERAPY?

PRIMARY RESEARCHER

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BACKGROUND

Kidney cancer accounts for 3% of all adult cancers. It is a highly heterogeneous, metastatic and treatment-resistant cancer. Prior to 2005, patients with locally invasive or metastatic disease received immunotherapy with modest survival benefit.

Since then, a greater understanding of the molecular mechanisms of kidney cancer has led to the development of many targeted therapeutics such as bevacizumab, sorafenib, sunitinib, pazopanib, temsirolimus and everolimus. These are collectively called multi-tyrosine kinase inhibitors.

However, the initial success of the targeted therapy has been hampered by the development of drug resistance by cancer cells. Two patterns of resistance have been observed: an inherent resistance called intrinsic resistance; and an adaptive (or acquired) resistance, constituting the majority of cases, where patients respond to therapy initially, followed by a short period of disease stability and then disease progression after 6-12 months of treatment.

AIMS

The aims of this project are to elucidate the molecular mechanisms of this new class of tyrosine kinase inhibitors, and investigate the mechanisms of resistance to these drugs. This has the potential for development of new treatment strategies.



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UNDERSTANDING INFLAMMATION AND FIBROSIS IN THE KIDNEY

PRIMARY RESEARCHER

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BACKGROUND

This project will further explore the signalling mechanism of PAR-2 induced inflammation in primary cultures of tubule cells using pathway-specific inhibitors, novel PAR-2 inhibitors, siRNA, PCR arrays and proteomic approach. One model of kidney injury together with a PAR2 antagonist will be assessed.

How elevated glucose levels as seen in diabetes potentiate inflammatory responses & fibrogenic responses in kidney cells will be investigated.

METHODS

Methods would include cell culture, Seahorse, immunohistochemistry, RNA analysis (qPCR). One novel thing would be to look at the interaction between PAR2 and pro-fibrotic TGFb.

This project will investigate whether adipose-derived mesenchymal stem cells protect against ischemia-reperfusion injury in the kidney. We will use some commercially available products from adipose-derived mesenchymal stem cells, and a model of kidney injury such as ischaemia-reperfusion injury.

ANALYSIS

Analysis of apoptosis, proliferation, cell differentiation, and fibrosis will be carried out.



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TRAUMA

THE MICRO ANATOMY OF FEAR MEMORY

PRIMARY RESEARCHER

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BACKGROUND

Fear and stress negatively impact on human quality of life and productivity. Pathological manifestations of fear and stress include the anxiety disorders and phobia. This project at TRI will investigate fundamental cellular and systems levels mechanisms of the micro anatomy of fear memory.

Evidence indicates that memory of a fearful event is formed in the amygdala. While we know that the amygdala is necessary for fear memories, how fear memories are encoded and regulated in the amygdala is unknown. Extinction of fear can reduce fear memory. Extinction memories are new memories and evidence indicates that the fear extinction memory is formed in the prefrontal cortex which suppress memory in the amygdala. Both these forms of memory require phosphorylation of the ERK/MAPK.

AIMS

This project aims to identify key aspects of the neural circuits and mechanisms involved during the formation and extinction of fear memory using cellular tools.

METHOD

This project will involve neuroscience research. The project will involve analysis of brain tissue contains cells labelled during the formation of a memory. This will involve both qualitative and quantitative measurement of brain cells using microscopes and computer software.

