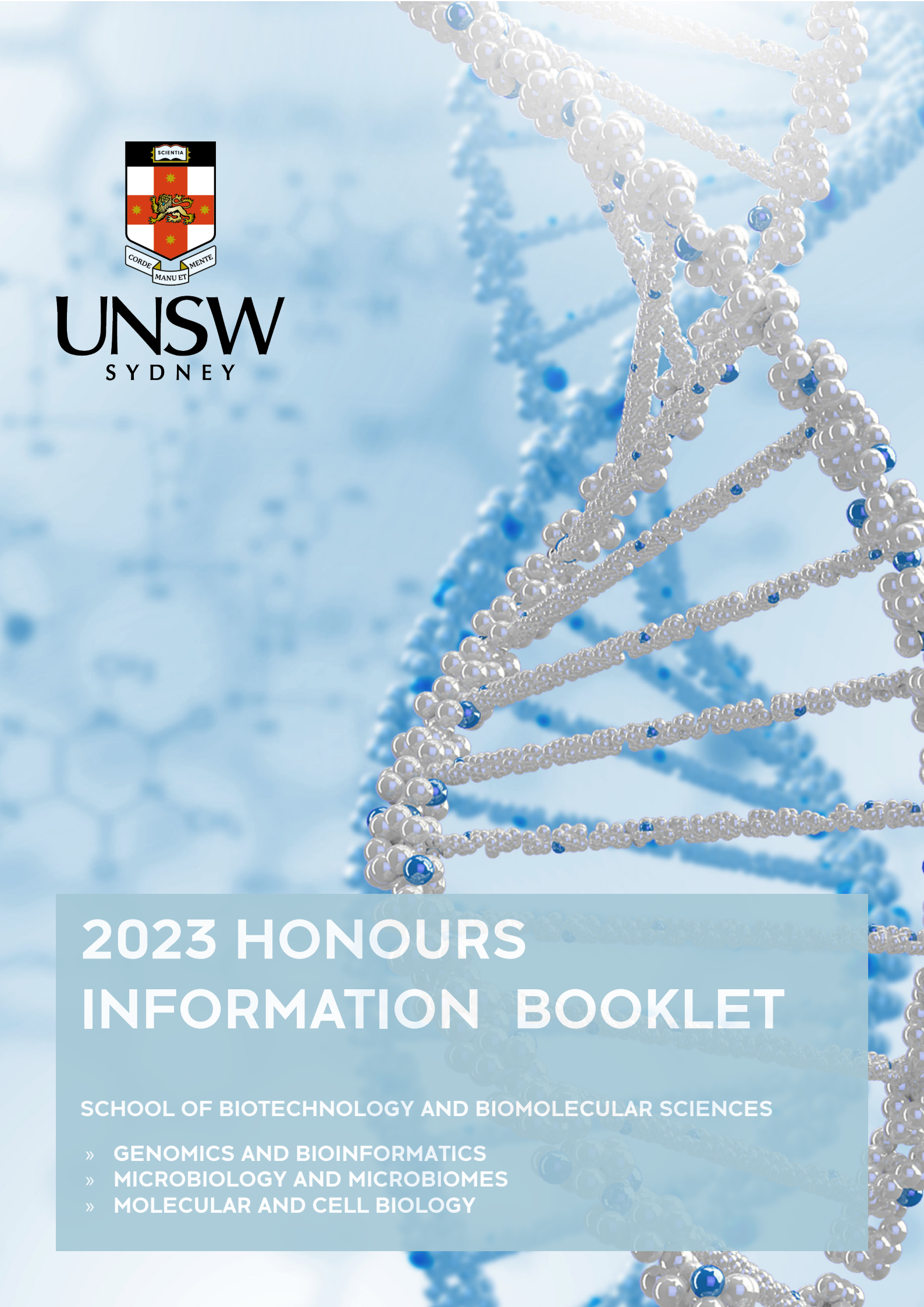

UNSW SYDNEY

2023 HONOURS INFORMATION BOOKLET

SCHOOL OF BIOTECHNOLOGY AND BIOMOLECULAR SCIENCES

- GENOMICS AND BIOINFORMATICS
- MICROBIOLOGY AND MICROBIOMES
- MOLECULAR AND CELL BIOLOGY

CONTENTS

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WELCOME FROM THE SCHOOL

This handbook provides a guide for students considering undertaking Honours in the School of Biotechnology and Biomolecular Sciences (BABS) at UNSW Sydney during 2023. To be eligible, students must have maintained a credit average or above during their undergraduate program.

The BABS Honours program comprises undertaking a full-time research project supervised by a BABS researcher or approved external supervisor in an affiliated institution. Honours is an intensive year, but it is immensely rewarding intellectually. All research in BABS is aimed at advancing science to make a real difference in the world. By investigating and understanding life at the molecular and cellular level, our students help solve real-world challenges.

Research in BABS is aligned to three discipline areas:

» Genomics and Bioinformatics

» Microbiology and Microbiomes

» Molecular and Cell Biology

As you will see in this booklet, there is a wide scope of projects to interest Honours students, with research spanning human bacterial pathogens, functional genetics, gene regulation, systems biology, viruses, cancer, neurobiology, extremophiles, synthetic and structural biology and more.

The work spans from hypothesis-driven 'blue sky' research that advances human knowledge, to application-focused research that has potential medical and industrial benefits for society.

Our Honours students benefit greatly from world-class facilities that include the Ramaciotti Centre for Genomics, which houses next-generation genomic sequencing technology.

Apart from imparting skills in scientific research, another aim of the BABS Honours program is to equip students with skills in information technology, science communication and critical thinking, which will not only increase confidence but also make graduates more employable in an increasingly competitive workplace.

Our research community of staff and senior graduate students will do everything they can to ensure each student's experience is as enjoyable and scientifically stimulating as possible.

We invite you to become a part of our research effort by undertaking Honours with us.

Professor Marcel Dinger
Head of School

Associate Professor Brendan Burns
Honours Coordinator

WHY DO HONOURS IN BABS?

A key benefit of doing Honours in BABS is that it provides an active, hands-on learning experience in a scientific research environment. Students become part of a research team within a lab in the School, with supervisory oversight provided on an individual basis by an experienced academic. In addition, interaction with other experienced researchers within the group in an informal, relaxed atmosphere complements the formal part of the Honours program, of completing the predetermined research project and writing a thesis.

The Program is designed to provide advanced training and knowledge in one of the School's majors:

» Biotechnology

» Genetics

» Microbiology

» Molecular and Cell Biology

Honours may lead to postgraduate studies, but that is not the only purpose of the Program. Honours is also an opportunity for the student to reflect on their future career.

Honours graduates have the opportunity to develop greater competence and confidence in the practical skills and laboratory methods acquired during their undergraduate program, while developing key attributes sought by employers, including:

» Development of critical thinking skills

» Extensive use of a variety of information and communication technologies

» Familiarity with a range of computer software for oral and written presentations

» Training in online database manipulation and data analysis

» Collaboration in industrial research and commercialisation of science nationally and internationally

The higher level of such attributes are well recognised by employers and greatly increase the possibility of gaining employment in industry, agriculture, medical or

Who is eligible for Honours?

Students must meet all requirements of their undergraduate degree (stages 1 to 3) before being considered eligible. Eligibility is contingent on academic merit, focused on performance in third-level Science subjects and overall WAM.

» Students with an average overall WAM of 65 or lower and/or an average of 65 or lower in third-level Science courses will usually not be accepted.

» Students who have achieved an average overall WAM of 65 or higher and an average of 65 or higher in third-level. Science courses may be admitted if an approved supervisor is available.

» Admission to Honours requires the prior agreement of an approved BABS supervisor.

The major of a current BABS undergraduate student will normally determine their Honours enrolment category, but there is some flexibility depending on the student's interests and availability of supervisor.

The selected research project of UNSW Medical Science students (3991 Program) and graduates from other Australian or overseas universities will determine the Honours category in which they enrol.

WHY DO HONOURS IN BABS?

Components of the Honours Program

The major component of Honours is a research project carried out under the supervision of a BABS staff member or an approved external supervisor, culminating in a thesis. There are, however, other aspects of the program that make the Honours year in BABS especially attractive.

BABS Honours orientation course

Orientation for BABS Honours students comprises a series of tutorials and seminars held during the first week of the term. Attendance is compulsory. During this time, students will be fully occupied with workshop activities and will be discouraged from attempting research work.

Research plan seminar

You will develop and present a plan of your research for the year, in consultation with your supervisor: Why? How? When? This is a 10-minute seminar where other students and staff will attend your presentation. Your supervisor will provide you with feedback on your research plan after your seminar.

Literature review

The literature review is an important component of the continuous assessment for all Honours projects. It comprises a major assignment of approximately 3,000 words (not more than 4,000 words) on your project topic, selected in consultation with your project supervisor. The aims of this review are for students to become familiar with the UNSW library and all its resources, and to develop a critical approach in assessing published literature in the area relevant to your research project.

Final research seminar

Towards the end of their project, students will present a 15-20 minute seminar to the School on the outcomes of their research. This is worth 10% of the final mark.

Research project thesis

This major component of the Honours year accounts for 90% of the final mark. A written practice thesis is due for lodgement before the student's final report will then be submitted as a final thesis. The final thesis mark is a combination of the written thesis, thesis inter-view, and overall lab aptitude throughout the Honours year.

BABS INDIGENOUS SCHOLARSHIP FOR HONOURS

BABS Indigenous Scholarship for Honours

The School of Biotechnology and Biomolecular Sciences is committed to improving Indigenous education opportunities and recognises that there may be impediments – financial or otherwise – that restricts Indigenous students from pursuing research avenues in science. As part of the university's overall strategy, the School is dedicated to increasing the number of Indigenous students participating in higher education. We believe an increase in the engagement of non-Indigenous staff and students with Indigenous knowledge and culture will be of substantial benefit to the School at social, environmental, and educational levels.

Successful applicants will have the opportunity to undertake Honours in a School that fosters equity and diversity, with a real opportunity to make a difference to people's lives through discoveries and sharing knowledge. The School is aware that Indigenous students bring their own rich tapestry of cultural experiences. Undertaking Honours in the School will afford students the opportunity to exchange ideas, learn from others, and both return to their communities and continue on a career path richer for the experience, and bearing tangible rewards in the form of improved research and teaching practices of substantial benefit to Australian science.

The School of BABS will offer a scholarship of $5,000, and work closely with Nura Gili, the university's Indigenous Programs Unit, to assess applicants who identify as Aboriginal and/or Torres Strait Islander. Applicants will be assessed on academic merit and their contributions (past, present, and ongoing) to society and their community, that demonstrates their values and how a Scholarship would be of benefit to them, with a view to develop these further.

Details on the application process can be found on the UNSW Scholarships website.

HOW TO APPLY FOR HONOURS IN BABS FOR 2023

Honours projects and supervisors

Information on available Honours supervisors and projects can be found in this booklet or on the BABS website. A total of five potential supervisors and projects must be selected and ranked in order of preference on the application form, bearing in mind that each supervisor has a limited capacity to take on new students. At least three choices must be from within BABS: a maximum of two choices may be external supervisors/ projects. Applicants will be allocated to supervisors based on academic merit and available resources.

Once you have decided which supervisors you wish to contact for further discussion, email is the preferred method of contact. It is essential to spend some time with prospective supervisors to discuss the details of a project before submitting your preferences. In your email, please ensure that you:

(a) Identify which research project/s you are interested in, and why
(b) Indicate which term you intend on commencing Honours (Term 1, 2 or 3)
(c) Advise your availability times for a face-to-face interview
(d) Attach a copy of your CV and academic transcript

Applicants in a UNSW embedded Honours program

e.g. Bachelor of Biotechnology (Honours), Advanced Science (Honours)

Complete the Category B 'Intention to Undertake Honours' form available on the Science Student Centre website:
science.unsw.edu.au/honours-apply

Internal UNSW applicants and external applicants

Applying for 4500 Honours

1. Complete the Category A 'Intention to Undertake Honours' form available on the Science Student Centre website:
science.unsw.edu.au/honours-apply

2. Apply for 4500 Science (Honours) on this website:
applyonline.unsw.edu.au

International students need to follow the steps on the UNSW International Office 'How to Apply' page:
international.unsw.edu.au/apply
(State that you are applying for Honours only).

Intention to Undertake Honours form due date

Please refer to Science Faculty Website
Honours: How to apply

Honours inquiries

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Please note that applications for honours will be accepted only when five supervisor and project preferences are listed.

GENOMICS AND BIOINFORMATICS

CLUSTER STRENGTHS:

- **Gene Regulation**
- **Systems Biology**
- **Neuogenomics**

Genomics and Bioinformatics is an invaluable hybrid of science, concerning the structure and function of genomes and the use of computational technology to capture and interpret biological data. While scientists previously focused on singular cells, the enormous development in bioinformatics over the last decade has enabled us to study cells on a mass scale.

We are focused on enabling medical breakthroughs and clinical application with our access to cutting- edge computational biology. UNSW Biotechnology and Biomedical Sciences houses the Ramaciotti Centre for Genomics, the largest and most comprehensive genomics facility at any Australian University with an extensive suite of bioinformatics tools and next generation sequencing.

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RESEARCH FOCUS

Transcription factors and gene regulation in blood cells.

Suitable for students who have majored in Molecular Biology, Genetics, Biochemistry or Biotechnology.

We study how transcription factors control cell fate and how the breakdown of this process leads to disease. We apply this knowledge with the ultimate aim of developing the next generation of artificial transcription factors and to develop new therapeutic strategies for blood diseases. Currently, our collaborative research group includes 7 PhD students and 2 Honours students. Two Honours positions will be available for 2023.

PROJECT 1
ENGINEERING THE NEXT GENERATION OF ARTIFICIAL TRANSCRIPTION FACTORS

The ability to artificially regulate gene expression offers immense promise for the treatment of human diseases. In this project, we will apply knowledge of how natural transcription factors regulate their target genes to engineer a new generation of more potent artificial factors.

PROJECT 2
REGULATING GLOBIN EXPRESSION: A POTENTIAL THERAPY FOR SICKLE CELL ANAEMIA AND THALASSAEMIA

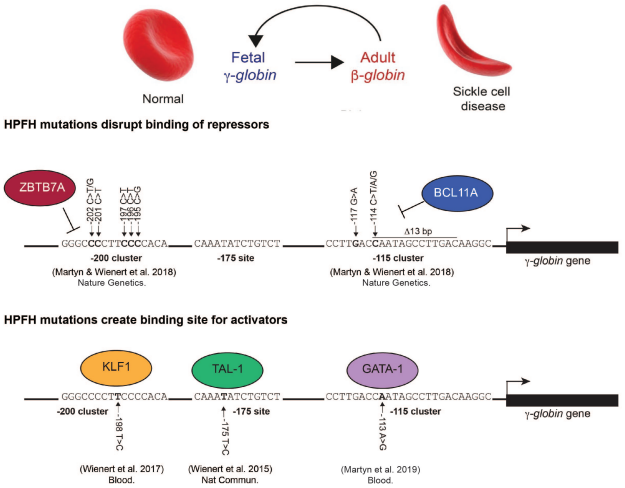
Sickle cell anaemia and thalassaemia are debilitating blood diseases that arise due to mutations in adult globin genes. In this project, we will investigate the networks involved in developmental regulation of globin gene expression, with an ultimate aim of reactivating the foetal globin genes.

Techniques

All projects offer the opportunity to learn a wide variety of molecular biology techniques, including chromatin immunoprecipitation (ChIP), western blotting, gel shifts, subcloning and bacterial transformation, site directed mutagenesis, CRISPR/Cas9 genome editing, PCR and real-time PCR, microarrays and next-generation technologies (RNA-seq and ChIP-seq), tissue culture, transient and stable transfections of mammalian cells, reporter gene assays and flow cytometry.

Recent publications

» 'Disrupting the adult globin promoter alleviates promoter competition and reactivates fetal globin gene expression.' Blood, 2022, 139(14):2107-2118
» 'Methylation of a CGATA Element Inhibits Binding and Regulation by GATA-1', Nature Communications, 2020, 11(1):2560
» 'Natural regulatory mutations elevate the fetal globin gene via disruption of BCL11A or ZBTB7A binding.' Nature Genetics, 2018 50(4):498-503
» 'Transcription factors LRF and BCL11A independently repress expression of fetal hemoglobin', Science, 2016, 351(6270):285-9
» 'Directing an artificial zinc finger protein to new targets by fusion to a non-DNA-binding domain', Nucleic Acids Research, 2016, 44(7):3118-30



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RESEARCH FOCUS

Human transcriptome, circular RNAs, neurological disorders and cancer, biomarkers of complex diseases.

Suitable for students who have majored in Biochemistry, Molecular Biology or Genetics.

Our research focuses on studying transcriptome in the human brain and peripheral tissues using short- and long-read RNA sequencing. We are particularly interested in the role of circular RNAs (circRNAs), linear RNA splicing patterns and RNA modifications in regulation of molecular physiology of human tissues. Moreover, we aim at identifying RNA transcripts which can serve as biomarkers of early onset of human complex diseases including neurological disorders and cancer.

PROJECT 1
INVESTIGATION OF TISSUE-SPECIFIC EXPRESSION OF CIRCULAR RNAs IN THREE MAMMALIAN SPEICIES

Recent advances in RNA sequencing technology allowed discovery of a new RNA species, circular RNAs (circRNAs; Figure 1). CircRNAs have been identified as a naturally occurring family of widespread and diverse endogenous noncoding RNAs that may regulate gene expression in mammals (Huang et al. 2017) and are perturbed as a result of neurodegeneration and cancer (Chen et al. 2016). They are unusually stable RNA molecules with cell type- or developmental stage-specific expression patterns.
Thousands of circRNAs have been identified, with the majority of studies sequencing brain and disease tissue samples. There is however an urgent need to understand circRNA expression patterns and their properties in peripheral, non-brain, healthy tissues not only in humans but also in other mammalian species used as experimental models for investigation of complex diseases. To address this challenge the project aims focuses on investigation of circular transcriptome landscapes in ten different peripheral tissues types derived from three mammalian species, including human, macaque and mouse.

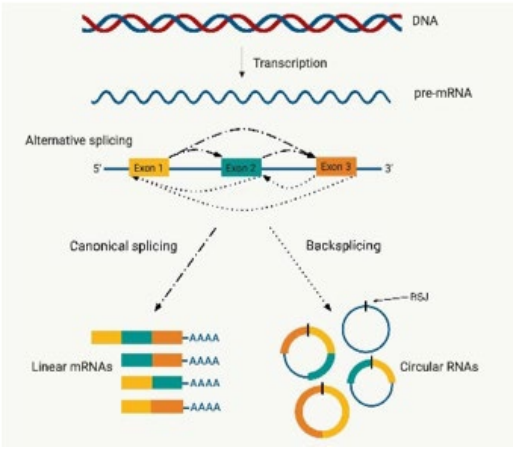

Figure 1. The formation of linear mRNAs and circular RNAs through canonical splicing and backsplicing, respectively. The mechanism of backsplicing leads to covalent linkage of the downstream 3'-end of a pre-mRNA sequence to an upstream 5'-end of the pre-mRNA strand. This process leads to generation of a backspliced junction (BSJ), denoted by the black line in circular isoforms, whoch is a unique feature of circRNAs. Linear mRNAs are formed through the canonical splicing pro-cess whereby introns are excised from the pre-mRNA strand, forming exonic isoforms of linear mRNA with no BSJ (adapted from Curry-Hyde et al. 2019).

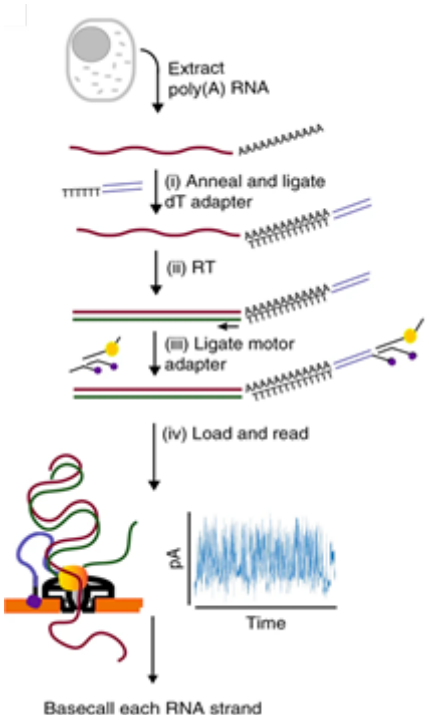

Figure 2. Principles of direct RNA sequencing using Oxford Nanopore technology (adapted from Workman et al. 2019).

PROJECT 2
EXPLORATION OF BREAST CANCER TRANSCRIPTOME USING NANOPORE DIRECT RNA SEQUENCING

Nanopore direct RNA sequencing technology has just only recently become available for genomic research. This revolutionary technique allows to investigate human transcriptome, including mitochondrial one, at an unprecedented resolution. Nanopore RNA sequencing differs from Illumina short-read RNA sequencing technology platform in that native RNA nucleotides, rather than copied DNA nucleotides, are identified as they thread through and touch a nanoscale sensor. Nanopore direct RNA sequencing shares the core features of nanopore DNA sequencing where a processive helicase motor regulates movement of a bound polynucleotide driven through a protein pore by an applied voltage. As the polynucleotide advances through the nanopore in single-nucleotide steps, ionic current impedance reports on the structure and dynamics of nucleotides in the channel as a function of time. This continuous ionic current series is converted into nucleotide sequence using a neural network algorithm trained with known RNA molecules (Figure 2).
Breast cancer is the leading cause of cancer-related death in women, worldwide. It is a heterogeneous malignancy with regard to molecular alterations, cellular composition, and clinical outcome, both between tumour subtypes and within a single tumour. Invasive ductal carcinoma (IDC) is the most common type of breast cancer as about 80% of all breast cancers are invasive ductal carcinomas. Despite numerous studies investigating gene expression profiles in IDC almost nothing is known about aberration of alternative splicing and epigenetic modifications of mRNAs specifically expressed in this malignancy. Therefore, the aim of this project is to apply nanopore direct RNA sequencing technique for discovery of novel transcriptional isoforms and RNA modification patterns in IDC.

References:

» Chen BJ, Mills JD, Takenaka K, Bliim N, Halliday GM & Janitz M (2016) Characterization of circular RNAs landscape in multiple system atrophy brain. J Neurochem, 139:485-496.
» Curry-Hyde A, Ueberham U, Arendt T & Janitz M (2020) Neural circular transcriptomes across mammalian species. Genomics, 112:1162-1166..
» Huang S, Yang B, Chen BJ, Bliim N, Ueberham U, Arendt T & Janitz M (2017) The emerging role of circular RNAs in transcriptome regulation. Genomics, 109:401-407.
» Workman ER, Tang AD, Tang PS, Jain M, Tyson JR, Razaghi R, Zuzarte PC, Gilpatrick T, Payne A, et al. (2019) Nanopore Native RNA Sequencing of a Human poly(A) Transcriptome. Nat Methods, 16:1297-1305.

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RESEARCH FOCUS

RNA at the immune interface; regulation of the immune response by RNA, transposable elements, RNA sensing and type-1 interferons in immune responses and autoimmune disease.

One of the most intriguing aspects of the immune system is its ability to react to foreign invaders, but not to self. To distinguish healthy cells (self) from infected cells or pathogens, the immune system utilizes multiple receptors and signalling pathways that enable specific recognition of proteins and nucleic acids. Recognition of foreign RNA occurs inside cells and depends upon unique features of pathogen RNA that allow our RNA sensors to see it as foreign. However, for some people, the immune system reacts inappropriately to self-RNA and this can trigger autoimmunity. The achievement of self-tolerance is even more impressive when we consider that we are colonized by multiple microbial species that are important for our health, and our genomes harbour an abundance of retrovirally sourced nucleic acid acquired from past encounters with retroviruses, known as retroelements. Whilst a challenge for self-tolerance, the retention of retroelements in the genome has been shown to serve multiple regulatory functions that influence the transcription of protein coding genes. Our own work has shown that retroelements can function to neutralise the deleterious effects of duplicated genes in immune gene families, favouring host survival during virus infection. We are employing both an inside and outside approach to study RNA in the immune system-by studying how the immune system senses RNA during immune responses and how retroelement RNA's regulate immune responses.

PROJECT 1 THE ROLE OF RETROELEMENTS IN REGULATION OF IMMUNE RESPONSES

Only about 1-2% of our genome is made up of protein coding genes, the rest is non-coding and about a half of that is made up of mobile DNA sequences known as transposable elements (TEs). Despite their abundance, we know very little about the function of TEs. The notion of TEs as genomic controlling elements was first revealed over six decades ago, when TEs were shown to alter gene expression in maize. Subsequent advances in sequencing technologies have revealed the striking abundance of TEs that harbour promoters, enhancers and transcription factor binding sites suggesting that TEs have been co-opted to regulate mammalian gene expression and cell phenotype. Our lab is interested in the function of TEs in the immune system. We are particularly interested in class I TE's known as retroelements as they have an evolutionary relationship with retroviruses. Our work has shown that retrotransposons regulate the immune response to virus infection and have been conserved over evolutionary time to improve host survival. The overarching objective of this research proposal is to determine the form and function of retroelements in the regulation of immune genes and networks during the immune response.

PROJECT 2 RNA SENSING IN HEALTH AND DISEASE

Ribonucleic acid (RNA) plays a central role in turning genetic information into your body's proteins. This remarkable molecule carries the genetic instructions for organisms including viruses. RNA viruses are recognised by the immune system by receptors inside cells, namely retinoic acid inducible (RIG-I) and melanoma differentiation-associated protein 5 (MDA-5). These receptors act to recognise RNA viruses, but they can also react to our own (self) RNA. We believe that the ability of self-RNA to trigger these receptors underlies the development of chronic inflammation and autoimmune disease. Accumulating evidence supports the association between human diseases and an entire network of RNA sensing genes in the immune system. In the context of autoimmunity, these studies pose the question of whether it is the type of RNA that triggers autoimmunity or differences in the functions of RNA signalling pathways. This project is designed to further our understanding of the immune stimulating features of RNA and how the pathways involved in RNA sensing are regulated in health and disease.

More detailed information on specific projects and ongoing research is available at:
https://www.babs.unsw.edu.au/cecile-king

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RESEARCH FOCUS

Human disease gene discovery, mutation-impact analysis and therapy development using state-of-the-art genetic sequencing technologies.

Suitable for students who have majored in Genetics, Molecular and Cell Biology or Microbiology.

Our research is focused on the discovery of new human disease genes, and analysis of the clinical-, RNA transcript-, protein- and tissue-level impacts of disease-causing mutations within known and emerging human disease genes. We use this information to increase genetic diagnosis rates for affected individuals and their families, to advance our understanding of the clinical characteristics, natural history, and underlying pathogenesis of the genetic disorders we study, and to develop potential new therapies for these disorders.

Our main area of research interest is the discovery of new genes responsible for congenital muscular dystrophies (CMDs) and congenital myopathies (CMYOs). CMDs and CMYOs are primary genetic muscle disorders affecting babies and young children. They cause significant muscle weakness and physical disability and can result in early death. Around half of all children with CMD/CMYO still do not have genetic diagnosis. In many cases this is because the causative gene has not yet been identified. In addition, there are no available treatments to prevent, halt, or slow the progression of most forms of CMD/CMYO – eve n when the genetic basis is known.

TEAM AREA OF INTEREST 1. CONGENITAL MYOPATHY/ DYSTROPHY DISEASE GENE DISCOVERY USING STATE- OF THE-ART GENOMIC SEQUENCING TECHNOLOGIES.

Our team offers projects that involve in-depth analysis of whole exome and whole genome massively parallel sequencing data from children with early-onset muscle disorders (e.g. CMD and CMYO) who do not currently have a genetic diagnosis despite extensive investigation. Patient sequencing data is analysed via a web-based portal in parallel with sequencing data from both unaffected parents ("trio analysis") in order to increase the chance of identifying the causative mutation(s). If potentially pathogenic variants in possible new disease genes are identified, students draw on existing literature and database-accessible information to determine the biological plausibility of the gene as a new muscle disease gene (e.g. Is the gene expressed in muscle? Does the gene encode a protein involved in a pathway known to be altered in other muscle diseases?). Students will so determine the likely pathogenicity of their variants of interest using (1) in silico-based, RNA-seq and protein-based analytical techniques, and (2) by finding additional patients with mutations within the same gene via our well-established collaborator network and clinical 'matchmaking' programs. Depending on the interests of the student and the discoveries made, these projects may extend to involve comprehensive clinical description of newly-identified disorders, cell-based functional assays, and/or animal studies undertaken in collaboration with other teams.

TEAM AREA OF INTEREST 2: ADVANCING OUR UNDERSTANDING OF NORMAL MUSCLE ISOFORM BIOLOGY AND MUSCLE DISEASE PATHOGENESIS USING STATE-OF-THE ART TRANSCRIPTOMIC (RNA-SEQ) TECHNOLOGIES

Our team also offers projects that involve analysis of control and disease striated (cardiac and skeletal) muscle transcriptomic (RNA-seq) data to determine (1) normal patterns of splicing and isoform/exon usage at various stages of development, as well as (2) abnormal splicing patterns and/or abnormal isoform/ exon usage caused by patient mutations. This area of research is greatly expanding our understanding of normal muscle isoform biology and genetic muscle disease pathogenesis. Data generated by these projects will also be used to inform the development of muscle-disease-focussed exon-skipping drug therapies aimed at "skipping" disease-causing mutations but retaining critical (highly used) neighbouring exons.

TEAM AREA OF INTEREST 3: ADVANCING OUR UNDERSTANDING OF DISORDERS CAUSED BY TTN (TITIN) MUTATIONS ("THE TITINOPATHIES")

This series of projects involves the use of state-of-the-art genomic and transcriptomic technologies, as well as detailed clinical phenotyping and natural history analyses, to advance our understanding of "The titinopathies". These are an important emerging group of cardiac and skeletal muscles disorders caused by mutations in one of the largest genes in nature – TTN (titin). This gene was much too large to be comprehensively sequenced on a routine diagnostic basis prior to the advent of massively parallel sequencing technology (MPS). MPS-facilitated diagnostic sequencing of TTN has revealed that mutations in this gene cause a number of important skeletal muscle and cardiac disorders. In fact, it now appears that congenital titinopathy, the most severe titinopathy, is the most common congenital myopathy (CMYO) worldwide. In addition, dominant TTN truncating mutations are the most common genetic cause of adult-onset dilated cardiomyopathy. In collaboration with an international army of clinicians and researchers, we have established a large cohort of titinopathy patients, 30 of which were described in a recent high impact publication (Oates et. al, Congenital titinopathy: comprehensive characterisation and pathogenic insights. Ann Neurol, 2018). The goal of this area of research is to broaden our understanding of the clinical, muscle pathology and imaging features, and the biological basis of this important group of disorders. These projects would suit a medical student, or a science student with an interest in human genetic diseases. The focus can be tailored to the specific interests of the student.

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RESEARCH FOCUS

Cancer Testis Antigens, their regulation and roles as RNA-binding proteins in development and cancer.

Suitable for students who have majored in Genetics, Molecular Biology, Biotechnology and Bioinformatics.

How a complex, multicellular organism develops from a single fertilised egg is among the most intriguing concepts in biology. This phenomenon is further augmented by the fact that metazoan organisms consist of many distinct cell types that largely differ in their morphology, function and gene expression patterns, yet contain identical genomic DNA. Nowadays, we know that such a vast variety of cell types is generated and maintained by mechanisms that in most cases do not involve alterations in the primary DNA sequence. One such epigenetic mechanisms is DNA methylation. Our interest in DNA methylation stems from the fact that this epigenetic mark can be stably propagated through cell division and that the presence or absence of DNA methylation correlates well with the activity of regulatory regions.

We have recently shown that a surprisingly small number of genes becomes silenced by promoter DNA hypermethylation during early vertebrate embryogenesis (zebrafish, mouse and human). Among these genes we found several Cancer Testis Antigens (CTAs) such as ddx4, dazl, elavl2 and zar1l. CTAs are a highly immunogenic protein family predominantly expressed in the male germline. Malignant transformation during oncogenesis results in aberrant CTA expression in cancerous tissues, however the exact role of CTAs remains unclear. CTAs are implicated in diverse biological processes such as: germline defence, meiosis, DNA repair, and transcriptional regulation. Due to their highly specific expression patterns and their ability to provoke strong immune responses, CTAs form excellent targets for cancer immunotherapy. We hypothesise that this highly specific DNA methylation-mediated silencing event is evolutionarily conserved due to the potentially deleterious effects that the reactivation of CTAs might have on somatic cellular integrity. Interestingly, almost all evolutionarily conserved CTA genes targeted by DNA methylation code for RNA binding proteins. The impact of these proteins on transcriptome complexity is currently unknown. Through a combination of molecular, cellular, computational as well as zebrafish transgenesis approaches we are trying to understand the roles of these genes in embryonic development and cancer formation in vivo.

1. Identification of CTAs transcriptomic binding sites in pluripotent and germline tissues (CTAs not silenced) during zebrafish development.

This project will focus on elucidating which RNAs are elavl2 and zar1l proteins (2 different CTAs) binding to during development. Whereas zar1l is mainly expressed in oocytes, early embryos and germ cells, elavl2 is also expressed in the developing central nervous system.

We will employ RIP-seq and iCLIP (Individual-nucleotide resolution UV crosslinking and immunoprecipitation), on pluripotent embryos (blastula, 128 cell) and germ cells, both of which are conditions where both CTAs are highly expressed and unmethylated. We will also perform RIP-seq/iCLIP in developing central nervous system samples where only elavl2 is expressed and unmethylated. You will gain skills in microscopy, advanced molecular biology, next generation sequencing and zebrafish handling/ techniques. This project involves both wet lab and dry lab work and the use of animal models (zebrafish).

2. Identification of ectopically expressed CTAs contribution to melanoma.

This project will focus on elucidating how ectopic expression of elavl2 and zar1l proteins contributes to melanoma formation and evolution. Human melanoma cell lines ectopically expressing elavl2 or zar1l will be used along with a series of reporters such H2B-mCherryFP and FUCCI (Fluorescence Ubiquitin Cell Cycle Indicator) to quantify cell proliferation, cell migration, invasion, drug response and cell cycle dynamics. There is also the possibility, depending on preliminary results, to perform RNA-seq to match the "overexpression phenotype" with changes in genes expression and/or Rip-seq to find out what RNAs are elavl2 and zar1l proteins binding to in melanoma cell lines. Alternatively, xenograft experiments in zebrafish to study tumour induced angiogenesis and metastasis will be done. You will gain skills in cell culture, live-cell microscopy and cellular and molecular biology techniques. This project involves mainly wet lab but, depending on the candidate preferences could also include dry lab.

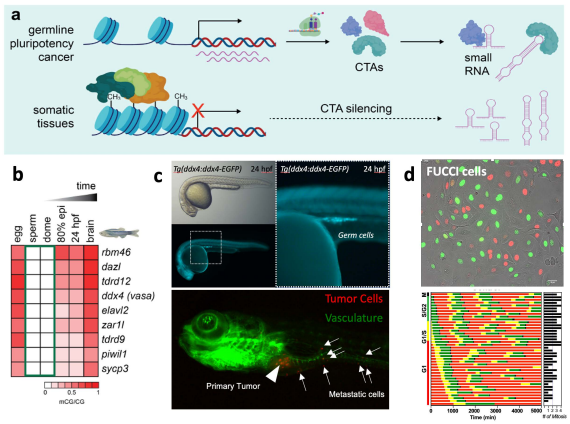

Figure 1. a) CTA regulation in normal and cancerous tissues and CTA-RNA interactions. b) 5mC-mediated silencing of CTAs in zebrafish. c) germ cells in a 24 hpf zebrafish embryo and 8 dpf zebrafish larvae showing metastasis from primary tumour (xenograft). d) FUCCI cells and cell cycle dynamics determined by live-imaging FUCCI cells over 72 hours.

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RESEARCH FOCUS

Computational Biomedicine, Systems Biology, Bioinformatics.

Big data and artificial intelligence – driving personalised medicine of the future

Big data has become a ubiquitous watchword of biomedical innovation advocating deployment of advanced data-driven artificial intelligence techniques and systems thinking to revolutionise biomedical research and practice. I lead AI- empowered Biomedicine Laboratory where we cutting-edge innovative machine-learning and network science methodologies to leverage large-scale molecular and clinical data to find hidden structures within them, account for complex interactions among the measurements, integrate heterogeneous data and make accurate predictions in different biomedical.
Honours students will be involved in cutting-edge multidisciplinary and collaborative ongoing research projects and encouraged to publish their research outcome. My research program focuses on three topical areas of

1. Minimally invasive biomarker discovery for personalised medicine and precision therapy

Recent advances in high-throughput technologies have provided a wealth of genomics, transcriptomics, and proteomics data to decipher disease mechanisms in a holistic and integrative manner. Such a plethora of -omics data has opened new avenues for translational medical research and has particularly facilitated the discovery of novel biomarkers for complex diseases such as cancers. My research lab – in close collaboration with experimentalists, clinicians, and oncologists – is adopting an innovative multi-disciplinary approach to tackle one of the biggest challenges of personalised cancer medicine, that is to identify robust and reproducible biomarkers in a minimally invasive way. We are integrating multiple data sources, network and temporal information using advanced machine learning and deep learning approaches to better understand the molecular complexity underpinning pathogenesis and to identify novel, precise and reproducible blood-based biomarkers for disease early-detection, diagnosis, prognosis and drug responses paving the way for personalised medicine.

2. Single-cell sequencing data analysis and integration

Cellular heterogeneity is one of the main clinical drivers of the current inefficiency in treating cancer and other complex diseases as molecular-based prescriptions or personalised medicine have often relied on bulk pro/filing of cell populations, masking intercellular variations that are functionally and clinically important. In recent years, however, there has been an increasing effort in shifting the focus from bulk to single-cell profiling. Single-cell sequencing will have a major global impact on the precision medicine through detecting rare disease-associated cells and identifying cell-type-specific biomarkers and therapeutic targets. Single cells, however, make 'big data', provoking substantial analytical challenges to decipher underlying biological and clinical insights. Hence, there is an emerging demand for scalable yet accurate analysis pipelines for rapidly increasing single-cell sequencing data and my research program is focused (during the last 18 months) to contribute to this significant field.

3. Computational drug repositioning and network pharmacology

Repositioning existing drugs for new indications is an innovative drug development strategy offering the possibility of reduced cost, time and risk as several phases of de-novo drug discovery can be bypassed for repositioning candidates.
Biopharmaceutical companies have recognised advantages of repositioning, and investment in the area is dramatically increasing. With the rapid advancement of high-throughput technologies and the explosion of various biological
and medical data, computational drug repositioning has become an increasingly powerful approach to systematically identify potential repositioning candidates. My lab is one of the few across Australia, advancing the field of computational drug repositioning. We are developing computational tools and databases which integrate massive amounts of biological, pharmacological and biomedical information related to compounds into advanced machine learning or network-based models to predict accurate repositioning candidates.

Selected References:

» Azad AKM, Dinarvand M, Nematollahi A, Swift J, Lutze-Mann L, Vafaee F (2020), 'A Comprehensive Integrated Drug Similarity Resource for In-Silico Drug Repositioning and Beyond', Briefing in Bioinformatics, doi:10.1093/bib/bbaa126.

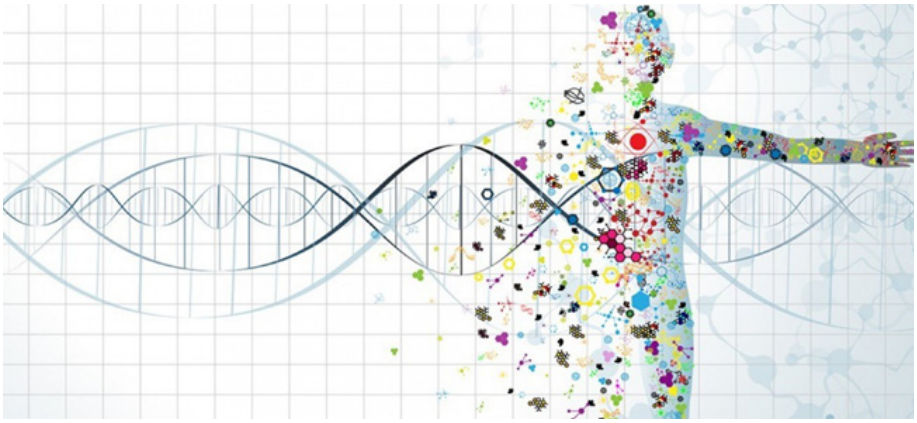
» Vafaee F; Diakos C; Kirschner M; Reid G; Michael M; Horvath LISA; Alinejad-Rokny H; Cheng ZJ; Kuncic Z; Clarke S, 2018, 'A data-driven, knowledge-based approach to biomarker discovery: application to circulating microRNA markers of colorectal cancer prognosis', npj Systems Biology and Applications, vol. 4, pp. 20 - 20, http://dx.doi.org/10.1038/s41540-018-0056-1

» Colvin EK; Howell VM; Mok SC; Samimi G; Vafaee F, 2020, 'Expression of long noncoding RNAs in cancer-associated fibroblasts linked to patient survival in ovarian cancer', Cancer Science, vol. 111, pp. 1805 - 1817, http://dx.doi.org/10.1111/cas.14350

» Ebrahimkhani S; Beadnall HN; Wang C; Suter CM; Barnett MH; Buckland ME; Vafaee F, 2020, 'Serum Exosome MicroRNAs Predict Multiple Sclerosis Disease Activity after Fingolimod Treatment', Molecular Neurobiology, vol. 57, pp. 1245 - 1258, http://dx.doi.org/10.1007/s12035-019-01792-6

» Chaudhuri R; Krycer JR; Fazakerley DJ; Fisher-Wellman KH; Su Z; Hoehn KL; Yang JYH; Kuncic Z; Vafaee F; James DE, 2018, 'The transcriptional response to oxidative stress is part of, but not sufficient for, insulin resistance in adipocytes', Scientific Reports, vol. 8, http://dx.doi.org/10.1038/s41598-018-20104-x

» Ebrahimkhani S; Vafaee F; Young PE; Hur SSJ; Hawke S; Devenney E; Beadnall H; Barnett MH; Suter CM; Buckland ME, 2017, 'Exosomal microRNA signatures in multiple sclerosis reflect disease status', Scientific Reports, vol. 7, http://doi.org/10.1038/s41598-017-14301-3



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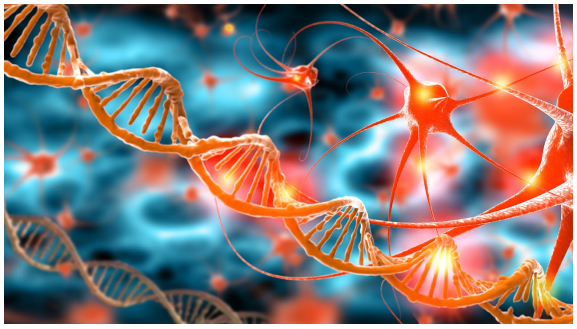
RESEARCH FOCUS

Genetics of neurodevelopmental disorders, human brain transcriptome dynamics in normal and disease states.

Suitable for students who have majored in Molecular Biology, Biotechnology or Bioinformatics.

The research in the Voineagu lab employs a combination of molecular biology, cell biology and bioinformatics. Honours projects are particularly suited for motivated students interested in neurogenetics and genomics. Honours students are involved in all aspects of our ongoing research and are encouraged to publish their work.

Theme 1: Uncovering the mechanisms that regulate gene expression in the human brain in health and disease.



PROJECT 1.1
BRAIN ON A DISH - MODELING NEUTODEVELOPMENT *IN-VITRO*

Brain organoids are three-dimensional cell culture systems that allow the development of brain-like structures *in-vitro,* and can recapitulate elements of brain development. This project offers the exciting opportunity to work closely with a PhD student on developing brain organoids from human induced pluripotent stem cells carrying mutations in the ZMYND8 gene, a gene that has been recently discovered as mutated in intellectual disability.

Skills gained: basic molecular biology, advanced cell culture. **Knowledge gained:** neurogenetics, cellular neuroscience. **Wet/Dry:** wet lab only.

PROJECT 1.2
DISCOVERING NOVEL ENHANCERS THAT REGULATE GENE EXPRESSION IN THE HUMAN BRAIN

Enhancers are distal regulatory regions that finely-tune gene expression during development and across cell types. We are carrying out a large-scale CRISPRi screen to discover novel enhancers in neuronal and glial cells. This project will focus on validating a set of enhancers identified by the CRISPRi screen using genome editing as well as luciferase reporter assays.

Skills gained: advanced molecular biology, basic cell culture, genome editing. **Knowledge gained:** gene expression regulation, transcriptomics, single-cell RNA-seq **Wet/Dry:** primarily wet lab; minor bioinformatics component.

PROJECT 1.3
EXPLORING THE NUCLEAR TRANSCRIPTOME AT SINGLE-CELL LEVEL

This project will utilise data already generated in the lab, which includes single-cell (sc) and single-nucleus (sn) RNA-seq from human primary astrocytes transduced with a pool of guide RNAs targeting enhancers and promoters. The project will test the hypothesis that snRNA-seq better captures the effect of CRISPRi-mediated gene silencing than scRNA-seq.

Skills gained: advanced transcriptomics, including scRNA-seq. **Knowledge gained:** gene expression regulation, transcriptomics, single-cell RNA-seq. **Wet/Dry:** bioinformatics only

Theme 2: Elucidating the biogenesis and function of circular RNAs in the human brain.

PROJECT 2.1
UNCOVERING THE ROLES OF CIRCULAR RNAs IN THE BRAIN THROUGH CO-EXPRESSION NETWORKS

Circular RNAs are a class of primarily non-coding RNA molecules that result from back-splicing, and are highly enriched in the brain. This project will employ co-expression networks to uncover the relationship between circRNA, mRNA and miRNA expression in the human brain.

Skills gained: advanced molecular biology, basic cell culture, genome editing. **Knowledge gained:** gene expression regulation, transcriptomics, single-cell RNA-seq. **Wet/Dry**: primarily wet lab

PROJECT 2.2 USING CAS13 PROTEIN TO KNOCK-DOWN CIRCULAR RNAs AND TO UNCOVER THEIR ROLES IN BRAIN CELLS

This project will explore the ability of novel molecular tools - the Cas13 family of nucleases - to knock-down circular RNAs by specifically cleaving the back-spliced junction. This approach will then be used to assess the effect of circRNA knock-down on gene expression in brain cells.

Skills gained: advanced molecular biology, basic cell culture, genome editing. **Knowledge gained:** gene expression regulation, transcriptomics, single-cell RNA-seq. **Wet/Dry:** primarily wet lab

Relevant publications:

- Coexpression networks identify brain region-specific enhancer RNAs in the human brain. Yao P, Lin P, Gokoolparsadh A, Assareh A, Thang MW, Voineagu I. Nat Neurosci. 2015 Aug;18(8):1168-74. doi: 10.1038/nn.4063.
- Chromosome conformation elucidates regulatory relationships in developing human brain. Won H, de la Torre-Ubieta L, Stein JL, Parikshak NN, Huang J, Opland CK, Gandal MJ, Sutton GJ, Hormozdiari F, Lu D, Lee C, Eskin E, Voineagu I, Ernst J, Geschwind DH. Nature. 2016 Oct 27;538(7626):523-527. doi: 10.1038/nature19847.
- Circular RNAs: The Brain Transcriptome Comes Full Circle. Gokool A, Loy CT, Halliday GM, Voineagu I. rends Neurosci. 2020 Oct;43(10):752-766. doi: 10.1016/j.tins.2020.07.007.

More detailed information on projects and ongoing research is available on the lab website:
www.voineagulab.unsw.edu.au

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RESEARCH FOCUS

Sex chromosome structure, function, regulation and evolution.

Suitable for students who have majored in Genetics, Molecular Biology and and Bioinformatics.

We work on unusual model species that are uniquely placed in the vertebrate phylogeny to unravel mysteries surrounding the evolution of sex chromosomes and their epigenetic regulation.

PROJECT 1
DNA METHYLATION AND X CHROMOSOME INACTIVATION

Dosage compensation is required to balance gene expression from the X chromosome between males (which only have one X) and females (with two Xs). X chromosome inactivation (XCI) is one aspect of dosage compensation, and is arguably the most spectacular example of epigenetic silencing in mammalian genomes. After decades of work in the field, we have recently demonstrated that DNA methylation is important to marsupial XCI.

This project will focus on the developmental timing of when unique patterns of DNA methylation (using whole genome bisulfite sequencing) are established on the inactive X chromosome. This project will be a world first in the field of mammalian X chromosome inactivation.

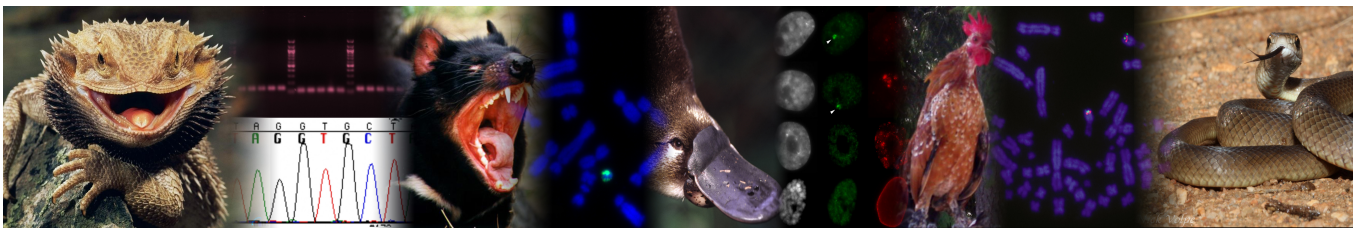
PROJECT 2
THE RNA BIOLOGY OF SILENCING WHOLE CHROMOSOMES

In the somatic cells of female placental mammals, a characteristic signature of epigenetic modifications accumulates on, and transcriptionally silences, one of the two X chromosomes (a process called X chromosome inactivation). It is known that long non-coding RNAs (lncRNAs) are central for directing the epigenetic machinery, which deposit these epigenetic modifications, to target.

This project will examine the lncRNAs the mediate epigenetic regulation of the X chromosome in model species, resulting in a critical understanding of how silencing of the X evolved. Techniques you will use for this project include: knockdown of critical proteins, RNA-FISH and immunofluorescence.

PROJECT 3
THE EPIGENETICS OF SEX DETERMINATION

There are essentially two different ways to determine if an embryo develops as male of female: 1) genetic sex determination, where genes on sex chromosomes trigger male of female developmental pathways. 2) temperature dependent sex determination, where the incubation temperature of the egg determines which development path will be triggered.
In one unusual species, the Australian central bearded dragon, there is a murky line where genetic sex determination can be overridden by temperature dependent sex determination. The aim of this project is to uncover the epigenetic mechanisms of how this happens. This world first project will provide critical insight into the mechanism of vertebrate sex determination.



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RESEARCH FOCUS

RNA and phenotypic complexity: how regulation of RNA impact protein function; alternative splicing; membraneless organelles; CRISPR single cell screens.

Research Program:

An important question in biology is how the complexity of biological systems has expanded while the number of protein coding genes has remained largely stable. Decades of research has shown that increased biological complexity has arisen in part by the dynamic generation of unique, cell-specific transcriptomes, as well as the dynamic sub-cellular control of these transcripts. Alternative splicing (AS) - the process by which multiple, distinct transcript and protein variants are expressed from a single gene – is a key driver of transcriptome complexity regulating more than 95% of multi-exon genes. However, the functional flexibility and complexity afforded by AS, and other post-transcriptional regulation, comes at a cost, since it increases the probability that RNA mis-splicing may arise and lead to human disease. By developing novel state-of-the-art genomic tools and large-scale screening approaches, my work has revealed instances in which splicing misregulation impacts both neurodevelopmental and somatic disorders.

Research Projects:

PROJECT 1

Alternative splicing and membraneless organelles in neuronal differentiation. This project will investigate the role of RNA in regulating the function of membraneless organelles and its role in controlling neuronal differentiation, as well as its implications on neurodevelopmental disorders.

PROJECT 2

Membraneless organelles and chemoresistance. This project will aim to understand the role of stress granules and P-bodies in chemoresistance.

PROJECT 3

Developing deep learning algorithms to discern impact of epitranscriptomic modifications on the genome. This project will develop algorithms to understand the genetic code controlling RNA modifications identified by nanopore long-read data.

Relevant recent publications:

Evolution of splicing:

"Evolutionary dynamics of circular rnas in primates" ELife (2021),
"Multilayered control of exon acquisition permits the emergence of novel forms of regulatory control" Genome Biology (2019)

Membraneless organelles:

"Systematic mapping of nuclear domain-associated transcripts reveals speckles and lamina as hubs of functionally distinct retained introns" Molecular Cell (2022),
"Regulatory expansion in mammals of multivalent hnRNP assemblies that globally control alternative splicing" Cell (2017)

Splicing and neuroscience:

"Differential contribution of transcriptomic regulatory layers in the definition of neuronal identity" Nature Communications (2021);
"Autism-misregulated eIF4G microexons control synaptic translation and higher order cognitive functions" Molecular Cell (2020)
"A highly conserved program of neuronal microexons is misregulated in autistic brains". Cell (2014);

Splicing algorithms:

"Efficient and accurate quantitative profiling of alternative splicing patterns of any complexity on a laptop" Molecular Cell (2018)
"The ribosome-engaged landscape of alternative splicing" Nature SMB (2016).

More information: https://weatheritt2.github.io

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RESEARCH FOCUS

Discovery and functional characterisation of intracellular networks.

Wet-lab projects suitable for students who have enjoyed their studies in biochemistry or molecular biology.

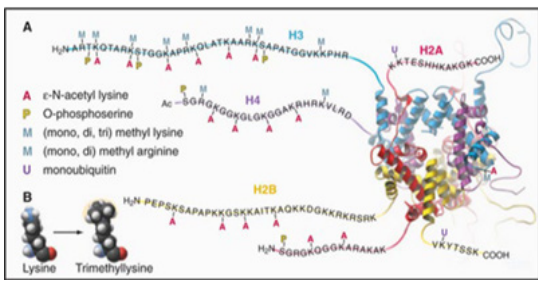
Dry-lab projects also available for students who enjoy bioinformatics and have some relevant IT skills.

Almost all proteins interact with other proteins to deliver their function. These form intricate networks, including protein-protein interaction networks and signalling systems, which are critical for the regulation of the cell.

Currently, we are focused on two particular projects. The first
project aims to discover the regulatory network of histones. This has a strong biological focus and is seeking to address a remarkable gap in our understanding of histone-mediated effects on gene expression. This project is a wet lab project. The second project aims to address a 'grand challenge' – to measure all interactions between proteins in a cell, in a single experiment.
This has a more technical focus and we have wet lab and dry lab (bioinformatics) researchers working on this project. We welcome all enthusiastic students to join the team!

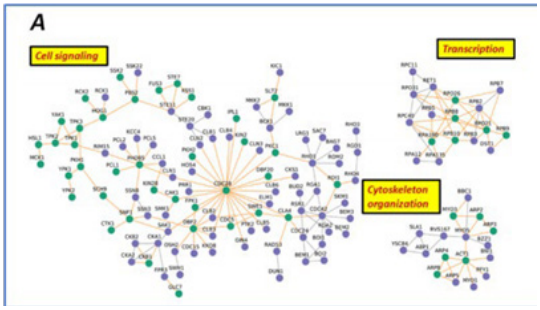
PROJECT 1
WHO'S CONTROLLING THE CONTROLLERS? DISCOVERING THE REGULATORY NETWORK OF HISTONES

Histones have many post-translational modifications, notably methylation, acetylation, phosphorylation and ubiquitin. These are used in exquisite combinations, and are used by the cell to define the genes to be transcribed and to control the compaction or relaxation of chromatin. The types of modifications that occur on histones are well known and, at least for the model organism we work with, the enzymes responsible for the modifications are also known. However the regulation of these enzymes is extremely poorly understood. We want to know who is controlling the (histone) controllers. This is a fundamental question which is of relevance for every eukaryote (microbes, animals and plants). It is also of high relevance for human diseases, most notably cancers, where the modifications on histones are dysregulated.



PROJECT 2
MASSIVELY PARALLEL MEASUREMENT OF PROTEIN INTERACTIONS IN THE CELL

One of the great 'grand challenges' of molecular cell biology is to understand which proteins in the cell physically interact with each other, to form protein complexes, molecular machines and interaction networks. To date, interactions have been studied by either purifying protein complexes one by one, or by using two-hybrid approaches to test whether two proteins interact. We are pioneering approaches to measure hundreds to thousands of protein interactions simultaneously, in a massively parallel way. This is done on a single sample, in a single experiment. This involves the use of protein crosslinking, advanced mass spectrometry techniques, and appropriate data analysis. We have already measured > 300 protein-protein interactions in the eukaryotic nucleus in a single experiment and will be applying these approaches to other eukaryotic organelles and cell fractions. This is an exciting project using breakthrough technology.



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RESEARCH FOCUS

How sequences specify phenotypes by deciphering gene regulation.

Suitable for Bioinformatics/ Molecular biology/ Biostatistics/ Computational biology students.

Dry and Wet labs.

The human genome contains roughly 20,000 protein-coding genes but hundreds of thousands of regions responsible for tuning the activation of these genes in space and time. We are interested in the interplay between these regions and the circuits they control. Those interactions between the genome and the epigenome ultimately specify cell diversity and animal form and function. Our lab uses computational and statistical methods, and evolutionary concepts to generate hypotheses and interrogate data. We are largely computational, but we also go beyond the dry lab to generate molecular data to address fundamental biological and biomedical questions.

PROJECT 1
INTERROGATING AGING IN THE REGULATORY GENOME IN SINGLE CELL

Aging is an unstoppable process and the strongest risk factor for common diseases in developed countries. We combine the power of comparative genomics and single-cell technologies to understand the key intrinsic signals involved in the loss of molecular identity and robustness in lung and cardiac aging, and explore the effect of exercise on remodeling gene regulatory networks in these organs. We will integrate single cell/nucleus RNA-seq and ATAC-seq in young and aged animals using advanced computational methods. Furthermore, we are also interested to characterize key cis-regulatory element associated with aging and the rejuvenate response through exercise. We are seeking highly motivated students with skills in computing (R, Unix), a passion for biology and quantitative/statistical thinking.

In this project, you will have the opportunity to work on the latest in single cell genomics data and collaborate with local and international experimental and computational researchers. Depending on your skills and interest, there will also be the opportunity to develop methods. There may be opportunities to contribute to publications for motivated students.

PROJECT 2
ALIGNING ENHANCERS: TRACING THE EVOLUTION OF MULTICELLULAR LIFE

Animal development requires the binding of proteins, namely, transcription factors (TFs) to short stretches of sequence motifs in the genome. The binding of TFs to the genome is responsible for the dynamic initiation and modulation of gene expression which allows for the diversity of cell types and organisms around us. One of the greatest challenges in molecular biology is to understand the rules governing the expression of genes.

A powerful method to understand functionally important sequence is by cross-species comparison. Conserved sequences suggest regions of functional importance. However, regulatory sequences are difficult to align across species due to the inherent degeneracy of sequence motifs and their tolerance to mutations. Hence, although many alignment algorithms have been developed, these methods are suboptimal for regulatory sequences, which tend to be poorly conserved.

This project will involve the development of new computational methods to align and discover conserved regulatory sequences between species. We will use methods in semantic text processing and machine learning. We also take advantage of a unique functional validation method in a zebrafish model system. This project is suitable for students with strong interests in computational biology.

RECENT PUBLICATIONS:

Wong ES*,...Francois F*, Degnan B* (2020). Deep conservation of the enhancer regulatory code in animals. Science *corresponding

Flochay S^, ES Wong^, Zhao B^... Garfield D, Furlong E (2021). Cis-acting variation is common, can propagate across multiple regulatory layers, but is often buffered in developmental programs Genome Research ^ equal contributions

Wong ES, Schmitt B, Thybert D, Marioni J, Ferguson-Smith A, Odom DS, Flicek P (2017) Interplay of cis and trans mechanisms driving transcription factor binding, chromatin, and gene expression evolution. Nature Communications 8(1):1092

Wong ES, Thybert D, Schmitt B, Stefflova K, Odom DS, Flicek P (2015) Decoupling of evolutionary changes in transcription factor binding and gene expression in mammals. Genome Research 25:167-78

MICROBIOLOGY AND MICROBIOMES

CLUSTER STRENGTHS:

- **Microbes in Health and Disease**
- **Microbes in the Environment**

Microbes are invisible companions that intertwine our biology and support our biological and geological systems. They are big players in infectious diseases but are also fundamental to producing nutrients for plants to grow and the dynamic transformation of matter. We aim to unravel the mechanisms behind these ubiquitous microbes and their vital function in every life process. Our research in Microbiology & Microbiomes explores the importance of microbes in the environment and microbial contributions to health and disease.

Our students are encouraged to use their critical and analytical aptitude and exercise a range of genomic tools to address global topics such as archaea, climate change and food production. We endeavour to translate our research into effective methods for the control and treatment of conditions like autism, cancer and diabetes. Driven by improvements in technology and the imaginations of our researchers, we aspire to unravel the many secrets of the microbial world.

RESEARCH FOCUS

Environmental microbiology (microbial diversity, adaptation, evolution, ecosystem function) and astrobiology (early life and human health).

Suitable for students who have excelled in Environmental Microbiology (MICR3071).

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Our research is focused on unravelling the evolutionary and ecological significance of early Earth microbial ecosystems.

Stromatolites and microbial mats are model systems for studying the origins and evolution of life on our planet. They are geobiological structures composed of complex and diverse microbial communities. We have access to unique field sites on the coast of Western Australia – in particular the World Heritage site of Shark Bay - and other locations around the world. We also work closely with the Department of Parks and Wildlife to ensure these unique ecosystems are carefully monitored in the face of threats such as climate change. In particular, the impact of extreme stressors on microbial communities and critical pathways in threatened mat systems are being assessed and critical to ascertain before any irreversible ecosystem tipping points are reached.

The study of microorganisms associated with these formations may also be applied to the search of extraterrestrial life (past or extinct), particularly with the discovery of unique bio-signatures. This work thus aligns well with the goals of the Australian Centre of Astrobiology and our collaborators at NASA. Our research provides new metagenome-based models into how biogeochemical cycles and adaptive responses may be partitioned in the microbial mats of Shark Bay, including the genetic basis for novel natural product synthesis. The traditional tree of life is also in flux, and new discoveries we are making of novel organisms and pathways is affording a dynamic and holistic view of these ecosystems.

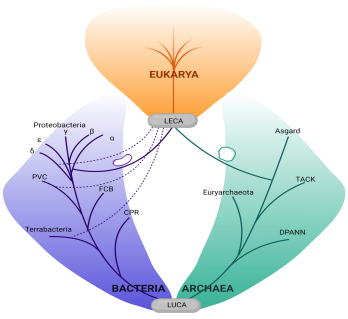
In particular, we are pursuing the role of 'microbial dark matter' in these systems including the enigmatic group of Asgard archaea. We aim to break down the traditional distinctions between prokaryotic and eukaryotic life using the Asgardians as a 'missing link'.

This research combines biogeochemical field measurements, laboratory analytical methods, and recent advances in functional genomics. In particular, there is the opportunity to employ next-generation sequencing platforms, including various 'meta' approaches (genomics, transcriptomics, proteomics). Students will use these and other modern microbial and molecular biology techniques to examine specific aspects of community function in these 'living rocks', from deciphering microbial interactive networks, novel adaptive responses and natural product synthesis.

Specific projects include:

- Exploring the unknown: illuminating microbial dark matter in mats
- Promiscuity in microbial mat communities: gene transfer and impact of viruses
- Searching for our great (cellular) ancestors: hunting the elusive Asgard archaea
- The canary in the coalmine: effects of environmental change on microbial communities
- Living at the edge: understanding microbial survival in an extreme environment
- Look who's talking too: communication in the third domain of life
- Mining for novel natural products: microbial mats as a source for unique metabolites

I also encourage students who want to think outside the box, so I always welcome ideas for other projects and happy to workshop potential!



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RESEARCH FOCUS

Exploring soil microbial processes in Antarctic and sub-Antarctic environments.

Suitable for students who have majored in Microbiology or Biotechnology and excelled in Environmental Microbiology (MICR3071) or Microbial Genetics (BABS3021).

PROJECT 1
ATMOSPHERIC CARBON FIXATION; A NOVEL BIOCHEMICAL PROCESS DOMINATING POLAR DESERT SOILS

The Ferrari lab recently discovered a biodiversity hotspot in the Windmill Islands, eastern Antarctica, where bacteria belonging to two novel phyla – WPS-2 and AD3 – dominated the site. We used shotgun sequencing to recover genomes from soils from this site and found that the majority of the community present are potentially fixing carbon through the consumption of molecular hydrogen and carbon monoxide gas.

The aim of Project 1 is to validate atmospheric carbon fixation as a novel primary production strategy in nutrient-starved polar desert soils. Methods to be applied include novel culturing, DNA- SIP/FISH, next generation sequencing, gas chromatography, and data mining to isolate the first trace gas fixer from this environment for characterisation.

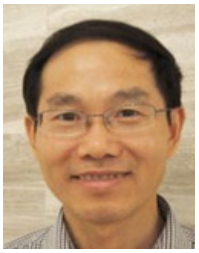
PROJECT 2
BIOREMEDIATION OF ANTARCTIC SOILS

This project will combine molecular and chemical techniques to evaluate the success of bioremediation efforts currently underway at Casey station, in eastern Antarctica.

The project will use quantitative PCR, barcode tag sequencing and multivariate analyses. The Ferrari lab and this project involves a ongoing collaboration with the Risk and Remediation group at the Australian Antarctic Division. Thus, the project has real industry outcomes that will provide immediate benefit to the sensitive Antarctic environment.

Figure 1. Mitchell Peninsula, Antarctica; a nutrient-limit-ed desert that hosts a unique microbial community that uses trace gases to survive.

Figure 2. Casey station where bioremediation of fuel spills is ongoing using engineered biopiles combined with nutrient amendment.



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RESEARCH FOCUS

Genomics and molecular evolution of bacterial pathogens.

Suitable for students who have majored in Microbiology, Genetics, Biotechnology or Bioinformatics.

Infectious diseases caused by pathogenic bacteria are a major threat to human health. Our group takes a multi-disciplinary approach to study pathogenic bacteria. We use omics (genomics, transcriptomics and proteomics) approaches to address how pathogens arise and cause disease, how they evolve and adapt – and how to identify these pathogens. Currently our research group includes 2 postdoctoral associates, 6 PhD students, 1 Msc student and 3 honour students.

In the past decade Next generation sequencing (NGS) has provided unprecedented amounts of genomic data for many bacterial pathogens. NGS has been increasingly employed to prospectively identify and track outbreaks as well as to define and examine large scale population structures and trends. NGS has major advantages over other pathogen typing methods as it promises a standardised universal solution for high-resolution typing. We have developed new bacterial typing methods that utilise whole genome sequencing data to cluster bacterial strains into groups of related isolates.

PROJECT 1
GENOMIC TYPING AND GLOBAL EPIDEMIOLOGY OF *SHIGELLA FLEXNERI*

Shigella causes sever bloody diarrhoea known as bacillary dysentery. There are four species within the genus *Shigella* but all are forms of invasive *Escherichia coli. Shigella flexneri* is the most prevalent species in developing countries, causing endemic and epidemic level disease. In recent years, multidrug resistant strains and novel serotypes of *S. flexneri* have emerged, raising serious public health concern. In this project we will develop a standardised new genomic typing system with an aim to provide insights into the spread of antimicrobial resistance and global spread of *S. flexneri.*

PROJECT 2
GENOMIC TYPING AND GLOBAL EPIDEMIOLOGY OF *VIBRIO PARAHAEMOLYTICUS*

Vibrio parahaemolyticus is an environmental organism as well as a foodborne pathogen. In humans, it mainly causes gastroenteritis which is associated with consumption of seafood. In the mid-1990s, a new serotype O3:K6 emerged causing outbreaks and spread across the globe. O3:K6 is now known to represent a new pandemic clone. This project will investigate the evolution of the pandemic clone and develop a standardised typing system for global surveillance.

Recent publications

- Payne M, et al. Multilevel genome typing: genomics-guided scalable resolution typing of microbial pathogens. Euro Surveill. 2020, 25(20):1900519
- Octavia S, et al. Delineating community outbreaks of Salmonella enterica serovar Typhimurium by use of whole-genome sequencing: insights into genomic variability within an outbreak', J Clinical Microbiology, 2015, 53:1063.
- Luo L et al. Elucidation of global and national genomic epidemiology of Salmonella enterica serovar Enteritidis through multilevel genome typing. Microbial Genomics, 2021, 7(7):000605.
- Zhang X, et al.Cluster-specific gene markers enhance Shigella and enteroinvasive Escherichia coli in silico serotyping. Microbial Genomics, 2021, 7(12):000704.

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RESEARCH FOCUS

Fungal infections of humans.

Suitable for students who have majored in Microbiology, Biotechnology, Molecular Biology or Genetics.

Opportunistic invasive fungal pathogens cause over two million life-threatening infections per year worldwide, with mortality ranging from 20–95%. The number of deaths per year is greater than those attributed to malaria, or breast cancer, or prostate cancer. Bloodstream infections caused by *Candida* species (candidaemia) are the most frequent life-threatening invasive fungal infections, with the majority caused by one species, *Candida albicans.*

C. *albicans* colonises the gut of most healthy individuals but does not usually cause serious disease because the physical barriers between our gut and the bloodstream, combined with our immune defences and the suppressive powers of the indigenous gut microbiota, prevent these infections. However, this opportunistic pathogen can cause serious, life-threatening disseminated disease when these barriers and defences are compromised (e.g. seriously ill patients in the ICU, during cancer chemotherapy or immunotherapy, organ/ stem cell transplantation, or when the gut microbiota is disturbed), which renders us vulnerable to infections from the C. *albicans* that colonises our gut. Despite the availability of antifungal drugs, over 40% of these systemic infections are fatal in certain patient groups.

There is an urgent clinical need for the development of diagnostics and new therapies for invasive candidiasis which research in my group aims to address in innovative ways. Some examples pf projects which may be available in my lab are listed below.

Gut fungi:

- Developing microbial therapeutics to clear C. *albicans* from the gastrointestinal (GI) tract of at-risk patient groups, thereby preventing life-threatening disseminated disease (e.g. [1]).
- Generating a better understanding of composition and functional role of the entire fungal component of the GI microbiota.

Fungal cell wall structure and biosynthesis:

- Imaging the precise ultrastructure of the cell wall of C. *albicans* cells grown in physiologically relevant conditions using state-of-the-art electron microscopy techniques (e.g. [2].)
- Solving the structure of the C. *albicans* chitin synthase enzymes (with Dr Kate Michie - Structural Biology Facility).

Antifungal polymers:

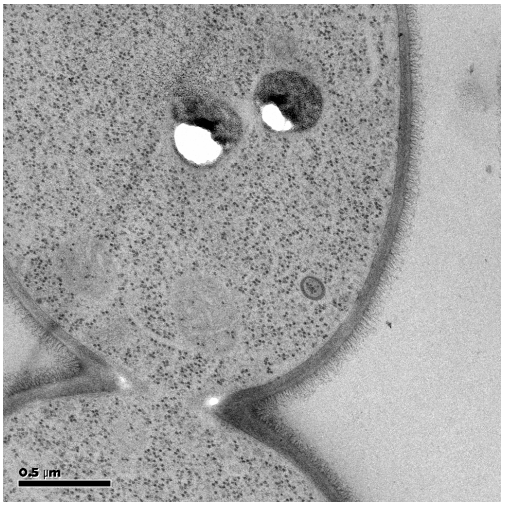
- Assessing the antifungal activity of polyacrylamides which resemble antimicrobial peptides and determining their mode of action (e.g. [3]) (with Prof. Cyrille Boyer - Chemical Sciences and Engineering).

References:

1. Ricci et al. (2021). Human gut bifidobacteria inhibit the growth of the opportunistic fungal pathogen Candida albicans. Preprint on bioRxiv https://doi.org/10.1101/2021.12.21.473717.

2. Lenardon et al. (2020) Scalar nanostructure of the *Candida albicans* cell wall; a molecular, cellular and ultrastructural analysis and interpretation. *The Cell Surface* 6C:100047

3. Schaefer et al. (2021) Rational design of an antifungal polyacrylamide library with reduced host cell toxicity. *ACS Applied Materials & Interfaces:* 13(23):27430-27444



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RESEARCH FOCUS

Gastrointestinal disease.

Suitable for students who have majored in Microbiology, Immunology and/or Cell Biology.

We seek to understand the interplay between host immunogenetic factors and gastrointestinal dysbiosis in gastrointestinal carcinogenesis (mainly gastric cancer (GC)) and other chronic inflammatory conditions (mainly inflammatory bowel diseases). A main focus of our research studies is to understand the role of Helicobacter pylori-induced inflammation in GC by addressing issues that are crucial to the host immune response to this bacterium. This could lead to the identification of novel markers of disease susceptibility, potentially resulting in intervention strategies and/or treatments for GC. In addition, it has been suggested that dysbiosis in the stomach is dynamic and correlates with progression to GC. Given that H. pylori gradually disappears from the gastric mucosa upon the development of intestinal metaplasia, identification of other microbial signatures associated with disease progression could improve prevention of GC. Thus, we are currently investigating the role of gastric dysbiosis and microbial metabolites in gastric carcinogenesis.

All projects involve a range of cutting-edge technologies, including genome editing, gastrointestinal organoids, high-throughput sequencing, microbiota/microbiome analyses, genotyping arrays, electron microscopy and confocal microscopy as well as more basic techniques such as cell culture, bacterial cultures, real-time PCR, ELISA, Western blotting, 2D gel electrophoresis and mass spectrometry.

PROJECT 1
THE ROLE OF AUTOPHAGY IN GASTRIC CANCER

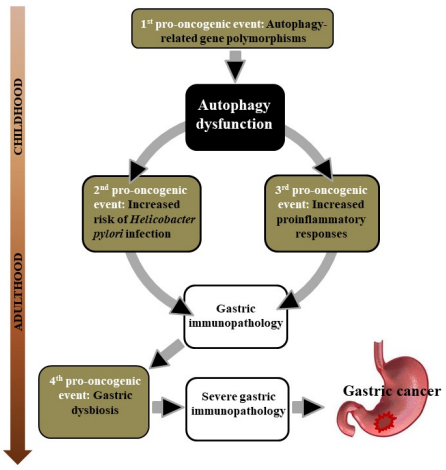
Did you know that GC is the fifth most common type of cancer in the world, affecting over 1M people in 2020? The bacterium *H. pylori* has been causally linked to the development of gastritis, peptic ulcer disease (PUD) and GC. Although 50% of the world's population is infected with *H. pylori*, only a small percentage develops PUD (10-15%), B cell MALT lymphoma (<1%) and GC (1-3%). These findings suggest that factors other than *H. pylori* infection (environmental risk and host genetic susceptibility) may contribute to more serious disease outcomes. In extensive studies by our group, we have not only demonstrated that polymorphisms involved in autophagy (*ATG16L1* and *IRGM*) dramatically modulate GC risk in Han Chinese, Australian Caucasian, Dutch and Colombian Mestizo populations, but we have also shown that *H. pylori* can modulate the expression of genes encoding core autophagy proteins and autophagy regulators in both immune and non-immune cells. This project aims at increasing our understanding of autophagy, an important cellular mechanism that remains understudied in *H. pylori* infection and GC, and will potentially identify novel markers of disease susceptibility and therapeutic targets.

PROJECT 2
DO MICROBIAL METABOLITES CONTRIBUTE TO GASTRIC CARCINOGENESI?

Dysregulated metabolism is currently known as a critical factor for cancer development, maintenance, and metastasis while tumour metabolic activity has been correlated with recurrence and poor prognosis. This project will advance our understanding of the underlying mechanisms by which microbial metabolites might contribute to gastric carcinogenesis, and how key organisms in the stomach modulate these processes.

PROJECT 3
CONTRIBUTION OF PATTERN RECOGNITION RECEPTORS TO GASTRIC CARCINOGENESIS?

As H. pylori is initially targeted by pattern recognition receptors (PRRs), mainly Toll-like receptors, NOD-like receptors and Sequestosome/p62-like receptors (autophagy), it is conceivable that dysfunction within genes of this arm of the immune system could affect the extent and direction of the host response against the infection, resulting in an increased risk of development of GC. There is also an interesting but understudied crosstalk between Toll-like receptors, NOD-like receptors and autophagy. With this project we aim to understand how these host immunogenetic factors contribute to GC via ex-vivo and in-vitro studies.



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RESEARCH FOCUS

Evolution of pathogens: computational biology and mathematical modelling.

Suitable for students who have majored in Genetics, Mathematics, Bioinformatics or Microbiology.

We are interested in understanding how bacteria and viruses evolve. We analyse genetic data and develop mathematical models to explain and predict the population dynamics of pathogens and other microorganisms. These projects would suit students interested in microbial evolution who would like to develop their skills in bioinformatics, computing and/or data analysis. Alternatively, you might be a student with a background in quantitative sciences such as maths, statistics, computing, physics or engineering and a growing interest in biology. These projects can be tailored to fit the academic background, research interests and career goals of individual students.

PROJECT 1
PATHOGENS EVOLVING BETWEEN AND WITHIN HOSTS

Pathogens are under strong selection to transmit effectively between hosts. They are simultaneously under selection to reproduce efficiently within hosts. How do these two processes interact? This project considers the evolution of pathogens as a process of natural selection operating at multiple scales. Using a computer simulation model of between and within host dynamics you will predict properties of sequenced isolates as a product of the joint dynamics.

PROJECT 2
HUMAN CULTURE AND ZOONOTIC DISEASE

How do technology and culture influence the transmission of infectious diseases? Technological advances have opened many opportunities for economic development, but they have simultaneously altered the way we interact with the environment. For instance, we have increased contact with wildlife and potentially raised the risk of zoonoses. For this project you will construct a simulation model to study the dynamics of human cultural practices and the dynamics of contact with wildlife species in order to explore the risk of zoonoses.

PROJECT 3
HOW OLD IS A BACTERIAL PATHOGEN?

Genomes contain information about the history of a species. For example, when free-living bacteria turn into pathogens they undergo reductive evolution and some genes become pseudogenes. One way to infer the age of a pathogen is by studying patterns of molecular evolution in genes and pseudogenes; this was done, for instance, to estimate the age of leprosy. In this project you will first refine existing methodology for this estimation procedure and then test it on other bacterial pathogens. This will require a combination of bioinformatics and mathematical or computational modelling.

PROJECT 4
PATHOGENS EVOLVING BETWEEN AND WITHIN HOSTS

At the time of writing this blurb in early 2021 the coronavirus pandemic has so far killed over 2.6 million people since it began in late 2019, and it continues to rage around the world. With adequate control measures (and perhaps some luck) we have successfully suppressed the epidemic in Australia. Several safe effective vaccines have been developed but the national vaccination program will take time to roll out. Meanwhile, new cases appear daily in hotel quarantine among international travellers. The virus occasionally escapes the quarantine system. What will happen next? You will construct and analyse mathematical models of alternative scenarios of the end of the epidemic in Australia. This project will require skills in mathematical modelling, including probability theory, and skills in computer programming.

For more information about us see
http://www.tanakalab.unsw.edu.au

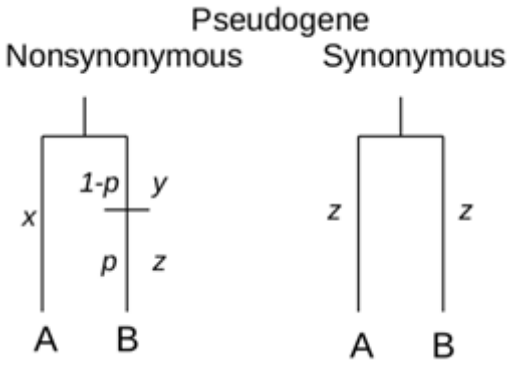
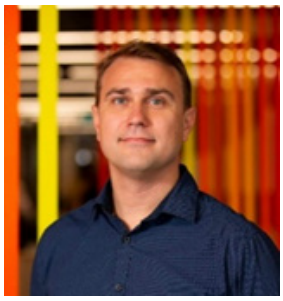


Figure: When a gene becomes a pseudogene its "nonsynonymous" rate of evolution increases (say from y to z) because the selective constraint is released. The unconstrained of rate of evolution (z) is the same as the synonymous rate of evolution.



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RESEARCH FOCUS

Gene regulation in bacterial pathogens.

Suitable for students who have majored in Microbiology, Genetics or Biotechnology.

My lab seeks to understand how genes involved in pathogenicity and antibiotic resistance are regulated in bacterial pathogens. A major focus of the lab is understanding how pathogens use regulatory non-coding RNA (ncRNA) to control virulence. We are using cutting edge RNA-sequencing techniques and molecular biology to study these processes and reveal exciting new gene regulatory pathways that contribute to disease.

PROJECT 1
UNDERSTANDING HOW NON-CODING RNAs CONTROL ANTIBIOTIC RESISTANCE IN THE SUPERBUGg, MRSA.

Methicillin resistant Staphylococcus aureus (MRSA) is a leading cause of bacteraemia, infective endocarditis and osteomyelitis. Treatment of severe MRSA bacteraemia is limited to the last-line antibiotic vancomycin and the World Health Organisation (WHO) has designated MRSA a Priority 2 pathogen for development of new interventions. We have discovered that a non-coding RNAs (the we have named SvaR) that controls cell wall turnover is required for intermediate resistance to vancomycin. In this project, we aim to understand how SvaR is regulated and why SvaR is required for vancomycin resistance in this important human pathogen. This project will involve genetic manipulation of MRSA, mutagenesis, CRISPRi knockdowns, and GFP reporters to characterise these pathways.

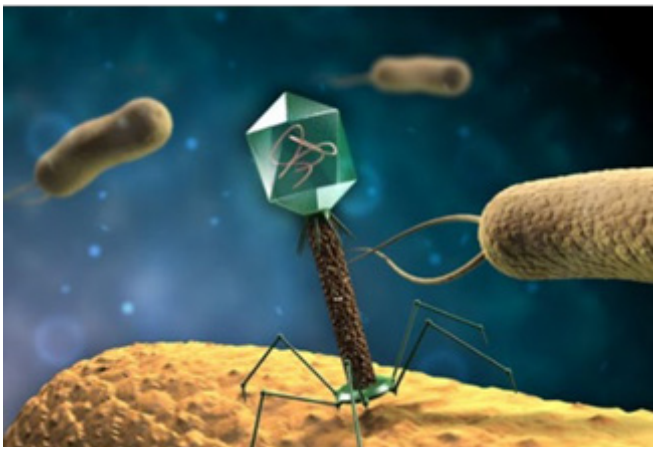
Please feel free to contact me at j.tree@unsw.edu.au if you would like to discuss research projects in the lab.

PROJECT 2
HIGH-THROUGHPUT ANALYSIS OF SRNA FUNCTION USING A BARCODED DELETION LIBRARY

We have demonstrated that EHEC produces at least 55 novel regulatory non-coding RNAs that are only found in pathogenic E. coli, however we know very little about the function of these RNAs in EHEC pathogenesis. In this project, we aim to construct a library of barcoded sRNA deletions using recombineering and/or CRISPR/Cas9-mediated deletion. Using this library we will simultaneously assay the fitness of every non-coding RNA by high-throughput DNA sequencing to measure the abundance of each deletion. This project will involve genetic manipulation of a bacterial pathogen, recombineering, CRIPR/Cas9-mediated recombineering, and high throughput DNA sequencing.

PROJECT 3
IS CARBON METABOLISM CONTROLLING PHTHOGENESIS IN ENTEROHAEMORRHAGIC E. COLI

In collaboration with colleagues at the University of Edinburgh, UK we have shown at carbon starvation and carbon metabolism pathways communicate through regulatory non-coding RNA. This project will seek to understand how two major regulatory RNAs interact to control carbon metabolism in the model bacterium, E. coli. These RNAs also control virulence gene regulation in EHEC and this project will more broadly seek to understand how major carbon metabolism regulators control virulence gene expression. This project will use genetic modification of pathogenic E. coli, mutagenesis, cutting edge RNA-sequencing techniques, and GFP reporters to characterise these pathways.



Bacteriophage are common vectors for transferring virulence genes between bacteria.

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RESEARCH FOCUS

Molecular virology.

Suitable for students who have majored in Microbiology, Biotechnology, Genetics or Molecular and Cell Biology.

Viral infections are a major global health threat and burden. Of the 55 to 60 million annual deaths worldwide, around one third are caused by infectious diseases. The possible eradication of viral diseases such as poliomyelitis and measles through vaccination programs in the future is very likely to be thwarted by the emergence of new viral pathogens, as we have recently seen with the pandemic coronavirus. Unless we understand the mechanisms, patterns and consequences of their rapid evolution, we will not be able to build rational strategies for controlling their spread.

The Molecular Microbiology Laboratory is part of the School of Biotechnology and Biomolecular Sciences (BABS), located in state-of-the-art OGTR PC2 facilities. Research in this multi-disciplined group encompasses molecular virology, viral discovery, molecular surveillance, drug discovery, host-virus evolution and tickborne disease, using both computational and wet lab techniques.

PROJECT 1
NOROVIRUS REPLICATION AND EPIDEMIOLOGY

Norovirus is the major cause of gastroenteritis outbreaks worldwide. We track and study the evolution of pandemic norovirus strains across the globe, which are responsible for around 670 million of cases and around 200,000 deaths each year.
Major pandemics of norovirus gastroenteritis occur around every three to five years, with six pandemics reported since 1996. These pandemics are often associated with novel noroviruses from a single genotype (GII.4), which escape herd immunity through both antigenic drift and recombination. Our group is part of international and national networks that trace and track pandemic noroviruses globally. We first identified and characterised two of the six pandemic viruses; Hunter 2004 and Sydney 2012, both responsible for pandemics of gastroenteritis. We have developed several norovirus molecular detection and bioinformatics tools over the last few years for molecular virology studies using both clinical and wastewater samples in Melbourne and Sydney. The aim of this project is to conduct a detailed molecular epidemiological and evolutionary analysis of Australian noroviruses. The project will determine if current outbreaks are associated with the emergence of novel virus variants or recombinant (hybrid) viruses.

PROJECT 2
ADENOVIRUS MOLECULAR EPIDEMIOLOGY

Human adenoviruses (HAdVs) have been known to infect the gastrointestinal tract in conjunction with the upper or lower respiratory tract and ophthalmologic tissue.

These icosahedral, dsDNA viruses can also infect other tissues including neurological tissue. In this study we argue against the current dogma and hypothesise that adenoviral gastroenteritis is not limited to typically 'enteric' species F (types 40 and 41). We have recently identified HAdV-A, B, and C Types associated with clinical gastroenteritis. Interestingly, unlike HAdV-F, these Types are more commonly attributed to tropism in respiratory tissues. Therefore, our findings implicate these Types with undiagnosed acute gastroenteritis. Using clinical and wastewater samples we aim to build on this hypothesis using cutting edge DNA amplification methods coupled with 3rd generation sequencing techniques and bioinformatics. We will be able to determine the prevalent HAdV species the Sydney and Melbourne populations covering around 3 million people. We also aim to find which unidentified types are associated with acute gastroenteritis in Sydney.

PROJECT 3
DISCOVERING NEW VIRUSES (2 honours places available)

In 2002, a metagenomics approach – the non-targeted sequencing of all DNA in a sample – was first used to find novel DNA viruses in a marine environment.
More recently, such techniques were also developed for the discovery of RNA viruses. For the first time, all viruses in a sample could be identified by their sequence, without the need for extensive culturing or PCR/RT-PCR techniques [44]. Since then, the advent of next generation sequencing (NGS) technologies has greatly facilitated this metagenomic approach to viral discovery. In contrast to Sanger sequencing-based studies, NGS allows the sequencing of millions of base pairs from a sample in a single run, massively increasing the number of viral genomes that can be discovered. NGS has thus revolutionised the field of viral discovery. The increase in readily-available computational power also permits rapid processing of this data, which can be compared to sequence databases, with, for example, the Basic Local Alignment Search Tool (BLAST) to identify the sample's taxonomic constituents

which for us are RNA viruses. These new techniques have revealed many divergent viral lineages are emerging many of which could pose challenges to the human population. Less than 1% of the earth's virosphere is estimated to be known, suggesting there are millions of potential human pathogens that we know nothing about.

In this space we have developed numerous workflows using Katana (UNSW super computer) for viral discovery by accessing public RNA sequencing reads. We have targeted numerous animals for viral discovery including; ***bats, Australian reptiles and amphibians,*** over a dozen marsupials, monetremes and ancient fish. So far, we have discovered over 100 new viruses, for which we have many full-length viral genomes. This first discovery project is dry lab based and will instruct you in many BINF applications including; sequence search-based systems, assembly, taxonomic and phylogenetic methods, as well as genome annotation and illustration. A background in computer science or programming is not required, however this project will utilise many bioinformatics techniques and analyses including unix command line, python scripting and R.

In a second more directed approach we have numerous viral discovery programs aimed at; ***the cane toad, paralysis tick, Tasmanian Devil and Australian fish.***

In these four metatranscriptomic projects we collect and sequence the entire RNA, usually from the liver, once ribosomal RNA has been removed. Our novel BINF workflow, run from Katana, is then used to pull out viral sequences. Because we have the original samples containing the novel viruses, this hugely increases our chances of retrieving the entire source virus using one of two techniques. We can i) propagate the virus directly in cell culture systems using the infected tissue, or, ii) determine the full-length genome of the virus from infected tissue using RT-PCR methods and then resurrect the virus using reverse genetics. Using these methods, we have discovered 12 novel cane toad viruses, several of which are excellent bio-control candidates. This project involves a combination of wet lab work involving nucleic acid and virus extraction from animal tissues, and PCR amplification methods to find viruses. This project also involves bioinformatic analysis of RNA-seq data and genomic data to find virus-like sequences.

PROJECT 4
PALEOVIROLOGY: FINDING ANCIENT VIRUSES IN ANIMAL GENOMES USING BIOINFORMATICS

The study of ancient viruses is termed paleovirology. The aim of this project is to find ancient viruses, or 'fossil remnants of viruses'.

The genomes of animals and insects contain traces of past viral infections through the integration of viral genetic material into the host germline, termed ***endogenous viral elements (EVEs).*** These viral fossils can be used to study viruses that existed thousands of years ago. Around 8% of the human genome is comprised of EVEs, of which the vast majority are retroviruses that naturally insert their genomes into the host genome as part of their replication cycle. For other viruses, germ line integration is rare, but has been documented in many organisms. Using bioinformatics, our lab discovers EVEs in diverse groups of animals. Using genomes from mosquitoes, flies, and ticks, marsupials, including the koala and the Tasmanian Devil, we have identified hundreds of new EVEs, some estimated to be from viruses circulating >100 million years ago. In addition, we have identified unique patterns that link EVEs to small RNA innate immune pathways in both the blacklegged tick Ixodes scapularis and in the Koala. We aim to find more viral fossils in the genomes of other animals, including monetremes which are ecologically threatened, and determine if they are used as a modern day viral defence for the host.

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RESEARCH FOCUS

Campylobacter and other mucosa- associated bacteria, chronic inflammatory diseases, cancer immunotherapy-associated microbes.

Multiple projects are available. These projects provide research training in bacterial pathogenesis, host response to infection, mucosal immunology, bacterial genome and metagenomic analysis, molecular diagnosis of bacterial infection, precision antibiotics, vaccines for mucosal associated bacteria, or cancer immunotherapy-associated gut microbes.

PROJECTS ON CAMPYLOBACTER CONCISUS AND INFLAMMATORY BOWEL DISEASE (IBD)

Campylobacter concisus is a commensal oral bacterium but some strains may cause enteric diseases. We found that csep1-6bpi positive C. concisus strains may cause Crohn's disease (a major form of IBD). The csep1-6bpi gene, which encodes a superantigen homologue, is located in the pICON plasmid or the C. concisus chromosome. Two Honours projects are available. One project focuses on the C. concisus bacterium, students can choose to work on one of the following research areas including charactering bacterial virulence factors, analysing C. concisus genomes, examining the relationship between C. concisus and other gut microbes, or validating molecular diagnostic methods for detection of virulent C. concisus strain in clinical samples. The second project focuses on host response to Csep1 and C. concisus.

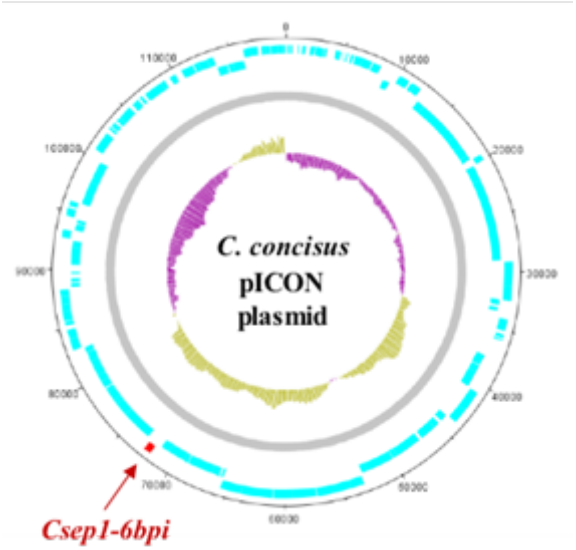


Figure 1. Circularised diagram of the pICON plasmid in C. concisus strain P2CDO4. (doi: 10.1038/s41426-018-0065-6)

PROJECTS ON PRECISION ANTIBIOTICS AND VACCINES

Two projects are available. The first project aims to develop precision antibiotics to specifically kill/inhibit individual bacterial species. As some bacterial species in the oral and gut microbiota may cause IBD. The development of precision antibiotics will enable selective elimination/inhibition of harmful bacterial species without affecting the balance of microbiota
in the gastrointestinal tract. Precision antibiotics may also be used to treat antibiotic resistant pathogenic bacterial species. The second project is to identify bacterial components that can be used as vaccines to control C. concisus and other mucosa- associated bacterial pathogens.

PROJECTS ON CANCER IMMUNOTHERAPY-ASSOCIATED GUT MICROBES

Blockade of immune checkpoint proteins is a means of cancer treatment. Recent studies found that some bacterial species in the gastrointestinal tract may affect the efficacy of immune checkpoint blockade therapy. This project investigates the mechanisms by which gut bacterial species affect immune checkpoint blockade therapy, aiming to provide additional strategies to improve cancer immunotherapy efficacy.

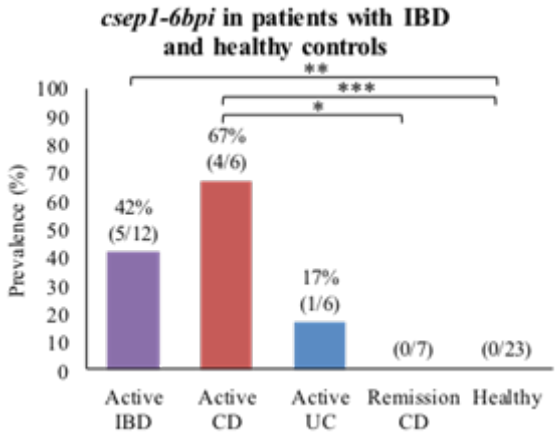


Figure 2. The prevalence of csep1-6bpi positive C. concisus strains in patients with active CD was significantly higher than that in remission CD and health controls (P = 0.021 and P = 0.0006, respectively).

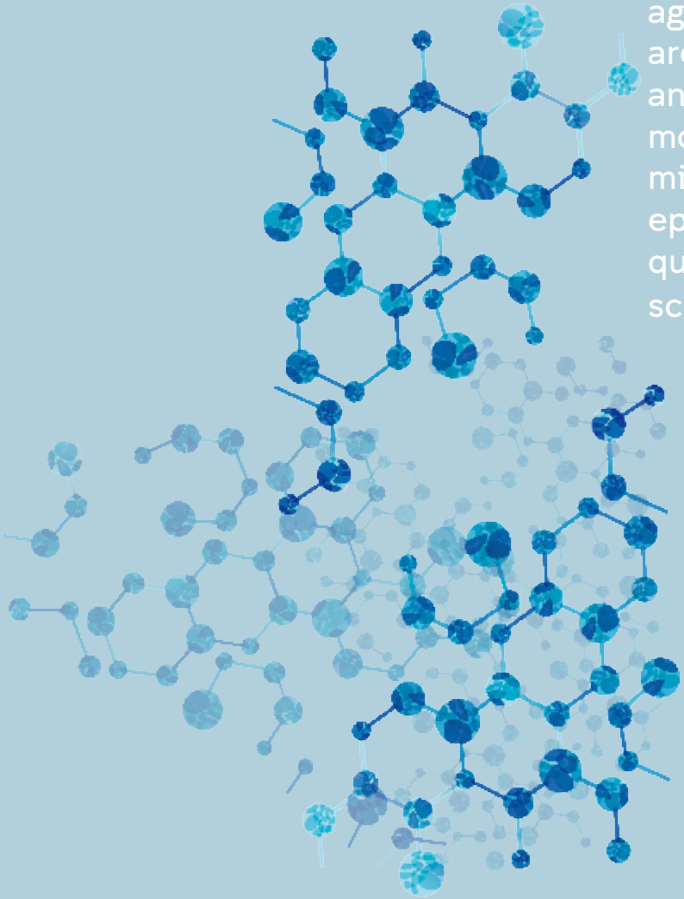
MOLECULAR AND CELL BIOLOGY

CLUSTER STRENGTHS:

- **Metabolism and Metabolic Disorders**
- **Structural and Synthetic Biology**

Since traditional biology focuses on living organisms as a whole, Molecular and Cell Biology explores the components and interactions that make up a cell. This gives us a deeper understanding of cell function and why diseases and disorders happen on a molecular level.

Molecular and Cell Biology has been pivotal in a wide range of fields and revolutionised the ability to manipulate cells and tissues for medical and therapeutic purposes such as vaccinations. Other developments have included DNA fingerprinting in forensics and pioneering crop modifications in agriculture. Our research centres on the areas of Synthetic Biology and Metabolism and Molecular Cell Biology. We incorporate molecular genetics, stem cell biology, microscopy, computer science and epidemiology to answer unsolved biological questions and train the next generation of life scientists.



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RESEARCH FOCUS

Synthetic and Evolutionary Biology

Suitable for students who have majored in Microbiology, Molecular Biology, Bioinformatics, Genetics, Biochemistry or Biotechnology.

My research group currently focuses on three streams of research:

1. The directed, molecular evolution of the bacterial flagellar motor to ascertain how the motor arose and to learn what constrains the evolutionary pathways that govern the emergence of such complexity.
2. The applications of synthetic bacterial flagellar motor in controlling fluid flows and in nanoscale propulsion.
3. Bottom-up synthetic biology using DNA nanotechnology to control lipid interactions and build synthetic cell-like networks.

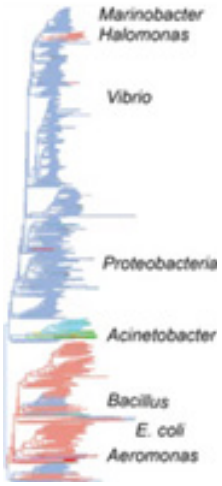
PROJECT 1
EVOLUTION ACROSS INTERFACES

In this project we explore the directed evolution of the flagellar motor in the lab by evolving it to swim under different energy sources and selecting for motility. Recent work in antibiotic resistance (eg by Michael Baym) has shown that the resistance of antibiotics occurs in lockstep when progressing through 10-fold increases in antibiotics. We aim to explore how motility evolves across interfaces, when a bacterium faces a change in environment between, for example, H+ and Na+ environments, and how the bacteria adapts to dwindling nutrient across this interface. This project has scope for designing and building custom tanks to optimise bacterial evolution using 3D printing and prototyping, as well as investigating microbiology and bacterial motility in multiple dimensions using layered swim devices.

PROJECT 2
ANCESTRAL RECONSTRUCTION OF THE BACTERIAL FLAGELLAR ROTOR

We recreate microbial 'Jurassic Parks' by resurrecting ancient flagellar motor componentry in contemporary hosts and measuring how well they work. This allows us to create ancient motors that have never existed in the present day to synthesise and evolve new motors as well as to learn about the process of evolution. We have examine in detail reconstructions of the stators that power the motor and now seek to examine how the rotor has evolved and can be engineered for new applications.

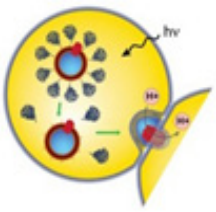
PROJECT 3
ORIGINS OF MOTILITY



The evolutionary origins of the bacterial flagellum have been a subject of scientific and public controversy – how can evolution produce such a complex system? We believe we can make progress on the issue by updating old phylogenetic work with new datasets and improved models, and combining this with experimental evolution work being done in our labs.

The project will be to assemble a well- organized database of flagellar proteins and explore sequenced bacterial genomes with genome browsers and similarity searches. The student will identify flagellar proteins and their evolutionary relatives, including recording their position in the genome. The student will also plan and conduct phylogenetic analyses, and then use synthetic biology to recreate these ancestors in a contemporary microbial 'Jurassic Park'.

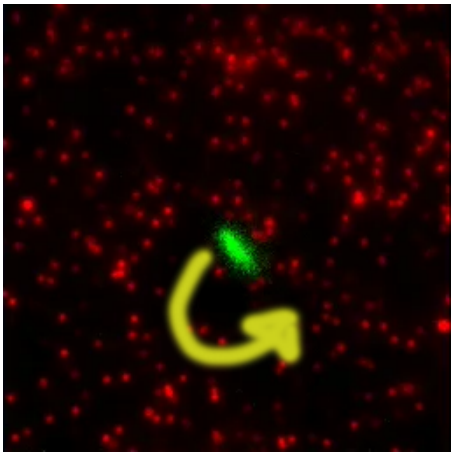
PROJECT 4
REGULATION OF MEMBRANE PROTEIN INSERTION IN ARTIFICIAL BILAYERS USING DNA ORIGAMI



Our droplet hydrogel bilayer system is an artificial bilayer system for interrogating membrane proteins, but it also allows us to explore new forms of synthetic biology where we can add individual protein function to a droplet, such as touch sensitivity or light sensitivity.Using a DNA origami nanostructures we can protect and controllably release our blocking DNA structures to direct the fusion of liposomes and control which reactions take place where in these droplets. This allows us to trigger functionality, on demand, using light and electrical signals. This project involves in vitro synthetic biology, DNA and lipid nanotechnologies and microscopy.

PROJECT 5
APPLICATIONS OF FLAGELLAR MOTOR TO FLUID FLOWS

We utilise the high efficiency and self assembly of the flagellar motor to drive rotation of cells on patterned surfaces to control mixing and fluid flows in microfluidics. We have projects involving designing and building new devices to apply the flagellar motor onto other things. This would suit someone with an interest in DIY/maker culture.



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RESEARCH FOCUS

Controlling cellular cholesterol.

Suitable for students who have majored in Molecular and Cell Biology or Genetics.

Cholesterol is a vital and versatile molecule that has become a byword for heart disease risk. But the cells in our body actually need cholesterol, and too little results in devastating developmental disorders. However, too much can contribute to several diseases, including atherosclerosis and cancer. Our bodies have therefore engineered an elaborate system for keeping the cholesterol content of our cells tightly controlled. The overall goal of our research is to understand more about how our cells control cholesterol levels. My Honours students are well supported in their projects by my lab team, and we tailor the research to suit a particular student's interests wherever possible. My team currently consists of one post-doc, five PhD students and one Honours student. Please feel free to email me to discuss the possibility of an Honours year in my lab at aj.brown@unsw.edu.au.

NEW FACTORS IN ACHIEVING CHOLESTEROL BALANCE

An imbalance of cholesterol plays a role in numerous diseases. Therefore, knowing precisely how cells regulate their cholesterol levels is central to understanding the development of these diseases, and to identify possible new treatments. Only one of the 20+ enzymes involved in cholesterol biosynthesis is targeted clinically (by statins). The statin class of drugs, worth >$30 billion a year, inhibit a very early step in cholesterol synthesis and have been effective in treating heart disease, but are not without their side effects, affecting the lives of up to 0.5 million Australians. Very little attention has been paid to later enzymes in the pathway. Our research investigates the regulation of new control points in cholesterol synthesis, which have been largely overlooked in the past.

Projects include:

1. **Degradation of enzymes** – what prompts their turnover and which E3 ubiquitin ligases are involved?

2. **Interactions between enzymes** – which enzymes interact with each other to facilitate cholesterol synthesis?

3. **Enzymes in disease** – what do known disease mutations do to the protein?

METHODS

mammalian cell culture, recombinant DNA techniques (cloning and mutagenesis), fluorescence microscopy, PCR and real-time PCR, gene/siRNA transfection, CRISPR/Cas9 genome editing, luciferase reporter assays, SDS-PAGE and Western blotting.

Suggested references (available on request)

- Sharpe LJ, Coates HW, AJ Brown. Post-translational control of the long and winding road to cholesterol. *J. Biol. Chem.* 2020; 295: 17549-17559.
- Brown AJ, Chua NK, Yan N. The shape of human squalene epoxidase expands the arsenal against cancer. *Nature Comm* 2019;10: 888.
- Capell-Hattam IM, Sharpe LJ, Qian L, Hart-Smith G, Prabhu AV, Brown AJ. Twin enzymes, divergent control: The cholesterogenic enzymes DHCR14 and LBR are differentially regulated transcriptionally and post-translationally. *J. Biol. Chem.* 2020; 295: 2850-2865
- Yoshioka H, Coates HW, Chua NK, Hashimoto Y, Brown AJ, Ohgane K. A Key Mammalian Cholesterol Synthesis Enzyme, Squalene Monooxygenase, Is Allosterically Stabilized by Its Substrate. *Proc. Natl. Acad. Sci.* U S A 2020; 117:7150-8.

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RESEARCH FOCUS

The aims of Dr Byrne's research are to find new drugs to target cancer cell metabolism and to investigate how diet and obesity promote cancer development

Dr Byrne was awarded her PhD in 2012 (Children's Cancer Institute, UNSW) and then trained as a postdoc at the University of Virginia (USA) where she gained expertise in cancer cell metabolism and obesity-related cancers, including liver and endometrial cancers. She returned to Australia in 2014 to the School of Biotechnology & Biomolecular Sciences (UNSW). Her laboratory focuses on identifying novel molecules to target cancer cell metabolism and to understand how different dietary components and obesity promote cancer development.

PROJECT 1
INVESTIGATING THE ANTI-CANCER POTENTIAL OF NEW MITOCHONDRIAL UNCOUPLERS

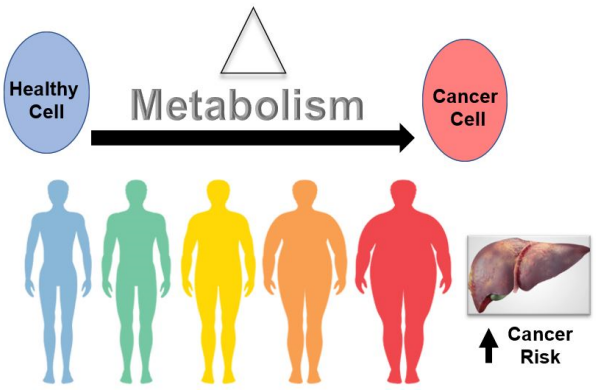
Mitochondrial uncouplers are small molecules that make mitochondria burn (oxidise) more nutrients, such as fats, without producing ATP. Thereby they 'uncouple' nutrient oxidation from ATP synthesis. Not surprisingly, these molecules have shown great promise for the treatment of obesity. However, mitochondrial uncouplers may also be effective anti-cancer agents because they disrupt the metabolism of cancer cells. This project will investigate the anti-cancer potential of new mitochondrial uncouplers developed in our laboratory. Specifically, the anti-cancer effects of these molecules will be tested alone and in combination with drugs currently used in the clinic for the treatment of cancer. This project will involve testing new uncouplers in vitro (cell culture models) and in vivo (mouse models of cancer). These experiments will help us determine whether these new uncouplers may be used for cancer treatment in the future.

Reference:

Shrestha, R., Johnson, E., and Byrne, F. L. (2021) Exploring the therapeutic potential of mitochondrial uncouplers in cancer, Molecular Metabolism 51, 101222.

PROJECT 2
UNRAVELLING THE LINKS BETWEEN DIET, OBESITY, AND LIVER CANCER

Liver cancer is strongly linked to poor diet and obesity. Previous research suggests that high fructose diets may promote obesity and liver cancer development. This project will use mouse models to determine how diets high in fructose promote the growth of liver tumours. This project will involve feeding mice diets with different ratios of sugars (e.g., fructose and glucose), monitoring tumour growth and body fat composition, and analysis of tumour tissues. It is hoped these experiments will identify therapeutic targets to prevent the tumorigenic properties of fructose.



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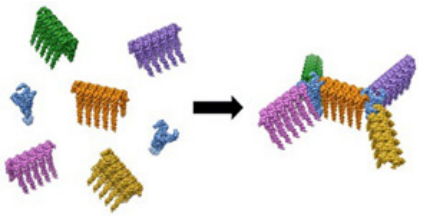
RESEARCH FOCUS

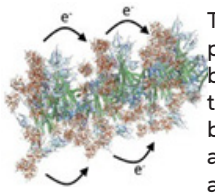
Synthetic biology and bioengineering of protein biomaterials.

Suitable for students who have majored in Biotechnology, Molecular Biology, or Microbiology.

The folding and assembly of proteins into intricate supramolecular architectures is critical to many biological functions, ranging from cellular scaffolding provided by cytoskeletal proteins to the encapsulation of nucleic acids in viral capsids. Improvements in our understanding of protein assembly is enabling the creation of biomaterials that mimic and complement biological systems. The research projects in my laboratory use synthetic biology to build functional materials and devices from self-assembling proteins.

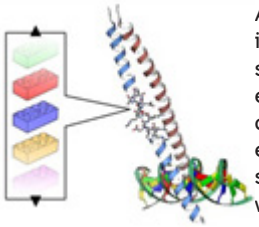


PROJECT 1
CONDUCTIVE PROTEIN NANOWIRES FOR BIOELECTRONICS AND BIOSENSORS



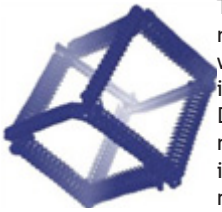
The recent discovery of conductive protein-based nanowires produced by bacteria has potential applications in the development of bioelectronics and biosensors. Exploiting this conductivity and the ability of proteins to self-assemble into complex structures may facilitate the fabrication of structured nanoscale devices that can directly interface with biological systems (e.g. enzymes or cells). This project will create novel protein nanowires by alignment of redox-active proteins on filamentous scaffolds. Subsequently, the protein nanowires will be used to mediate the transmission of electrons for novel electrical devices, biosensors or bio-batteries.

PROJECT 2
DESIGN OF SYNTHETIC TRANSCRIPTION FACTORS



An aim of synthetic biology is to engineer useful genetic systems inside living cells – for example, to make cells produce drugs or detect changes in the environment. The challenge is: can synthetic genetic circuits interfere with the rest of the cell? In this project, we will build synthetic transcription factors (synTFs) that can be used to regulate synthetic genetic circuits. Conversely, synTFs can also be used to modulate natural genes in a controllable manner. The applications of synTFs extend from the design of synthetic living systems to targeted gene/protein therapies for genetic diseases.

PROJECT 3
SELF-ASSEMBLING BIOMATERIALS FOR NANOTECHNOLOGY



The fabrication of nanoscale devices requires architectural templates upon which to position functional molecules in complex arrangements.Protein and DNA are attractive templates for nanofabrication due to their inherent self-assembly and molecular recognition capabilities. This project will will engineer a new class of biotemplates that use DNA origami to link filamentous proteins into three-dimensional templates of controllable size and symmetry. Subsequently, these novel biotemplates will serve as a foundation upon which to build functional nanodevices including molecular machines and biosensors.

Suggested references (available on request):

» Glover DJ, Giger L., Kim SS, Naik RR & Clark DS, 2016, 'Geometrical assembly of ultrastable protein templates for nanomaterials', Nature Communications, 7: 11771.
» Glover DJ & Clark DS, 2016, 'Protein calligraphy: A new concept begins to take shape', ACS Central Science, 2: 438-444.

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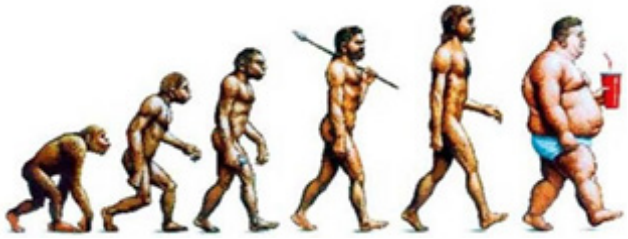
RESEARCH FOCUS

Mechanisms linking altered nutrient metabolism to obesity, cancer and diabetes.

Suitable for students who have majored in Molecular Biology, Biotechnology or Bioinformatics.

OBESITY: THE OTHER PANDEMIC



According to the World Health Organization more than 1.9 billion adults worldwide are overweight and of these over 600 million are obese. Australia is more overweight than the world average, with the Australian Bureau of Statistics estimating that 67% of the adult population is overweight, including 31% obese. Current lifestyle and drug interventions are not sufficient to reverse obesity. Obesity is associated with shortened lifespan and is a major risk factor for metabolic diseases including cardiovascular diseases, fatty liver disease, and many types of cancer. Identification of drugs that safely reverse obesity could increase healthspan, decrease disease burden, and improve quality of life on a global scale. My lab is focused on developing new drugs that reverse obesity. Our molecules are mitochondrial uncouplers that lower metabolic efficiency so that more fat is burned to produce a given amount of ATP energy. We are seeking honours students to join projects that will test new mitochondrial uncouplers for bioactivity in vitro and for safety and efficacy to reverse obesity, reverse fatty liver disease, and slow ageing in mice.

Publications in 2020:

» Alexopoulos, A.J.; Chen, S-Y.; Brandon, A.E.; Salamoun, J.; Garcia, C.J.; Beretta, M.; Olzomer, E.; Byrne, F.B.; Shah, D.; Lawrence, R.; Carrive, P.; Tucker, S.P.; Cooney, G.J.; Santos, WL, Hoehn KL. Mitochondrial uncoupler BAM15 reverses diet-induced obesity and insulin resistance in mice. Nature Communications. May 14;11(1):2397. doi: 10.1038/s41467-020-16298-2

» Salamoun J, Garcia C, Hargett S, Murray J, Chen SY, Beretta M, Alexopoulos S, Shah D, Olzomer E, Tucker S, Hoehn KL*, and Santos WL*.6-Amino-[1,2,5]oxadiazolo[3,4-b]pyrazin-5-ol Derivatives as Efficacious Mitochondrial Uncouplers in STAM Mouse Model of Non-alcoholic Steatohepatitis. Journal of Medicinal Chemistry. Jun 11;63(11):6203-6224. doi: 10.1021/acs.jmedchem.0c00542. *co-corresponding.

» Childress E, Salamoun J, Hargett SH, Alexopoulos SJ, Chen SY, Shah D, Santiago-Rivera J, Garcia C, Dai Y, Tucker SJ, Hoehn KL*, and Santos WL*. [1,2,5]Oxadiazolo[3,4-b]pyrazine-5,6-diamine Derivatives as Mitochondrial Uncouplers for the Potential Treatment of Non-alcoholic Steatohepatitis. Journal of Medicinal Chemistry. Feb 4. doi: 10.1021/acs.jmedchem.9b01440 *co-corresponding.

» Byrne FL, Olzomer EM, Marriott GR, Quek LE, Katen A, Su J, Nelson ME, Hart-Smith G, Larance M, Sebesfi VF, Cuff J, Martyn GE, Childress E, Alexopoulos SJ, Poon IK, Faux MC, Burgess AW, Reid G, McCarroll JA, Santos WL, Quinlan KG, Turner N, Fazakerley DJ, Kumar N, and Hoehn KL. Phenotypic screen for oxygen consumption rate identifies an anti-cancer naphthoquinone that induces mitochondrial oxidative stress. Redox Biology. Jan;28:101374. doi: 10.1016/j.redox.2019.101374.

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RESEARCH FOCUS

Protein biotechnology.

Suitable for students who have majored in Biotechnology, Biochemistry or Microbiology.

PROJECT 1
SEARCHING FOR NOVEL ENZYMES FOR DIPEPTIDE SYNTHESIS

Gamma-glutamyl transferase is a ubiquitous enzyme and is found to have use in the production of the dipeptide gamma glutamyl cysteine. Currently, the enzyme is sourced from native mammalian tissue. This project will explore alternative native and recombinant methods to generate active enzymes for improved industrial application of this enzyme.

PROJECT 2
RECOMBINANT REDUCTIVE DEHALOGENASES (RDAses)

Reductive dehalogenases are enzymes involved in the reductive dechlorination of polychlorinated hydrocarbons, such as hexachlorobenzene. Microbial processes to degrade hexachlorobenzene and other chlorinated hydrocarbons have been described, however the anaerobic processes in particular are relatively slow, because of low cell densities, slow growth rates and low substrate concentrations. This project will aim to evaluate an alternate host for facilitating a dehalogenation process.

PROJECT 3
RECOMBINANT SPIDER SILKS

Spider major ampullate silk is nature's toughest fibre. In order to commercialise silks for specialist functions, a recombinant approach has been pursued in bacterial and yeast hosts. The fibres generated from the proteins nonetheless have not performed as well as spider silks on tensile and other mechanical performance tests. New genomic data is now telling us that the best performing spider silks are a unique mix of MaSp1 and MaSp2 and other ampullate proteins (spidroins; (e.g. MaSp3 and 4). Some of these 'other' spidroins have only recently been discovered and sequenced. This project will systematically isolate, amplify, and express each of the spidroins in a microbial host. The proteins will then be purified and concentrated before being spun into threads using microfluidic techniques. This work will provide us insights into the mechanisms by which the expression of particular genetic patterns and the subsequent proteins are utilized to produce, both naturally and synthetically, nature's toughest fibres.

PROJECT 4
PATHWAY ENGINEERING FOR TERPENE BIOSYNTHESIS – INDUSTRY LINKED PROJECT

Cultured Terpenes and terpenoids comprise a large group of structurally diverse metabolites, produced predominantly by plants, with applications ranging from pharmaceuticals, agrochemicals, through to flavours and fragrances. Most eubacteria, plants and cyanobacteria share the same metabolic pathway (MEP pathway) supplying the cell with terpenes and terpenoids that fulfill various essential functions in photosynthesis, cellular metabolism, cellular defense, etc.. Besides transcriptional control of pathway gene expression, optimisation of the MEP pathway involves identifying limitations at the protein level. Soluble and functional expression of recombinant enzymes in the MEP pathway are crucial to the creation of core chassis strains.

In collaboration with researchers at Bondi, this project involves characterisation and optimisation of terpene/terpenoid synthase expression using a range of biochemical characterisation methods. Comparing expression levels of enzymes from different genetic backgrounds, enzyme fusions and solubility-tagged enzymes allows for an understanding in future rational enzyme engineering approaches and pathway optimisation. The project combines techniques in protein biochemistry (SDS-PAGE, Western Blot, chromatography techniques) and can be further extended to develop novel techniques to increase solubility and function of crucial enzymes involved in terpene synthesis.

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RESEARCH FOCUS

Regulation of energy expenditure in adipose tissue.

Suitable for students who have majored in Molecular Biology, Genetics, Biochemistry or Biotechnology.

We study mammalian metabolism and gene regulation, with the aim of identifying biological pathways to target for anti-obesity therapies. White adipose tissue can be converted to 'beige' adipose tissue, which burns energy to produce heat rather than storing energy. We aim to better understand beige adipose tissue so that this knowledge can be harnessed to reverse obesity. Currently, our collaborative research group includes 7 PhD students and 2 Honours students. Two Honours positions will be available for 2023.

PROJECT 1
CONTROLLING OBESITY: TRANSCRIPTIONAL REGULATION OF THERMOGENESIS

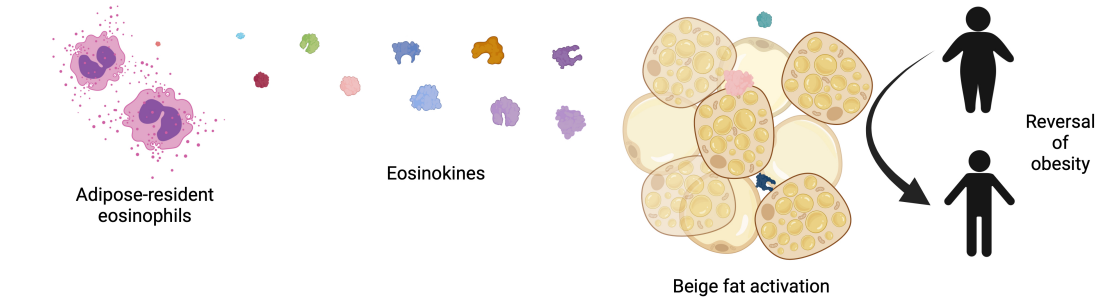
Obesity is one of the Western world's greatest medical challenges. In this project, we will investigate signalling molecules and downstream targets controlling fat cell development and energy expenditure. We are particularly interested in understanding how cells of the immune system, which naturally reside within adipose tissue, are able to signal to adipocytes and cause them to burn fat rather than store it. Our hypothesis is that eosinophils, an immune cell that resides within adipose tissue, produces signalling molecules which we call "eosinokines" that drive beiging of white adipose tissue (see diagram below).

Techniques:

Our projects offer the opportunity to learn a wide variety of molecular biology and cell biology techniques, including chromatin immunoprecipitation (ChIP), western blotting, gel shifts, subcloning and bacterial transformation, site directed mutagenesis, CRISPR/Cas9 genome editing, PCR and real-time PCR and next-generation sequencing technologies (RNA-seq and ChIP-seq), tissue culture, transient and stable transfections of mammalian cells, reporter gene assays and flow cytometry.

Recent publications:

» 'Shades of white: new insights into tissue-resident leukocyte heterogeneity'
FEBS J., 2022, 289(2):308-318.
» 'Eosinophil Function in Adipose Tissue Is Regulated by Krüppel-like Factor 3 (KLF3)' Nature Communications, 2020, 11(1):2922.
» 'Krüppel-like Factor 3 (KLF3) Suppresses NF-κB driven Inflammation in Mice.' J Biol Chem., 2020, 295(18):6080-6091.
» 'EoTHINophils: Eosinophils as Key Players in Adipose Tissue Homeostasis' Clin Exp Pharmacol Physiol, 2020, 47(8):1495-1505.



We propose that eosinophils drive beige fat activation by producing novel signalling proteins that we term 'eosinokines' which we aim to harness to reverse obesity

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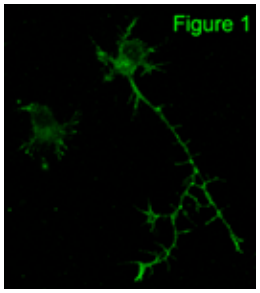
RESEARCH FOCUS

Neurobiology, neuroscience, recognition and cell adhesion in neurons.

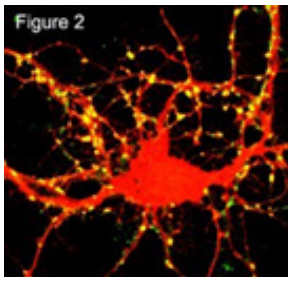
Suitable for students who have majored in Biotechnology, Biochemistry or Molecular Biology.

In the brain, information is transmitted, processed and memorised by neurons. To perform these functions, neurons must grow and form networks, in which individual neurons are connected to other neurons by specialised contacts called synapses. Neurons use synapses to communicate with other neurons and to process and store information. Formation of the networks and synapses is regulated by neural cell adhesion molecules (see our review Sytnyk et al. 2017). Our laboratory uses cutting-edge techniques of modern biochemistry, molecular biology, microscopy, biophysics and bioinformatics to understand the molecular and cellular mechanisms of neuronal network formation and regulation in health and disease. We also develop new technologies aimed at improving brain performance, enhancing learning and maintaining memory by analysing properties, functions and regulation of the neural cell adhesion molecules.

PROJECT 1
MECHANISMS OF THE NEURONAL NETWORK DEVELOPMENT



Neurons must grow long axons and develop extensively branched dendrites to make synapses with other neurons. Neural cell adhesion molecules (labelled in green in the image on the left) accumulate at the growing tips of axons and dendrites and regulate the speed and direction of the growth (see our work Sheng et al., 2015). The project will investigate how growth and recognition between neurons are regulated by the key neural cell adhesion molecules. The results of this work will help to characterise molecular mechanisms linking changes in levels of neural cell adhesion molecules to abnormal brain development.



The numbers and function of synapses (yellow dots in the image on the left) are regulated by neural adhesion molecules to encode memories during learning. In Alzheimer's disease, synapse disassembly results in memory loss. It is caused by the degradation of adhesion molecules in synapses (see our work Leshchyns'ka et al., 2015).

PROJECT 2
SYNAPTIC MECHANISMS OF MEMORY FORMATION AND MAINTENANCE

The project will study the molecular mechanisms of synapse regulation by neural cell adhesion molecules and mechanisms of adhesion loss in neurodegenerative disorders. Cellular and animal models of learning and brain disorders associated with synapse loss will be used.

Neurons must grow long axons and develop extensively branched dendrites to make synapses with other neurons. Neural cell adhesion molecules (labelled in green in the image on the left) accumulate at the growing tips of axons and dendrites and regulate the speed and direction of the growth (see our work Sheng et al., 2015). The project will investigate how growth and recognition between neurons are regulated by the key neural cell adhesion molecules. The results of this work will help to characterise molecular mechanisms linking changes in levels of neural cell adhesion molecules to abnormal brain development.

PROJECT 3
ENDOGENOUS AND ARTIFICIAL MODULATORS OF CELL ADHESION

Cell adhesion molecules are cell surface glycoproteins, the function of which is regulated by neurons at different stages of brain development and in response to a variety of external stimuli, for example during learning. This project will aim to identify and characterise new endogenous regulators of cell adhesion molecules and test artificial regulators of cell adhesion molecules to analyse their pharmacological potential in various disease models. Recombinant protein production, mass spectrometry, protein-protein interaction assays, various protein analysis tools, and cellular models will be used.

References:

» Leshchyns'ka I et al. 2015, 'Aβ-dependent eduction of NCAM2- mediated synaptic adhesion contributes to synapse loss in Alzheimer's disease', Nature Communications, 6:8836.
» Sheng L et al., 2015, 'Neural cell adhesion molecule 2 promotes the formation of filopodia and neurite branching by inducing submembrane increases in Ca2+ levels', Journal of Neuroscience, 35:1739-52.
» Sytnyk V et al, 2017, 'Neural cell adhesion molecules of the Immunoglobulin superfamily regulate synapse formation, maintenance, and function', Trends in Neuroscience, 40:295-308.

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RESEARCH FOCUS

Cellular metabolism of cholesterol and fatty acids, heart disease, cancer, obesity, and diabetes.

Suitable for students who have majored in Biochemistry, Cell or Molecular Biology or Biotechnology.

We work on two areas: the cellular dynamics of lipid droplets, adipocyte development, obesity and diabetes; and cholesterol trafficking in eukaryotic cells and its role in heart disease and cancer.

PROJECT 1
OXYSTEROL BINDING PROTEINS, INTRACELLULAR CHOLESTEROL TRAFFICKING AND NEUROLOGICAL DISEASES

Aberrant distribution of cholesterol causes heart disease and cancer. We have identified novel proteins that regulate cholesterol transport in cells. We now aim to identify additional regulators of cellular cholesterol distribution, and to understand how these proteins may regulate heart and brain function. The students will learn key techniques in cell biology such as cell culture, fluorescence microscopy etc.

Selected References:

» Ghai R, Du X, ..., Wu JW and Yang H. (2017) ORP5 and ORP8 bind phosphatidylinositol-4, 5-bisphosphate (PtdIns(4,5) P2) and regulate its level at the plasma membrane. Nature Communications, 8: 757.
» Wang H., Ma, Q., Qi, Y., Dong, J., Du, X., Rae, J., Brown A.J., Parton R.G., Wu J.W. and Yang H. (2019) ORP2 delivers cholesterol to the plasma membrane in exchange for phosphatidylinositol 4, 5-bisphosphate (PI(4,5)P2). Molecular Cell. 73, 1–16.

PROJECT 2
SEIPIN, LIPID DROPLETS, ADIPOSE TISSUE DEVELOPMENT AND HUMAN OBESITY

Human obesity is, in essence, the accumulation of lipid droplets, which are storage granules of fat. We have uncovered a role for a human disease gene – SEIPIN – in lipid droplet formation. Our recent data suggest that Seipin may regulate the metabolism of fatty acids and phospholipids.
Our current aim is to determine the molecular function of SEIPIN, and how it regulates lipid droplet morphology and adipocyte development. We are also studying other proteins that regulate lipid storage. Students will learn techniques in molecular biology such as CRISPR and lipid analyses.

Selected References:

» Liu L, Jiang QQ, ..., Zhao D and Yang H, 2014, Adipose-specific knockout of seipin/BSCL2 results in progressive lipodystrophy', Diabetes, 63:1–12.
» Pagac M, Cooper DE, ..., Coleman RA and Yang H (2016) SEIPIN regulates lipid droplet expansion and adipocyte development through modulating the activity of glycerol-3- phosphate acyltransferase. Cell Reports, 17, 1546–1559.
» Yan R., Qian H., Lukmantara I., Gao M., Du, X., Yan N. and Yang H. (2018) Human SEIPIN Binds Anionic Phospholipids. Developmental Cell, 47, 1–9.

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RESEARCH FOCUS

Structural Biology, synthetic biology, protein structure and function, biophysics, protein chemistry, X-ray crystallography, cryo-electron microscopy.

Suitable for students who are interested in understanding how proteins work at the atomic level. Students who have majored in Biochemistry, Molecular and Cell biology, Molecular Biology, Microbiology or Biotechnology.

Our research focuses on understanding how proteins work at the atomic level. Proteins are nature's choice for making cellular machines. Each protein machine is composed of well-ordered structural domains that are linked together to create a dynamic, functioning system. By mapping the structures of a protein in action, we can create a series of snapshots that reveal how the protein works in the cell. We also track protein evolution across large timescales to gain a deeper understanding in the context an organism. While traditionally, we have studied natural protein systems in order to understand function, a new challenge is to use our knowledge to design and create new protein machines using the tools of synthetic biology.

PROJECT 1

How do protein motors work? Nature has evolved spectacular protein motors such as myosin and kinesin that can "walk" down protein tracks (actin filaments and microtubules, respectively). Although these motor proteins have been studied for decades, producing a plethora of atomic structures and detailed mutagenic studies, we still have no idea how these proteins harness chemical energy (ATPase) to produce motion. A novel way to explore this question is to use a synthetic biology approach: take existing protein modules of known function and link them together to create artificial protein motors. Our lab is part of an international team that is striving to achieve this goal. We have developed a successful strategy to link functional modules together to make an artificial motor protein that will "walk" along a DNA nanotube track. This project will explore a new motor design using the same components as our current motor.

PROJECT 2 (jointly supervised with Dr Kate Michie)

How does a eukaryotic cell control the shape of the plasma membrane and associated vesicles? Underlying the eukaryotic plasma membrane is a layer of actin filaments called the cell cortex or cortical cytoskeleton. The protein ezrin (and its paralogues, the ERMs) couple membranes to cortical actin filaments. Ezrin is responsible for the maintenance of surface structures (such as microvilli) and the invagination of the plasma membrane during processes such as phagocytosis. Our key question is how does ezrin do this? We have determined crystal structures of ezrin in two states, however, we still lack a structure of the active, membrane bound form of ezrin.

Preliminary cryo electron microscopy studies show that ezrin alone can deform membrane vesicles and cluster them together. The aim of this project is to determine how ezrin achieves this, with the ultimate aim of obtaining the structure of ezrin bound to a membrane, and, finally, to actin filaments.

PROJECT 3

How do light harvesting proteins capture sunlight and transmit the energy so as to power photosynthesis? Aquatic organisms have evolved elaborate light harvesting antenna systems where proteins control the capture and transfer of energy between chromophore molecules. During evolution, at least five distinct light harvesting antenna systems have been discovered. Our research focuses on the light harvesting antennae of two classes of algae: the cryptophytes and red algae, where the former evolved from the latter via secondary endosymbiosis. The aim of this project is to explore the dramatic changes that have occurred in the antenna complexes during evolution using synthetic biology approaches. By creating protein chimeras, we will explore how changes in sequence result in dramatic structural changes in protein complexes.

References:

» Linke, H, Höcker, B, Furuta, K, Forde, N & Curmi, PM (2020) Synthetic biology approaches to dissecting linear motor protein function: towards the design and synthesis of artificial autonomous protein walkers. Biophys Rev 12:1041-1054.
» KA Michie, A Bermeister, NO Robertson, SC Goodchild, PMG Curmi, (2019) 'Two sides of the coin: ezrin/radixin/moesin and merlin control membrane structure and contact inhibition'. International Journal of Molecular Sciences 20 (8), 1996.
» Rathbone, H, Michie, K, Landsberg, M, Green, B & Curmi, P. (2021) Scaffolding proteins guide the evolution of algal light harvesting antennas. Nature Communications 12, 1890.
» Harrop, S.J., Wilk, K.E., Dinshaw, R., Collini, E., Mirkovic, T., Teng, C.Y., Oblinsky, D.G., Green, B.R., Hoef-Emden, K., Hiller, R.G., Scholes, G.D. & Curmi, P.M. (2014) Single-residue insertion switches the quaternary structure and exicton states of cryptophyte light-harvesting proteins. Proc. Natl. Acad. Sci. USA 111, E2666-E2675.

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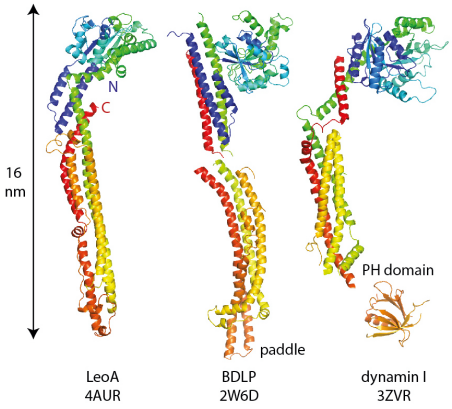
RESEARCH FOCUS

Structural Biology, X-ray crystallography, protein structure and function, protein-lipid interactions, biophysics, protein chemistry.
Suitable for students who are interested in the atomic level details of how proteins function. Students may have majored in Biochemistry, Molecular and Cell biology, Molecular Biology, Biotechnology or Microbiology

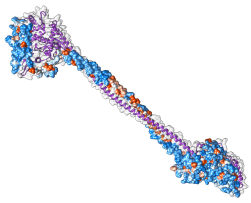
We focus on the question How does biology control the shape of the intrinsically flexible material of lipid membranes? How is the membrane tethered to the cell cytoskeleton? We use a range of biochemical and biophysical methods (including X-ray crystallography and cryo-electron microscopy) to investigate the structure of a number of types of proteins that interact with the cell membrane and with the cell cytoskeleton to control cell and organelle shapes. We are interested in these processes in all three domains of life.

PROJECT 1

In this project we ask the question: **how does a dynamin-like protein identified in Helicobacter pylori function?** All domains of life encode membrane-modelling dynamin family proteins. The archetypal Dynamin 1 assembles on a lipid bilayer and induces membrane curvature, eventually pinching off invaginating vesicles as a part of the neurotransmitter recycling pathway. We are working to understand what dynamin-related proteins are doing in bacteria. Specifically, we will address why these proteins are important for the survival of H. pylori which has impact on the development new therapeutic avenues for treating H. pylori infection. To achieve these goals, we will determine how dynamin-like proteins bind to membrane using X-ray crystallography and cryo-electron microscopy.



PROJECT 2 (jointly supervised with Professor Paul Curmi)



How is the cell cortex coupled to the membrane? This project focuses on the structural basis for the activation and control of human ezrin in this process. Underlying the cell membrane is the actin cytoskeleton (called the cell cortex), which maintains membrane shape, controls membrane movement (such as in cell motility), maintains specialised membrane structures and controls vesicular processes and trafficking. The protein Ezrin is central to the interaction between cellular membranes and the cell cortex. Previously we solved the 3D crystal structure of ezrin, now we want to understand how the structure of ezrin changes when the protein binds to lipid, and how this protein binds to actin filaments the make up the eukaryotic cell cortex.

References:

» KA Michie, A Bermeister, NO Robertson, SC Goodchild, PMG Curmi, 2019 'Two sides of the coin: ezrin/radixin/moesin and merlin control membrane structure and contact inhibition'. International Journal of Molecular Sciences 20 (8), 1996
» KA Michie, A Boysen, HH Low, J Møller-Jensen, J Löwe, 2014 'LeoA, B and C from enterotoxigenic Escherichia coli (ETEC) are bacterial dynamins', PloS one 9 (9), e107211
» KA Michie, J Löwe, 2006 'Dynamic filaments of the bacterial cytoskeleton' Annu. Rev. Biochem. 75, 467-492

APPROVED EXTERNAL HONOURS SUPERVISORS

Honours may also be undertaken with the following approved external supervisors located in institutions affiliated with the School of BABS. Students should contact these supervisors directly for information on available projects. Please note that it is UNSW policy that a BABS academic must be assigned as the primary supervisor; the external supervisor will be the designated co-supervisor.

Dr. Scott Berry
Single Molecule Science, UNSW School of Medical Sciences
E scott.berry@unsw.edu.au
T +612 9348 10790
Research area:
Quantitative microscopy to study regulation and variability of gene expression in single cells. We are interested in the mechanisms used by mammalian cells to regulate gene-specific and global RNA abundance – ranging from epigenetic memory and cellular decision-making to global mRNA metabolism in the context of cellular physiology.
More information: https://berrygroup.github.io

A/Professor Till Böcking
Single Molecule Science, UNSW School of Medical Sciences
E till.boecking@unsw.edu.au
T +612 9385 1179
Research area:
Mechanisms of molecular motors; imaging of cellular processes; single molecule biophysics.

Dr. Arcadi Cippponi
Senior Research Officer, Genomic Cancer Medicine, The Kinghron Cancer Centre
E a.cipponi@garvan.org.au
T +612 93555756
Research area:
The development of in vitro models to define cancer risks associated with germline mutations in tumour suppressor genes. The spatial resolution of transcriptional landscapes in human cancer samples. The ex-vivo functional and transcriptional profiling of DNA repair defects in primary human cells.

Professor Antony Cooper
Head, Neuroscience Division, Garvan Institute of Medical Research
E a.cooper@garvan.org.au
T +612 9295 8238
Research area:
Discovery of underlying mechanisms and biomarkers of neurodegeneration and Parkinson's Disease using neurogenomics, cell and molecular approaches on a range of in vitro and in vivo approaches.

Professor Peter Croucher
Garvan Institute of Medical Research
E p.croucher@garvan.org.au
T +612 9295 8613
Research area:
Cellular and molecular mechanisms responsible for physiological and pathological regulation of the skeleton.

Professor Sally Dunwoodie
Victor Chang Cardiac Research Institute
E s.dunwoodie@victorchang.edu.au
T +612 9295 8613
Research area:
Identifying genetic and environmental factors that impact embryogenesis and cause birth defects.
Combining human whole genome sequencing, bioinformatics, mouse models, embryo imaging, molecular/cell biology and metabolomics.
More information:
https://www.victorchang.edu.au/about-us/our-scientists/prof-sally-dunwoodie

Dr Lawrence Lee
Single Molecule Science, UNSW School of Medical Sciences
E lawrence.lee@undw.edu.au
Research area:
Synthetic biology.

Professor Bill Rawlinson AM
Director, Serology & Virology Division, SEALS Microbiology, Prince of Wales Hospital
E w.rawlinson@unsw.edu.au
T +612 9382 9113
Research area:
Molecular biology of viruses, particularly cytomegalovirus, clinical virology, enteroviruses and diabetes, and respiratory viruses.

Dr Omid Faridani
UNSW Lowy Cancer Research Centre,
Garvan Institute of Medical Research,
E o.faridani@unsw.edu.au
Research area:
We develop technologies mainly in two areas: 1) **single-cell sequencing** and 2) **liquid biopsy.** Our lab is located at two sites: UNSW Lowy Cancer Research Centre and Garvan Institute (faridanilab.com). Honour students are welcome to discuss the projects in any of these two areas.

Professor Seán O'Donoghue
BioVis Centre, Garvan Institute of Medical Research
E s.odonoghue@unsw.edu.au
T +612 9295 8329
Research Area
Systems biology, computational biology, bioinformatics.

FREQUENTLY ASKED QUESTIONS

What is the application process?

Applications for Honours are online: https://www.science.unsw.edu.au/study-us/undergraduate/honours-degrees/honours-how-apply

Before applying you will want to consider potential projects and supervisors, based on your interests (and supervisor eligibility). The School often hosts Honours networking events, which is an opportunity for potential students to meet future supervisors and vice versa. In addition, it is advised that you reach out to potential supervisors in advance of applying – via email or in person chat – to show your interest and gauge whether honours in a given research group is a good fit for you.

Once you have an idea of supervisors and projects you prefer, head to the application link; bear in mind the relevant deadlines for applications that will change for each term and that are given on the school website (https://www.babs.unsw.edu.au/study/undergraduate/honours).

It is important when you apply to list at least five supervisor preferences, in the event that your first preference is unable to take you on for any reason.

How are students allocated to supervisors?

The way the system works after all students submit their applications, the School processes them to establish a student is eligible for Honours (based on completing their BSc. as well as WAM requirements). BABS has a minimum of 65 average WAM, though there is some potential wiggle room if you are close. Once those boxes are ticked, any supervisor who has an applicant that has put them first preference is given the application where the supervisor lets the School know if they will take that student on (note: a given supervisor can take a maximum of THREE students per Honours cohort (ONE student if they are an external supervisor)).

These supervisor caps are in place to ensure both an equitable distribution of students across school academics, and also to ensure a given supervisor does not overload which can negatively affect the experience of students in their group.

Assuming you are eligible, there is a good chance you will get your first preference, but if a supervisor cannot take a given student on for any reason (e.g. they have too many students who put them as first preference, they are at capacity, other commitments, etc), then the School goes to the next supervisor preference on a student list, and so on. Thus, it is important really that students list more than just a first preference of supervisor to ensure applications are processed smoothly.

What is the application process for someone who has honours as part of their degree? (For example, Bachelor of Biotechnology (Honours).

Same as above, more details here.

What is involved in a typical honours program? How many hours are required every week?

Honours is classified as a full-time, so important to keep that in mind (especially if you are juggling a part-time job etc). It really depends on the project – and you as a student – there is no prescribed expectation re hours. You will get out of it what you put in. However, it is important not to go overboard, as this can have a negative impact on your physical and mental health. Your supervisors should not be putting unreasonable and excessive demands on you – at the end of the day Honours is about you, not what a supervisor can get out of you.

How do we apply for external supervisors?

Eligible externals supervisors are listed on the BABS website, more details can be found here. Any external supervisor must be approved and establish a connection with the School, including nominating a BABS academic to act as co-supervisor for any student they supervise.

Can someone apply to both a SOMS and BABS honours and pick between them at a later stage?

As far as we are aware yes; as above, bear in mind that not every supervisor in SOMS is an eligible supervisor in BABS.

What happens when all the supervisors on your preference list are not available/full?

This is very rare to happen, but in any event the School will endeavour to find a supervisor by doing additional callouts and liaising with the student.

Do you have to speak with all the supervisors on your preference list before submitting your application?

This not compulsory, but advisable. This is so if a given supervisor does indeed get your application, they will have some idea who you are, showing your enthusiasm, commitment, interest in their work and such – all about leaving a good impression with a potential supervisor.

With supervisor that work with multiple projects, do you just focus on one of their projects or you are able to have a go at all of it?

For your Honours you will only have the capacity to focus on one project; while you may get a chance to work on the periphery of other projects in the group, it is important you work on a defined project to ensure you can realistically achieve goals.

FREQUENTLY ASKED QUESTIONS

How many candidates can each supervisor accept?

As above, a given supervisor can take a maximum of THREE students per Honours cohort (ONE student if they are an external supervisor)). This is to ensure both an equitable distribution of students across school academics, and also that a given supervisor does not overload which can negatively affect the experience of students in their group.

Will concessions be made this year due to the current COVID situation? Has a reduction of project funding occurred? If so, how has it impacted the honours projects?

Each supervisor manages their own funds, there may have been some impact on project funding due to COVID-19 but difficult to say for everyone. Specific supervisors may have adjusted their projects to be, for example, more bioinformatic-based to cope with both (any) restricted budgets and necessary social distancing requirements.

What is the tuition fee for an honours year?

Please see the university handbook here for list of relevant fees.

Other FAQs from the honours booklet and school website

Can I start Honours in Term 3?

Yes, the School of BABS offers Honours intake in all terms (1, 2 and 3).

What is included in the overall WAM and stage 3 Science WAM?

Every course completed in stages 1 to 3 is included in the overall WAM. This includes general education courses. Stage 3 Science WAM includes level 3 courses run by the Faculty of Science with the prefix: AVIA. BIOS. BEES, CLIM, GEOS, IEST, MSCI, ENVS, BABS, BIOC, BIOT, MICR, CHEM, COMP, FOOD, MATS, MATH, ANAT, NEUR, PATH, PHAR, PHSL, PSYC, PHYS, VISN or SCIF.

I only have one more course left to complete for my program. Can I start Honours and complete my last course at the same time?

No. Students must successfully complete all requirements from stages 1 to 3 of their degree before commencing Honours.

I have one more course to complete for my program, but I will be completing this in the summer session before Honours commences in Term 1. Am I still allowed to apply for a Term 1 start?

Yes. Your Honours application will be assessed as normal. If your application is successful, you will be given a conditional offer based on you passing your remaining summer session course.

I have met with a potential supervisor and they have agreed to supervise me. Does this mean I am guaranteed acceptance into Honours?

No. Potential supervisors may express their interest in supervising you for Honours and you may include them in your Project Preference List, however only the School can formally accept students into Honours and allocate students to supervisors.

Why is there a limit on the number of external supervisors we can nominate in our project preference list?

There are two reasons for this limit:
(a) to ensure that an optimum number of students undertake their Honours project while located within BABS;
(b) to ensure all students have the best possible chance to be allocated a supervisor.

External supervisors are restricted to accepting only one student per intake, making placements very competitive. Please note that for external supervisors, it is UNSW policy that a BABS academic based in the School be assigned as the primary supervisor and will co-supervise the student.

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