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2020 HONOURS INFORMATION BOOKLET

SCHOOL OF BIOTECHNOLOGY AND BIOMOLECULAR SCIENCES

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

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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 2020. 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

Dr 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 research organisations.

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 interview, 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:
scholarships.unsw.edu.au/scholarships/id/1382/4391

HOW TO APPLY FOR HONOURS IN BABS FOR 2020

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

The due date is 8 November 2019 for Term 1 commencement; TBA for Term 2 and 3 commencement.

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 dates

For commencement in Term 1 2020:
8 November 2019

For commencement in Term 2 and 3 2020:
TBA

Honours inquiries

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

RESEARCH PROJECTS

GENOMICS AND BIOINFORMATICS

CLUSTER STRENGTHS:

- Gene Regulation
- Systems Biology
- Neurogenomics

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.

Professor Bill Ballard

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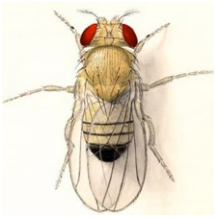
RESEARCH FOCUS

Mitochondria as a model to study biochemical and bioenergetic link between genotype and phenotype; Genetics and behaviour of the Australian Dingo

Suitable for students who have majored in Genetics and/or Biochemistry

PROJECT 1
NUTRIGENOMICS, AGEING AND ENERGY METABOLISM

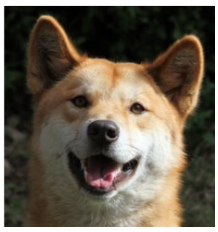


Nutrigenomics is the scientific study of the interactions between nutrition and genes. Our recent studies have shown that diet interacts with mitochondrial DNA type to influence energy metabolism, development time and longevity in Drosophila flies. At this time, we do not know the underlying mechanisms involved. This project would involve raising flies and performing physiological and biochemical assays. Skills you will develop include: working with model organisms, media preparation, quantitative PCR and oxygen respirometry. This laboratory project would be conducted in the Drosophila insectary and biochemical lab at UNSW. It will inform our understanding of how diet can be manipulated to maximally effect survival and performance of an organism's genotype.

Reference:

- Towarnicki, S.G. & J.W.O. Ballard. 2018. Mitotype interacts with diet to influence longevity, fitness and mitochondrial functions in adult female Drosophila. Front. Genet. doi.org/10.3389/fgene.2018.00593

PROJECT 2
GENETIC VARIATION IN THE AUSTRALIAN DINGO



What makes dogs so friendly? Recent studies have suggested that genetic variation in a gene associated with human Williams-Beuren syndrome (WBS) influences sociability in dogs. WBS is a multisystem congenital disorder characterized by hypersocial behaviour. This project would involve targeted resequencing of the candidate canine WBS region in dingoes and German Shepherd Dogs to look for variation within and among breeds. Answering this question will help us determine whether dingoes were ever domesticated. This project will allow you to develop skills in DNA isolation and amplification techniques, and bioinformatic analysis.

Reference:

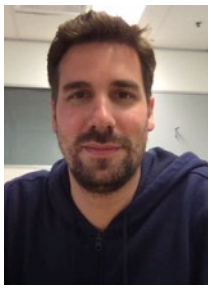
- Ballard, J.W.O. & L.A.B. Wilson. 2019. The Australian dingo: untamed or feral? Front. Zool. 16 :2, doi: 10.1186/s12983-019-0300-6

PROJECT 3
SOCIABILITY IN THE AUSTRALIAN DINGO

We have completed a sociability study comparing dingoes and German Shepherd dogs. The purpose of the study would be to analyze videos from this study to determine whether eye-gaze and eye contact differs between dingoes and German Shepherds dogs. This project would be conducted in collaboration with Professor Richard Kemp in the Department of Psychology. Students will experience a multidisciplinary approach to genetics, and may allow for further field work at the Bargo Dingo Sanctuary.

Reference:

- Von Holdt et al. 2017. Structural variants in genes associated with human Williams-Beuren syndrome underlie stereotypical hypersociability in domestic dogs. Sci Adv, e1700398



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RESEARCH FOCUS

The research in the Developmental Epigenomics lab aims to understand the contributions of the epigenome to embryonic development, evolution, and disease. We are particularly interested in how DNA methylation patterns are established, maintained and altered during those processes. 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 in both vertebrates and invertebrates.

DECODING THE BLUEBOTTLE: SYSTEM-LEVEL CHARACTERISATION OF THE INDO-PACIFIC MAN O' WAR

Siphonophores are predatory colonial animals from the phylum Cnidaria, which also includes corals, sea anemones, and jellyfish. Sometimes regarded as a metaorganism, each colony is formed by several different individual polyps also known as zooids. Unlike in other cnidarians, in siphonophores each zooid type has a specialised morphology and a specific role. In Australia, the siphonophore Indo-pacific man o' war (Physalia utriculus), also known as the bluebottle, frequents our beaches in swarms every year resulting in thousands of painful stings.

The bluebottle, just like other siphonophores such as coral, is a colony of zooids. However, major differences exist between bluebottle zooids and those of coral, for example. Whereas the zooids in a coral colony are all functionally identical, in the bluebottle the zooids have specialised to the extent that they are no longer able to survive on their own. The relative yearly abundance of the bluebottle on Australian beaches thus allows for the opportunity to undertake systematic characterisation of its complex life cycle. The major goals of this research are to characterise the bluebottle at the molecular level through understanding its genome, transcriptome, and epigenome of functionally specialised zooids, and the toxin composition responsible for its painful sting.

We aim to reveal for the first time how complex colonial meta-organisms made of highly differentiated individuals have evolved, in a process that mirrors major evolutionary transitions towards integrated complexity.

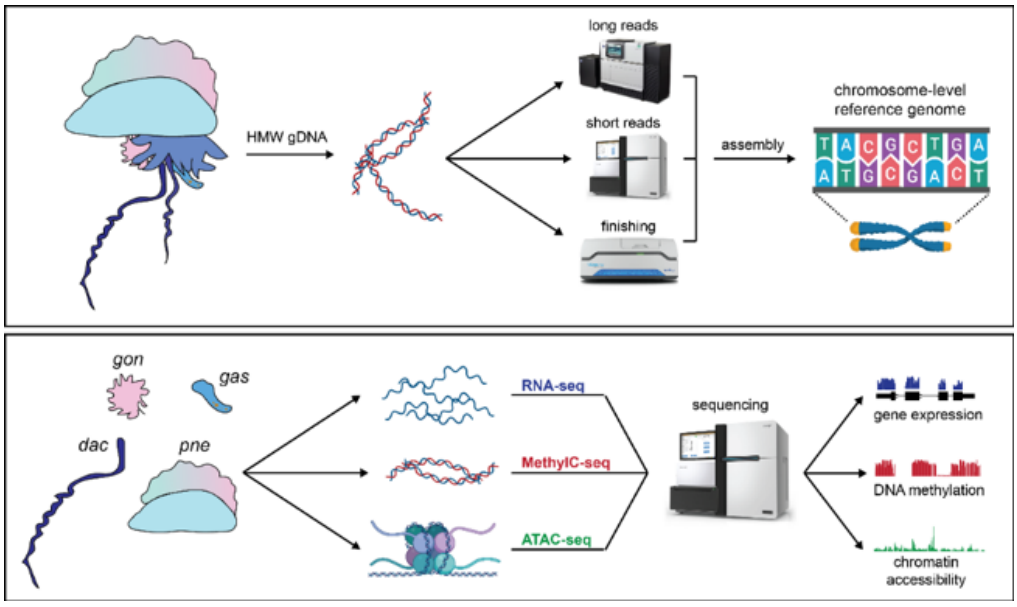

Figure 1. Schematics of the genome sequencing and assembly strategy and diagram of functional genomics techniques that will be employed to characterise zooid-specific transcriptomes, DNA methylomes, and accessible chromatin.

Professor Merlin Crossley

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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 2 Postdoctoral Associates, 6 PhD students and 2 Honours students. Two Honours positions will be available for 2020.

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

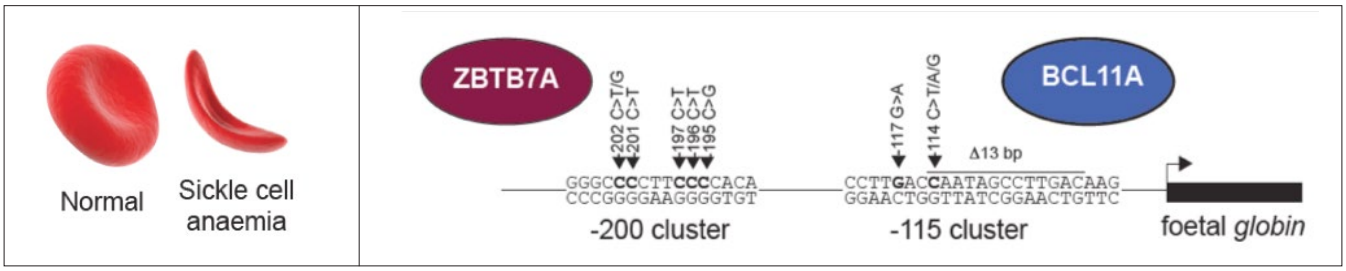
Sickle cell anaemia and thalassaemia are debilitating blood diseases that arise due to mutations in adult globin genes. In this project, we will investigate the signaling cascades and networks involved in developmental regulation of globin gene expression, with an ultimate aim of reactivating the foetal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

- 'Natural regulatory mutations elevate the fetal globin gene via disruption of BCL11A or ZBTB7A binding.' *Nature Genetics*, 2018 50(4):498-503
- 'KLF1 drives the expression of fetal hemoglobin in British HPFH.' *Blood*, 2017 130(6):803-807.
- '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
- 'Editing the genome to introduce a beneficial naturally occurring mutation associated with increased fetal globin', *Nature Communications*, 2015, 6:7085



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RESEARCH FOCUS

Molecular genetics, Genomics

Suitable for: Students who have majored in Molecular Biology, Genetics, Bioinformatics, Microbiology or Biotechnology

Our research focuses on establishing new links between phenotype and genotype, particularly between rare and complex disease and underexplored regions of the genome, such as pseudogenes, repetitive elements, and those folding into non-canonical DNA structures or are transcribed into noncoding RNAs.

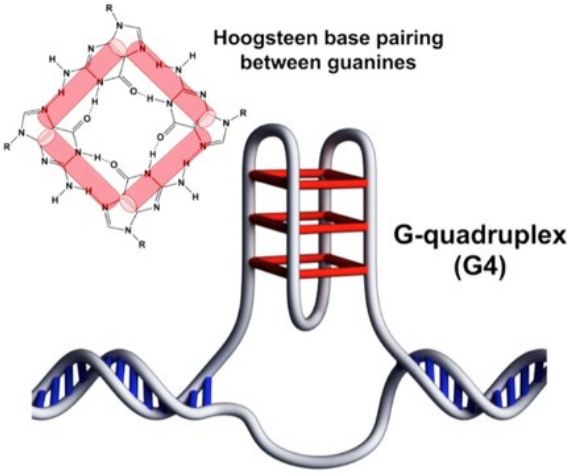
Four-stranded nucleic acids including G-quadruplexes and i-Motifs are emerging as biologically relevant DNA/RNA structures. Formation of these structures in cells have biological implications and aberrations that affect their stability can result in pathological conditions. We aim to develop novel biological and computational tools to study these structures. Currently, we have Honours projects available to investigate regulatory roles of these structures using a variety of molecular biology techniques, advanced microscopy, next generation sequencing, and bioinformatics analyses. Students will be encouraged to gain experiences in both wet and dry lab.

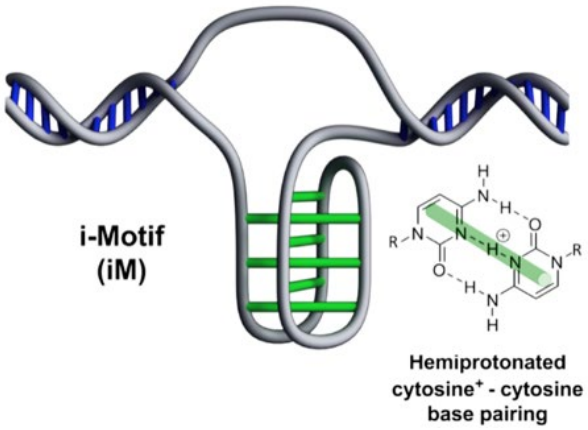
PROJECT 1
INVESTIGATING THE BIOLOGICAL RELEVANCE OF I-MOTIF RNA

Cytosine-rich sequences can form i-Motif structure. We have recently demonstrated that i-Motif DNA structures are formed in the nuclei of human cells and may have regulatory functions. In general, i-Motif RNA structures are less stable than their DNA counterparts and no regulatory function has been assigned to them. In this project, we will investigate sequences in the human transcriptome that can form i-Motif RNA with the ultimate goal of understanding their regulatory roles.

PROJECT 2
DETERMINING THE RELATIONSHIP BETWEEN STRUCTURE AND FUNCTION OF TERRA

Telomeric repeat-containing RNA (TERRA) is a long non-coding RNA transcribed from human telomeric regions. TERRA involves in regulation and protection of chromosome ends and it induces a genome-wide alteration of gene expression in some type of cancer cells. Interestingly, TERRA can fold into a G-quadruplex structure. In this project, we will examine to what extent the formation of a G-quadruplex structure by TERRA is important for its function, with an emphasize on its potential role in the cancer development.





References:

- Zeraati M; Langley DB; Schofield P; Moye AL; Rouet R; Hughes WE; Bryan TM; Dinger ME*; Christ D*, 2018, 'I-motif DNA structures are formed in the nuclei of human cells', Nature Chemistry, vol. 10, pp. 631 - 637
- Thomson DW; Dinger ME, 2016, 'Endogenous microRNA sponges: Evidence and controversy', Nature Reviews Genetics, vol. 17, pp. 272 - 283
- Clark MB; Mercer TR; Bussotti G; Leonardi T; Haynes KR; Crawford J; Brunck ME; Cao KA L; Thomas GP; Chen WY; Taft RJ; Nielsen LK; Enright AJ; Mattick JS; Dinger ME, 2015, 'Quantitative gene profiling of long noncoding RNAs with targeted RNA sequencing', Nature Methods, vol. 12, pp. 339 - 342

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SENIOR LECTURER

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RESEARCH FOCUS

Investigation of the human transcriptome in neurological diseases and cancer using RNA sequencing and bioinformatics

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

Our research focuses on studying circular transcriptome in the human brain and peripheral tissues using RNA sequencing. We are particularly interested in the role of circular RNAs (circRNAs) in regulation of molecular physiology of human tissues. Moreover, we aim to identify circRNAs which can serve as biomarkers of early onset of human complex diseases.

PROJECT 1
INVESTIGATION OF CIRCULAR RNA EXPRESSION PATTERNS IN ENDOMETRIAL CANCER

Recent advances in RNA sequencing technology allowed discovery of a new RNA species, circular RNAs (circRNAs; Fig. 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. Endometrial cancer (EC) is the most common gynaecological malignancy in women living in developed countries such as Australia and is the only gynaecological cancer that is increasing in incidence. This has been attributed to obesity epidemic. Indeed, of all malignancies, EC has the highest association with obesity. The biomolecular and genetic profiles of obesity-related EC compared to cancers that occur in non-obese women is an exciting area that is currently of great interest. This is because of the potential identification of biomolecular pathways that can be targeted specifically with therapeutic agents to prevent or treat obesity related cancers in the uterus. The primary aim of this project is to investigate how the circRNAs expression is perturbed in EC tumour tissue in obese post-menopausal women and how these aberration correlate with expression of protein coding genes. The project will involve RNA-Seq data analysis combined with experimental validation of identified circRNA candidates.

PROJECT 2
CIRCULAR RNAS AS BIOMARKERS OF FRONTOTEMPOLAR LOBAR DEGENERATION

Frontotemporal lobar degeneration (FTLD) is the most common form of dementia after Alzheimer's disease. FTLD is characterised by progressive neurodegeneration of the frontal and temporal lobes. Clinical symptoms observed in FTLD patients include progressive changes in behavior and personality, executive dysfunction, and a decline in language skills. The disease mechanisms of FTLD remain poorly understood, but some studies indicate perturbation of RNA expression and metabolism. Expression patterns and characteristics of circRNAs make them ideal candidates as potential biomarkers for complex diseases. The overall aim of this project is to examine the hypothesis that the expression of circRNAs in FTLD brain is perturbed and this alteration is related to FTLD-specific neurodegeneration. The project will employ meta-analytical and experimental approaches to investigate differentially expressed circRNAs as well as to discover novel circular transcripts characteristic for FTLD. The outcome of this project will lead to development of new strategies in monitoring onset and progression of the disease as well as identification of new molecular targets for treatment of this disorder.

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 (2019) Neural circular transcriptomes across mammalian species. Genomics, in press.
- 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.

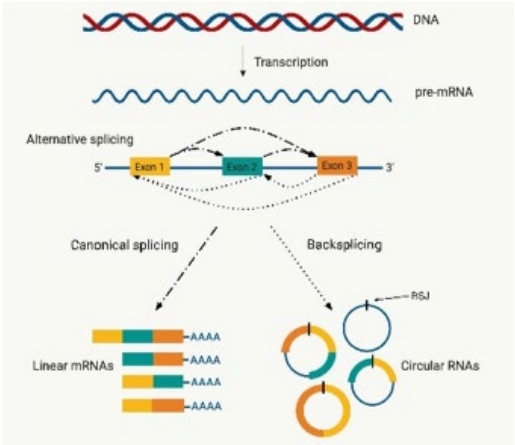

Figure 1. The formation of linear mRNAs and circular RNAs through canonical splicing and backsplicing, respectively. The mechanism of backsplicing leads to covalent linkage of the downstream 3'-end of a pre-mRNA sequence to an upstream 5'-end of the pre-mRNA strand. This process leads to generation of 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 process 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).

Associate Professor Vincent Murray

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RESEARCH FOCUS

Cancer chemotherapy; anti-tumour drugs; bleomycin

Suitable for students who have majored in Bioinformatics with an interest in Molecular and Cellular Biology

This is a Bioinformatics project. The aim of this project is to investigate the genomic locations of bleomycin cleavage in human cells.

The glycopeptide antibiotic, bleomycin, is used as a cancer chemotherapeutic agent to treat testicular cancer, squamous cell carcinoma, and Hodgkin's lymphoma. Its mechanism of action is thought to involve DNA damage and DNA cleavage. Both double-strand and single-strand breaks are formed by bleomycin although double-strand breaks are thought to be most important for the anti-tumour activity of bleomycin.

In our previous studies [1-3], the genome-wide pattern of DNA cleavage at transcription start sites (TSSs) for the anti-tumour drug, bleomycin, was examined in human HeLa cells using next-generation DNA sequencing. It was found that actively transcribed genes were preferentially cleaved compared with non-transcribed genes. The bleomycin cleavage pattern at highly transcribed gene TSSs was greatly enhanced compared with purified DNA and non-transcribed gene TSSs. The pattern of bleomycin enhanced cleavage had peaks that were approximately 200 bp apart, and this indicated that bleomycin was identifying the presence of phased nucleosomes at TSSs. Hence bleomycin can be utilised to detect chromatin structures that are present at actively transcribed genes.

Hence bleomycin can be used as a probe of chromatin structure. In this project, it is proposed that other genomic features of chromatin (other than TSSs) are investigated. These features include splice sites, promotor sites, transcription stop sites, repeated sequences, etc. A similar pipeline to the TSS procedure will be used to assess these genomic features of human cellular genomic DNA.

References:

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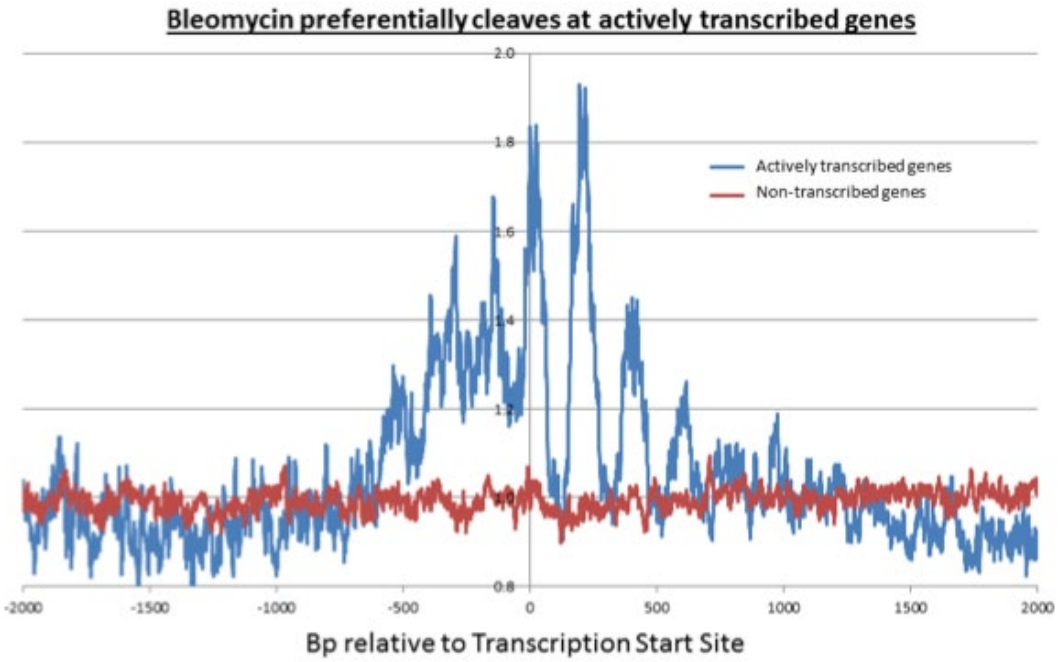
- Chen JK, Yang D, Shen B, Murray V (2017) Bleomycin analogues preferentially cleave at the transcription start sites of actively transcribed genes in human cells. International Journal of Biochemistry and Cell Biology 85:56-65.
- Murray V, Chen JK, Yang D, Shen B (2018) The genome-wide sequence specificity of DNA cleavage by bleomycin analogues in human cells. Bioorganic & Medicinal Chemistry 26:4168-4178.



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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 – even 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 also 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

Eukaryotic genomics using long-read PacBio sequencing; applying biological sequence analysis and molecular evolution to study the molecular basis of protein-protein interactions

Suitable for students who have majored in Biochemistry, Molecular Biology, Microbiology or Genetics. Would suit students with some programming experience and interests in evolution/genomics, or vice versa

PROJECT 1
DIPLOID GENOME ASSEMBLY WITH PACBIO LONG-READ SEQUENCING

The latest generation of long-read sequencing is revolutionising genomics. We are using Oxford Nanopore Technologies (ONT) and PacBio single molecule real-time (SMRT) long-reads, and 10x Chromium “linked reads”, to sequence and assemble a number of organisms including novel bacterial, yeast and vertebrate genomes. A number of student projects are available in collaboration with BABS and industry, including: improving PacBio de novo whole genome assembly; completing and annotating genomes; comparative genomics to identify molecular mechanisms for novel biological functions; improving genome size prediction from sequencing data.

PROJECT 2
MOLECULAR MIMICRY IN HOST-PATHOGEN INTERACTIONS

Many viruses hijack host cellular machinery through the molecular mimicry of host Short Linear Motifs (SLiMs). It is likely that pathogenic bacteria may employ similar strategies. This project will apply state-of-the-art SLiM prediction tools developed in our lab to published datasets of host-pathogen protein-protein interactions. This will help us understand how pathogens mess with their hosts – and how to stop them!

PROJECT 3
YEAST AS A MODEL FOR PROTEIN INTERACTION DYNAMICS

In addition to giving us bread and beer, the yeast Saccharomyces cerevisiae is an awesome eukaryotic model organism. This project will compare protein-protein interactions in humans and yeast to learn how both organisms exploit SLiMs and post-translational modifications to dynamically control the complex inner workings of their cells.

References:

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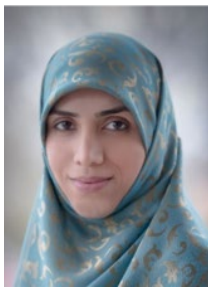
- Edwards RJ, Davey NE & Shields DC, 2007, ‘SLiMFinder: A probabilistic method for identifying over-represented, convergently evolved, short linear motifs in proteins’, PLoS ONE, 2(10): e967.
- Edwards RJ, Davey NE, O’Brien K & Shields DC, 2012, ‘Interactome-wide prediction of short, disordered protein interaction motifs in humans’, Molecular BioSystems, 8: 282-295.
- Edwards RJ et al. (2016). ‘PacBio sequencing and comparative genomics of three Saccharomyces cerevisiae strains’ [version 1; not peer eviewed], F1000Research 5:172 (poster).
- Edwards RJ et al. (2018) Pseudodiploid pseudo-long-read whole genome sequencing and assembly of Pseudonaja textilis (eastern brown snake) and Notechis scutatus (mainland tiger snake) [version 1; not peer reviewed], F1000Research 7:753 (poster).



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RESEARCH FOCUS

Systems Biology, Computational Biology, Bioinformatics

There is a well-recognised hierarchy of systems in life, from the genetic and cells to the organism and population levels. These systems are complex and exhibit emergent properties not possessed by individual components. Systems biology builds on this fundamental concept, creating a trans-disciplinary field that describes how individual components are organised into (temporal/spatial) networks to predict their emergent behaviour. My research group is focused on applying a 'systems' way-of-thinking triggered by advanced machine learning approaches to integrate diverse datatypes towards a better understanding of biological systems and unravelling the molecular complexities underlying pathogenesis. Honours students will be involved in cutting-edge multidisciplinary and collaborative ongoing research projects and encouraged to publish their research outcome.

PROJECT 1
DEEP OMICS!

Deep learning has revolutionized research in image processing and speech recognition and will soon transform research in molecular biomedicine. Deep learning models can capture multiple levels of representation directly from raw data without the need to carefully engineer features based on fine-tuned algorithmic approaches or domain expertise. Omics data is one of the most prominent examples of feature-rich and high-dimensional heterogeneous data and thus multi-omics data analysis and integration have increasingly become a deep learning harvesting field in computational biology. We are developing deep learning models to leverage large omics data for finding hidden structures within them, for integrating heterogeneous data and for making accurate predictions in different biomedical applications ranging from single-cell omics analysis and multi-omics biomarker discovery to human functional genomics and drug discovery.

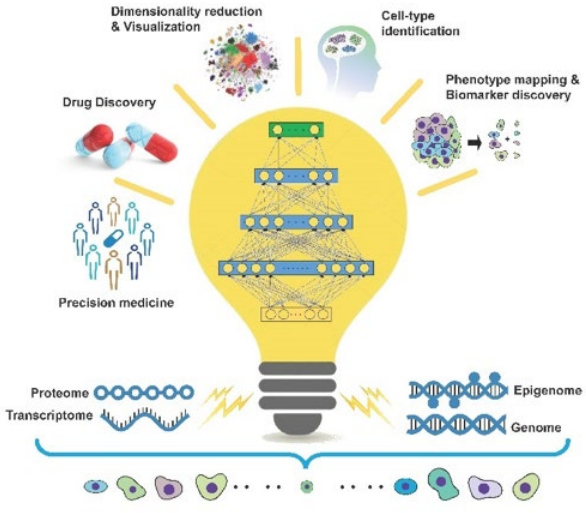
PROJECT 2
NETWORK BIOLOGY AND SYSTEMS-BASED BIOMARKER DISCOVERY

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 multi-factorial diseases (e.g., cancers, diabetes, neurodegenerative diseases). We have a number of collaborative projects on integrating multiple data sources, network and temporal information using advanced computational approaches to better understand the molecular complexity underpinning pathogenesis and to identify novel and precise biomarkers for disease early-detection, diagnosis, prognosis and drug responses paving the way for personalised medicine.

PROJECT 3
COMPUTATIONAL DRUG REPOSITIONING

De novo drug discovery is an expensive and time-consuming process. During the past years, there has been a surge of interest in drug repositioning to find new uses for existing drugs. Repositioning is economically attractive when compared with the cost of de novo drug development; it can reduce the traditional timeline of 10-17 years and make drugs available for use in 3-12 years. The number of repositioning success stories is rapidly increasing, and more companies are scanning the existing pharmacopoeia for repositioning candidates.

Computational repositioning is an emerging multidisciplinary field to develop automated workflows that can generate hypotheses for new indications of a drug candidate using multitude of high dimensional molecular data. This project is aimed to use transcriptomics, drug-target interactions, and/or genome-wide association studies (GWAS) to systematically generate repurposing hypotheses for candidate drug molecules.



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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.

PROJECT 1
THE ROLE OF THE NEURONAL SPLICING FACTOR A2BP1/RBFOX1 IN AUTISM SPECTRUM DISORDERS (ASD)

ASD are among the most heritable neuropsychiatric conditions, and at the same time genetically very heterogeneous, with hundreds of genetic loci implicated in the disease (Voineagu 2012). Given the genetic heterogeneity of ASD, a challenging yet fundamental question is whether the wide variety of genetic changes ultimately dysregulate a common set of molecular pathways, amenable as therapeutic targets. We recently demonstrated that despite genetic heterogeneity, shared abnormalities of gene expression could be detected in post-mortem brain tissue from ASD cases (Voineagu et al. 2011). A key finding of this study was that the neuronal splicing factor A2BP1 (Ataxin-2 binding protein 1) was downregulated in a large subset of ASD brains. While A2BP1 has been previously implicated in ASD, the mechanisms of its transcriptional dysregulation and the functional consequences of altered A2BP1-dependent splicing in ASD remain unknown. This project aims to (a) identify the genetic and epigenetic causes of A2BP1 transcriptional dysregulation in ASD brain, (b) elucidate A2BP1-dependent alternative splicing targets in the human brain, and (c) investigate the cellular and transcriptional consequences of A2BP1 dysfunction.

PROJECT 2
GENOMIC DIVERSITY IN THE HUMAN BRAIN: THE FUNCTIONAL ROLE OF EXPANDABLE DNA REPEATS

Although genetic variation can potentially occur anywhere in the genome, certain genomic regions are particularly susceptible to genetic changes. These regions are called hotspots of genomic instability, and are frequently underlied by repeated DNA sequences. One class of hotspots of genomic instability particularly relevant to brain function consists of expandable DNA repeats. These are tandem DNA repeats, most often trinucleotide repeats (TNRs) such as (CGG)n, (CAG)n, (GAA)n, which have an intrinsic propensity to increase in length during germline transmission. TNR expansions cause more than 30 neuro-psychiatric disorders, including Huntington's disease, Fragile X syndrome and Friedriech's ataxia (Mirkin 2007A). A surprising characteristic of human disorders caused by TNRs is that they affect primarily the brain (Mirkin 2007), although the mutation is present in all tissues, suggesting that the human brain is particularly vulnerable to this type of genetic variation. Somatic TNR expansions have been documented in the human brain at some of the TNR disease loci (Telenius et al. 1994; McMurray 2010). However, the human genome contains over 30,000 TNRs (Kozlowski et al. 2010) and whether somatic TNR expansions occur in the brain on a genome-wide scale is currently unknown. This project aims to identify somatic TNR instability events in the normal human brain and assess their effect on gene expression.

Recent publications by our Honours* students:

- Nicholls L*, Ramadas R & Voineagu I, 2014, 'From molecular pathways to ASD therapy: insights from syndromic forms of autism', in Hu V (ed), Autism Research: New Horizons for Diagnosis and Treatment, World Scientific Publishing, pp. 23-46.
- Yao P*, Lin P, Gokoolparsadh A*, Assareh A, Thang MW, Voineagu I. Coexpression networks identify brain region-specific enhancer RNAs in the human brain. Nature Neurosci. 2015 Aug;18(8):1168-74. doi: 10.1038/nn.4063.

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

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RESEARCH FOCUS

Sex chromosome structure, function, regulation and evolution

Suitable for students who have majored in Molecular Biology

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 1
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

Discovery and functional characterisation of intracellular networks

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

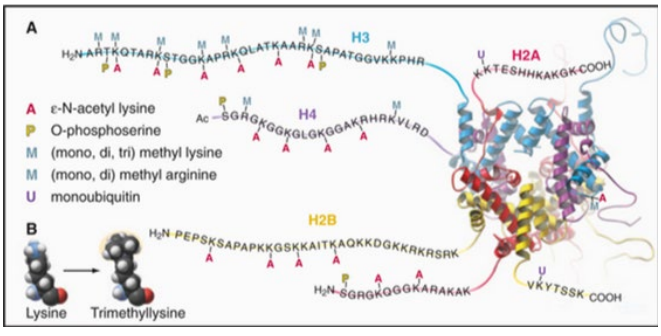
Dry-lab projects also available for students who enjoy bioinformatics and have some relevant IT skills

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!

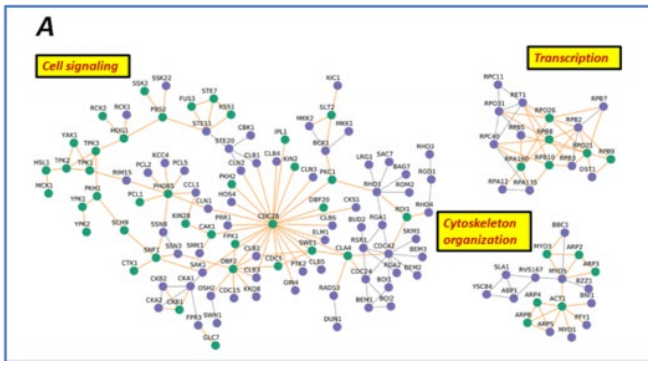
PROJECT 1
WHO'S CONTROLLING THE CONTROLLERS? DISCOVERING THE REGULATORY NETWORK OF HISTONES

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.



RESEARCH PROJECTS

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.

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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)

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.

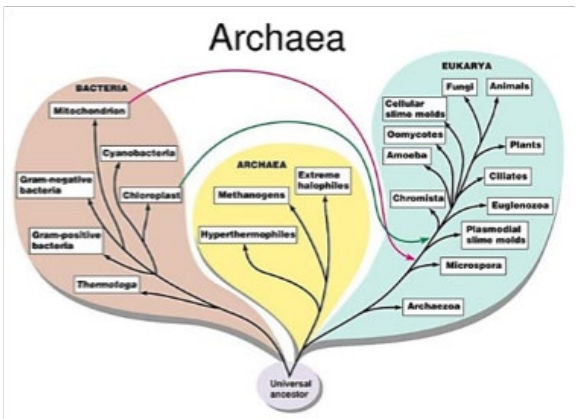
In particular we are pursuing the role of ‘microbial dark matter’ in these systems including the enigmatic group of Asgard archaea. We aim to break down the traditional distinctions between prokaryotic and eukaryotic life using the Asgardians as a ‘missing link’.

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 ex amine 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
- Hunting the elusive Asgard archaea:
  culture and evolutionary analyses
- The canary in the coalmine:
  effects of environmental change on microbial mat 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

Antarctic aquatic microbiology

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

If you are interested in Antarctic research – research relevant to the environment and health of the planet – then read on.

My group studies Antarctic microorganisms. We study lab-cultivatable microbes, particularly archaea, and use samples we obtained from Antarctic expeditions. The work includes both lab-based experimentation and bioinformatic analyses.

Research is orientated at discovering which microbes live in Antarctica, what processes they perform, how they evolved, and how they will be affected by ecosystem changes. Honours projects can be based in microbial ecology, microbial physiology, microbial genetics, genomics/proteomics and metagenomics/metaproteomics.

Specific projects:

- Grow and isolate new strains and previously uncultivated lineages of Antarctic life
- Study how and why microbes interact (e.g. host-virus, host-parasite, host-host)
- Identify microbial taxa present and the functions they perform in Antarctic lakes
- Study temporal changes (e.g. seasonal) and biogeographic distinctions in microbial populations
- Study genomic variation to determine what causes variation, what genes vary and why they vary

All students will be linked to established members of the group, and projects will be aligned to those of existing research staff and PhD students to facilitate hands-on mentoring.

See description of research, publications, research funding, and related links and videos on my web page:

research.unsw.edu.au/people/professor-rick-cavicchioli

Selected articles:

- Hamm JN et al, 2019, 'Unexpected host-dependency of Antarctic Nanohaloarchaeota'. Proceedings of the National Academy of Sciences USA, pnas.org/cgi/doi/10.1073/pnas.1905179116
- Cavicchioli R et al, 2019, 'Scientists' warning to humanity: microorganisms and climate change. Consensus Statement'. Nature Reviews Microbiology, doi.org/10.1038/s41579-019-0222-5
- Tschitschko B et al, 2018, 'Genomic variation and biogeography of Antarctic haloarchaea' Microbiome 6: 113.
- Erdmann S et al, 2017, 'A plasmid from an Antarctic haloarchaeon uses specialized membrane vesicles to disseminate and infect plasmid-free cells' Nature Microbiology, 2: 1446–1455.
- Cavicchioli R, 2015, 'Microbial ecology of Antarctic aquatic systems' Nature Reviews Microbiology, 13: 691–706.

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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.

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

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 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 3 postdoctoral associates, 1 Bioinformatician, 5 PhD students and 1 honours student.

Projects on respiratory tract pathogen *Bordetella pertussis* (co-supervised by Dr Laurence Luu)

Pertussis, commonly known as whooping cough, is an acute respiratory disease caused by *B. pertussis*. Despite widespread vaccination, pertussis remains a public health burden. Australia is currently experiencing a prolonged pertussis epidemic, with nearly 40,000 cases at its peak in 2011.

PROJECT 1
PROTEOMIC ANALYSIS OF *B. PERTUSSIS* DURING *IN VIVO* ATTACHMENT TO HUMAN RESPIRATORY EPITHELIAL CELLS

The current resurgence of pertussis has spurned renewed interest in understanding the pathogenesis of *B. pertussis* infections. Currently, most proteomic studies have been performed under *in vitro* conditions which may not reflect the proteomic changes of the bacterium during infection. The aim of this project is to elucidate key proteomic changes which contribute to colonisation when *B. pertussis* cells are co cultured with human respiratory epithelial cells. This project involves proteomics, mass spectrometry, tissue culture and bioinformatics analysis.

PROJECT 2
ELUCIDATING ESSENTIAL GENES IN *B. PERTUSSIS* UNDER INFECTION RELEVANT CONDITIONS

To combat the global re-emergence of pertussis, an improved pertussis vaccine is required to better target current strains. The simplest strategy to improve the vaccine is the addition of new antigens. Essentials genes required for infection would be ideal targets to prevent adaptation as these genes cannot be inactivated. This project will use TraDIS to elucidate the essential genes in *B. pertussis* under different infection relevant conditions. TraDIS is a technique that combines transposon mutagenesis and genome sequencing to determine the essentiality and function of every gene under specific conditions.

Projects on the use of new genomic methods to study major bacterial pathogens (co-supervised by Dr Michael Payne)

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 3
GENOMIC TYPING AND GLOBAL EPIDEMIOLOGY OF *NEISSERIA GONORRHOEAE*

Neisseria gonorrhoeae causes the sexually transmitted infection, gonorrhoea and infected an estimated 87 million people in 2018. The number of isolates with whole genome sequencing data available has grown to over 13, 000 and is increasing rapidly. This project will use these data to develop a standardised new genomic typing system with an aim to provide insights into the spread of antimicrobial resistance and global spread of *Neisseria gonorrhoeae* infections.

PROJECT 4
GENOMIC TYPING AND GLOBAL EPIDEMIOLOGY OF *STAPHYLOCOCCUS AUREUS*

Staphylococcus aureus, commonly known as golden staph, can cause a range of infections from skin lesions to severe bacteraemia and is especially common in hospital acquired infections. Methicillin resistance *Staph. aureus* (MRSA) is a major threat to global health due to its high resistance to drugs normally used to treat the infection. There are nearly 60,000 *Staph. aureus* isolates with NGS data publicly available. This project will use these data to develop new genomic typing methods to create a standardised system for examining the population structure of *Staph. aureus* and global spread of antimicrobial resistance.

Recent publications:

- Luu LDW, et al. Proteomic Adaptation of Australian Epidemic *Bordetella pertussis*. Proteomics. 2018, 18:e1700237.
- Xu Z, et al. Pertactin-Negative and Filamentous Hemagglutinin-Negative *Bordetella pertussis*, Australia, 2013-2017. *Emerging Infectious Disease*. 2019, 25:1196-1199
- Xu Z, et al. Genomic epidemiology of erythromycin-resistant *Bordetella pertussis* in China. Emerging Microbes & Infection. 2019, 8:461-470.
- Octavia S, 2015, Delineating community outbreaks of *Salmonella enterica* serovar Typhimurium by use of whole-genome sequencing: insights into genomic variability within an outbreak', J Clinical Microbiology, 53:1063.
- Fu S et al, 2015, 'Defining the core genome of *Salmonella enterica* serovar typhimurium for genomic surveillance and epidemiological typing', *J Clinical Microbiology*, 53:2530.

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RESEARCH FOCUS

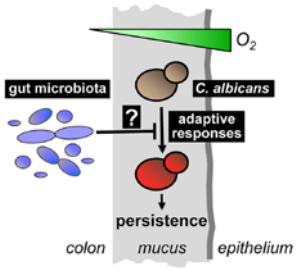
Fungal infections of humans

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%. At least as many, if not more people die from invasive fungal diseases every year than from malaria or tuberculosis. There is therefore an urgent clinical need for the development of diagnostics and new therapies for fungal diseases which research in my group aims to address in innovative ways.

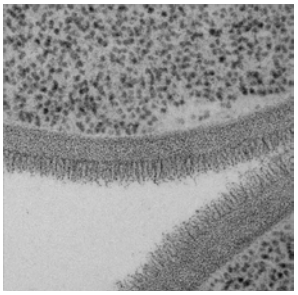
Candida albicans is the most common serious fungal pathogen of humans. This fungus colonises the gut of most healthy individuals but does not usually cause serious disease because the physical barriers between our gut and the bloodstream, combined with our immune defences and the suppressive powers of 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, organ/stem cell transplantation, or when the gut microbiota is disturbed), which renders them vulnerable to infections from the *C. albicans* that colonises their gut. Despite the availability of antifungal drugs, over 40% of these systemic infections are fatal in certain patient groups.

PROJECT 1
CANDIDA ALBICANS COLONISATION OF THE COLON



Utilising a novel *in vitro* system which mimics conditions in the human colon, projects in this area are aimed at advancing our understanding of the mechanisms by which this major pathogen adapts to and evolves in a key host niche, how this adaptation can be compromised by natural bacterial components of certain healthy GI microbiota, and how, in the future, this can be exploited to prevent *C. albicans* infections arising from the GI tract.

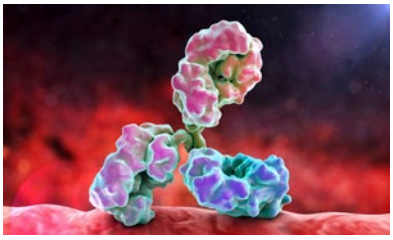
PROJECT 2
FUNGAL CELL WALL STRUCTURE AND BIOSYNTHESIS (CO-SUPERVISED BY JOANNA BIAZIK-RICHMOND, ELECTRON MICROSCOPE UNIT, MARK WAINWRIGHT ANALYTICAL CENTRE)



Understanding precisely how the cell wall components are arranged is important to properly understand the innate immune system's response to pathogenic fungi. In this project, state-of-the-art electron microscopy techniques including high pressure freezing, freeze-substitution, transmission electron microscopy, electron tomography and 3D modelling, will be utilised to image the precise ultrastructure of the cell wall of *C. albicans* cells grown in physiologically relevant conditions.

PROJECT 3
ANTIBODY-BASED THERAPIES AND DIAGNOSTICS FOR FUNGAL INFECTIONS

Antibodies that recognise components of the fungal cell surface may provide bio-tools for the development of diagnostic and therapeutic agents with utility against fungal infections. Using phage-display technology, antibody fragments which recognise specific cell surface components of *C. albicans* have been isolated. Projects in this area are aimed at improving production yields and demonstrating the therapeutic and diagnostic utility of these antibodies.



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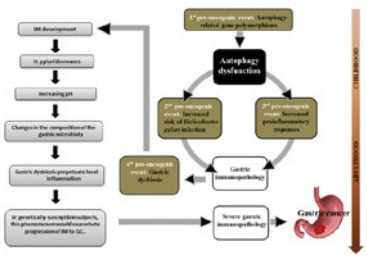
Our research focuses on the role of microorganisms and immunogenetics in the aetiology of gastrointestinal disease. We seek to understand the role of the gastric pathogen *Helicobacter pylori* on the intestinal microbiota and the effect of host genetic polymorphisms in Crohn's Disease (CD) and ulcerative colitis (UC), both forms of Inflammatory Bowel Disease (IBD). A further area of our research studies is to understand the role of *H. pylori*-induced inflammation in gastric cancer (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, the third leading cause of cancer-related deaths worldwide. 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 another microbial signature associated with disease progression could improve prevention of GC. Thus, we are currently investigating the role of gastric dysbiosis in gastric carcinogenesis.

All projects involve a range of cutting-edge technologies, including high-throughput sequencing, genome editing, gastrointestinal organoids, bacterial community analyses, 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 INFLUENCE OF *H. PYLORI* INFECTION ON THE GASTROINTESTINAL MICROBIOTA OF IBD PATIENTS

IBD is a chronic relapsing idiopathic inflammatory disease of the gastrointestinal tract, whose cause remains unclear. The overall aim of this Honours project is to use highly sensitive cutting-edge technology to identify specific bacteria or groups of bacteria that may be associated with IBD. In addition, we aim to elucidate the protective effect of *H. pylori* on IBD development by investigating the effect of *H. pylori* infection on the intestinal flora and the immune response. Supervised by Prof Mitchell and Dr Castaño-Rodríguez.

PROJECT 2
THE ROLE OF AUTOPHAGY IN *H. PYLORI*-RELATED GASTRIC CANCER



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. We are interested in the role of host genetic polymorphisms in genes involved in innate immunity including autophagy, NOD-like receptors and Toll-like receptors.

Supervised by Dr. Castaño-Rodríguez.

Dr Natalia Castaño-Rodríguez

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RESEARCH FOCUS

Gastrointestinal disease

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

PROJECT 3
DO MICROBIAL METABOLITES CONTRIBUTE TO GASTRIC CARCINOGENESIS?

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 metabolites might contribute to gastric carcinogenesis, and how key organisms in the stomach modulate these processes. Supervised by Dr Castaño-Rodríguez.

Relevant Publications

- Castaño-Rodríguez N, Kaakoush NO, Lee WS, Mitchell HM. Dual role of Helicobacter and Campylobacter species in IBD: A systematic review and meta-analysis. Gut, 2015. dx.doi.org/10.1136/gutjnl-2015-310545
- Castaño-Rodríguez N, Kaakoush NO, Goh K-L, Fock KM, Mitchell HM. Autophagy in Helicobacter pylori infection and related gastric cancer. Helicobacter, 2015. dx.doi.org/10.1111/hel.12211
- Castaño-Rodríguez N, Kaakoush NO, Mitchell HM. 'Pattern-recognition receptors and gastric cancer', Front Immunol, 2014. dx.doi.org/10.3389/fimmu.2014.00336
- Castaño-Rodríguez N, Goh KL, Fock KM, Mitchell HM, Kaakoush NO. Dysbiosis of the microbiome in gastric carcinogenesis. Sci Rep, 2017. dx.doi.org/10.1038/s41598-017-16289-2
- Paramsothy S, Kamm MA, Walsh A, van den Bogaerde J, Samuel D, Leong RW, Connor SJ, Ng WSW, Paramsothy R, Kaakoush NO, M. Mitchell HM, Xuan W, Lin E & Borody T. Multi-donor intense faecal microbiota transplantation is an effective treatment for resistant ulcerative colitis: A randomised placebo-controlled trial, Lancet, 2016. dx.doi.org/10.1016/S0140-6736(17)30182-4
- Paramsothy S, Paramsothy R, Rubin DT, Kamm MA, Kaakoush NO, Mitchell HM, Castaño-Rodríguez N. Faecal Microbiota Transplantation for Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. J Crohns Colitis, 2017. dx.doi.org/10.1093/ecco-jcc/jjx063.

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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
DRUG-RESISTANT TUBERCULOSIS

Tuberculosis kills 1.5 million people each year and although effective treatment exists the prevalence of drug resistance is rising. Some strains of the TB bacterium are resistant to all first-line drugs. This project aims to understand patterns of drug resistance in tuberculosis infections by analysing molecular epidemiological data using available and new software. This work will be complemented with computer simulations of TB epidemiology and evolution.

PROJECT 2
RAPIDLY EVOLVING VIRUSES

Viruses evolve rapidly adapting to their environment within hosts. This includes escaping the host immune response. For many viruses rapid evolution is promoted by high mutation rates. But how can viruses survive when many mutations render viruses inviable? The situation is made worse by population bottlenecks, which are part of the virus life-cycle but which decrease the efficiency of natural selection. This project aims to model virus dynamics to explain how rapid evolution is possible in viruses.

PROJECT 3
MOLECULAR EPIDEMIOLOGY WITH WHOLE GENOME SEQUENCES

The post-genomic era has delivered a deluge of delicious DNA data. With unprecedented genetic resolution we can examine how populations of bacteria change over time. Whole genome sequencing of bacterial isolates has now become routine in the course of investigating outbreaks. We are now faced with the challenge of making sense of the observed patterns of variation. This project will generate ways to visualise and analyse single nucleotide polymorphisms to better understand how bacteria mutate within hosts and during the course of an outbreak.

For more information about us see
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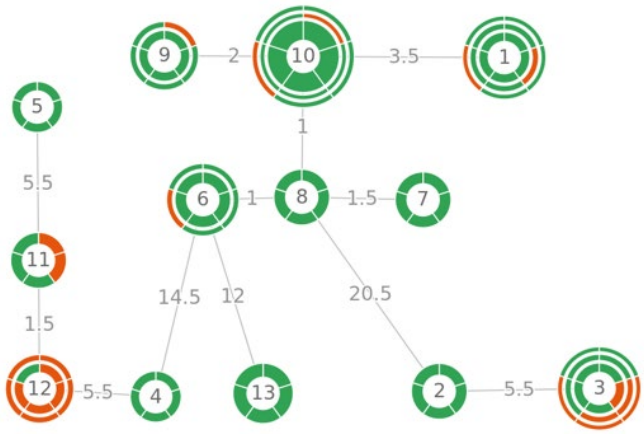

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RESEARCH FOCUS

Bacterial virulence

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

My lab has an ongoing interest in how genes involved in pathogenicity are regulated in bacterial pathogens. A major focus of the lab is understanding how pathogens use regulatory non-coding RNA (ncRNA) to control virulence. It is now apparent that all bacterial pathogens produce hundreds of ncRNAs, however we have a poor understanding of their functions. We are using cutting edge techniques to study these processes and reveal exciting new gene regulatory pathways that contribute to disease.

PROJECT 1
RNA-BASED REGULATION OF TOXIN-ANTITOXIN SYSTEMS IN PATHOGENIC *E. COLI*

Enterohaemorrhagic E. coli (EHEC) causes sporadic outbreaks of severe diarrheal disease that may lead to renal failure and death. We have recently published a map of non-coding RNA interactions in EHEC in the high impact journal EMBO (Waters et al EMBO J 2017). One of the strongest non-coding RNA interactions we recovered was with the toxin-antitoxin system MazEF that is known to promote formation of an antibiotic-tolerant state, termed a persister cell.

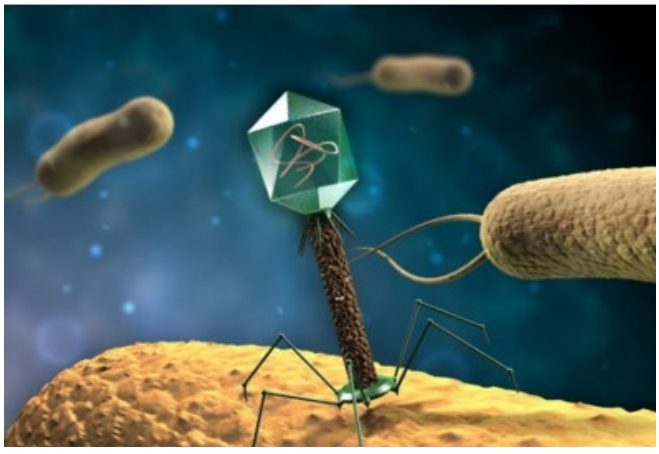
This project will use cutting edge RNA-sequencing techniques (CLIP-seq) to understand the function of MazEF in EHEC. It will also use gene deletion techniques, mutagenesis, QPCR, and GFP reporter strains to understand how non-coding RNAs modulate expression of the toxin-antitoxin system to promote EHEC pathogenesis.

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
UNDERSTANDING HOW CARBON METABOLISM CONTROLS VIRULENCE

In collaboration with colleagues at the University of Edinburgh 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

The Molecular Microbiology Laboratory lab is part of the School of Biotechnology and Biomolecular Sciences (BABS) and located in state-of-the-art facilities. Research in this multi-disciplined group encompasses molecular virology, antiviral drug discovery, viral evolution, viral biocontrol and paleovirology.

PROJECT 1
NOROVIRUS REPLICATION AND EPIDEMIOLOGY

Norovirus is the major cause of gastroenteritis outbreaks worldwide and is responsible for around 219,000 deaths each year. Major pandemics of norovirus gastroenteritis occur around every three years, with six pandemics since 1996. These pandemics are associated with novel noroviruses from a single genotype (GII.4), which escape herd immunity through both antigenic drift and shift. 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 global epidemics of gastroenteritis. We have developed a number of norovirus molecular detection and bioinformatics tools over the last few years for molecular virology studies. The aim of this project is to conduct a detailed molecular epidemiological and evolutionary analysis of Australian noroviruses, using both clinical samples and wastewater. The project will determine if current outbreaks are associated with the emergence of novel virus variants or recombinant (hybrid) viruses.

PROJECT 2
ANTIVIRAL RESEARCH: DEVELOPMENT OF SMALL COMPOUND ANTIVIRALS

Traditionally, antiviral drugs have been ‘one drug, one bug’, meaning a new drug is required to treat every virus. There is an active hunt for new, effective antivirals to treat and prevent viral infections, and drugs which target multiple viruses could be invaluable as a first line of defence. Our research focuses on the development of broad-spectrum, small compound antivirals, to combat positive sense RNA viruses in the Caliciviridae (norovirus, feline calicivirus), Flaviviridae (hepatitis C virus, Zika virus, dengue virus) and Hepeviridae (hepatitis E virus). Our main target is the viral RNA-dependent RNA polymerase (RdRp) because of its key role in viral replication. We have produced purified, soluble and active recombinant RdRps from many viruses, using Escherichia coli expression systems and used these to identify novel RdRp inhibitors. Promising inhibitors are taken forward to cell culture where we use live viruses and replicons to test their suitability as broad-spectrum drugs. In silico modelling is also performed on promising compounds to predict possible binding interations. The aim of the antiviral project is to conduct screening campaigns against the viral RdRps to identify lead compounds for potential antiviral therapies.

PROJECT 3
DISCOVERING NEW CANE TOAD VIRUSES

In 1935, 101 Hawaiian cane toads were introduced into Queensland to control the cane beetle. Now, over 2 billion feral toads ravage 1.2 million km2 of northern Australia and threaten native species. One way to eliminate the cane toad is to find new, deadly, toad-specific viruses. Previous cane toad viruses were not suitable for biocontrol as they could affect native amphibians. The aim of this project is to increase our understanding of the cane toad and to find new viruses that can infect it. Our lab is collaborating with several institutions and we have already sequenced the entire 2 Gb cane toad genome for the first time. We are performing RNA-seq and PCR-based techniques on toad tissues sourced from diverse locations to find viruses that are infecting toads in nature. This project involves a combination of wet lab work involving nucleic acid and virus extraction from toad tissues, and PCR amplification methods to find viruses. This project also involves bioinformatic analysis of toad RNA-seq data and genomic data to find virus-like sequences.

PROJECT 4
PALEOVIROLOGY: FINDING ANCIENT VIRUSES 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 genome, termed endogenous viral elements (EVEs). These viral fossils can be used to find viruses that existed thousands of years ago. Around 5% 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 life cycle. For other viruses, germ line integration is rare, but has been documented in many organisms. Using bioinformatics, our lab aims to find EVEs in diverse groups of animals. Using genomes from mosquitoes, flies, and ticks, we have identified hundreds of EVEs, and identified unique patterns and a link to innate immune pathways in the blacklegged tick Ixodes scapularis. We aim to find more viral fossils in the genomes of other animals, including marsupials, which are ecologically threatened.

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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.*

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.

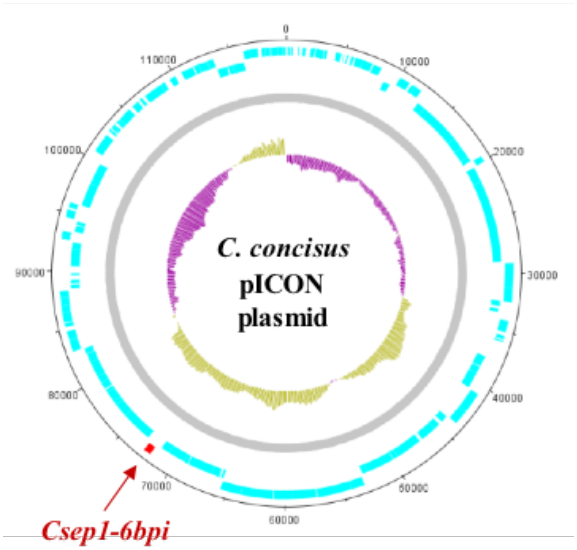

Figure 1. Circularised diagram of the pICON plasmid in *C. concisus* strain P2CDO4. (doi: 10.1038/s41426-018-0065-6)

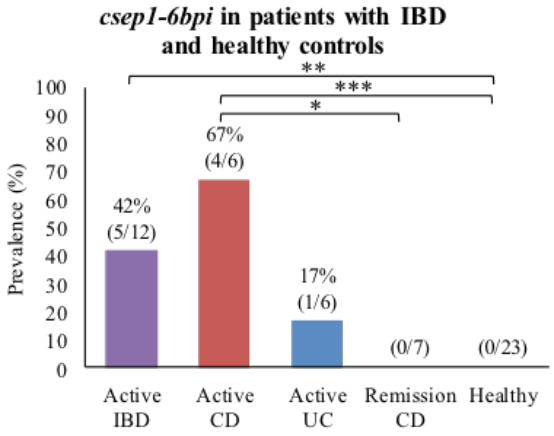

Figure 2. The prevalence of *csep1-6bpi* positive *C. concisus* strains in patients with active CD was significantly higher than that in remission CD and health controls ($P = 0.021$ and $P = 0.0006$, respectively). (doi: 10.1038/s41426-018-0065-6

RESEARCH PROJECTS

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

Evolutionary Biophysics

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

My research group currently focuses on two streams of research:

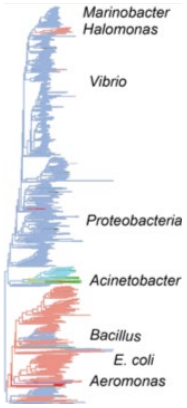
1. The directed, molecular evolution of the bacterial flagellar motor to ascertain how the motor arose and to learn what constrains the evolutionary pathways that govern the emergence of such complexity.

2. Bottom-up synthetic biology using DNA nanotechnology to control lipid interactions to investigate mechanosensing and build systems for intracellular communication.

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 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 can evolve 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.

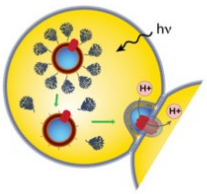
PROJECT 2
ORIGINS OF MOTILITY



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 sequence-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.

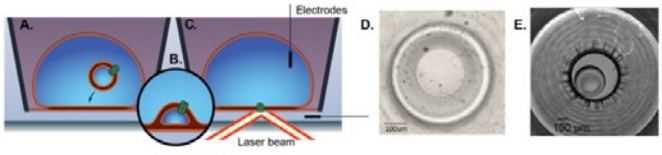
PROJECT 3
REGULATION OF MEMBRANE PROTEIN INSERTION IN ARTIFICIAL BILAYERS USING DNA ORIGAMI



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 novel DNA origami structure we can protect and controllably release our blocking DNA structures, known as DNA caltrops, to regulate the insertion of membrane proteins into these droplets. This allows us to trigger each functionality, on demand, using a small DNA ligand which removes the DNA caltrop from the proteoliposome.

PROJECT 4
MECHANISM OF MECHANOSENSING IN PIEZO1

Droplet Hydrogel Bilayers constitute the only method capable of simultaneous single channel current and fluorescence measurements. They have been used to characterise the functionality of alpha-haemolysin for use in nucleobase recognition in DNA sequencing and they have been arranged in multiple arrays to parallelise high throughput channel measurements. We recently established this platform in Australia to apply force and measure the mechanosensitive response MscL in custom bilayers. We are now using this platform to investigate the force-sensitive ion channel PIEZO1, in which single point mutations cause blood disorders such as xerocytosis and which is generally linked to cancer progression and post-traumatic osteoarthritis. Our next goal is to combine fluorescence with electrophysiology using double-labelled PIEZO1 constructs for localisation and single molecule FRET.



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RESEARCH FOCUS

Exploring potential health benefits of thiol antioxidants in human cell line models and nematodes

Suitable for students who have completed any BABS major and have a solid understanding of the electron transport chain and oxidative phosphorylation

PROJECT
ANTIOXIDANTS: Γ-GLUTAMYLCYSTEINE

γ-glutamylcysteine (GGC) is the immediate precursor to the tripeptide glutathione, which is considered the "master" antioxidant for all aerobic organisms. Many human disorders and diseases such as Alzheimer's, Parkinson's – and ageing itself – are related to the body's inability to maintain sufficient levels of glutathione within its cells.

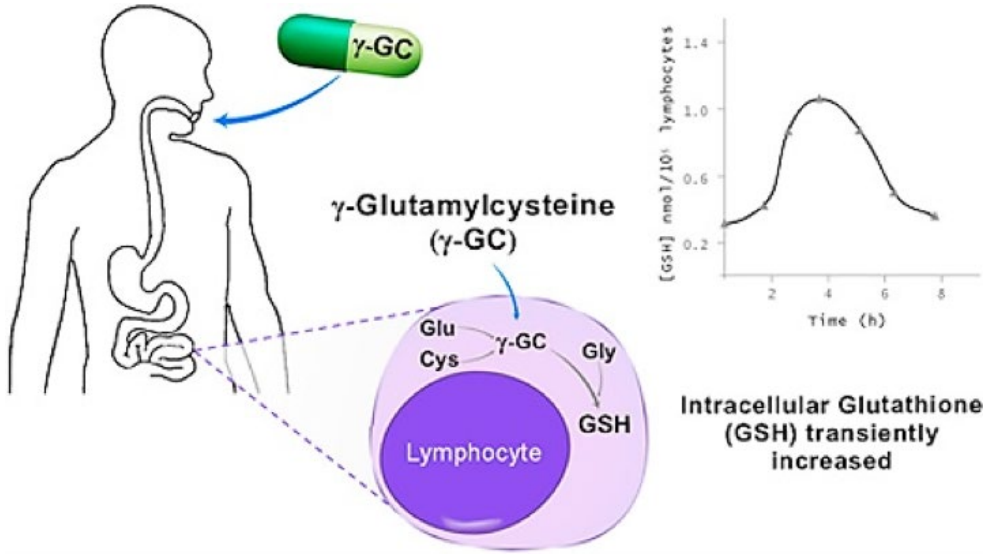
It is widely thought in the scientific community that any treatment that can replenish glutathione levels in cells would offer broad therapeutic benefits. For many instances of chronic glutathione depletion, the problem lies with damaged regulatory control of the enzyme responsible for synthesising GGC (GGC synthetase) from glutamate and cysteine. That is, GGC becomes a limiting substrate for the final synthesis reaction catalysed by glutathione synthetase (condenses GGC with glycine to form glutathione).

There are only a few natural sources of GGC, with garlic, egg white and the whey fraction of milk having the highest amounts.

High purity GGC has not been commercially available in sufficient quantities for widespread testing of its therapeutic potential. In 2006, my research group developed a biocatalytic process for GGC manufacture which we patent protected and licensed. The company is now manufacturing and commencing to sell GGC for cosmetic and dietary supplement applications in the US, where GGC has "GRAS" (generally regarded as safe) status.

As the next step towards demonstrating therapeutic benefits, we have recently completed and published a human clinical trial here at UNSW that has demonstrated that orally administered GGC can significantly increase glutathione levels in white blood cells, suggesting that GGC has systemic bioavailability. Further human clinical trials to explore any efficacy of GGC in the treatment of various diseases are being planned.

The 2020 Honours projects will continue our exploration of the therapeutic potential of GGC using human cell line and nematode models for glutathione depletion and oxidative stress. It is intended to publish any significant findings.



Oral administration of γ-glutamylcysteine increases intracellular glutathione levels above homeostasis in a randomised human trial pilot study. Redox Biology, vol. 11, April 2017, pp. 631-636.

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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. In fact, 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.

PROJECT 1
NEW FACTORS IN ACHIVEING 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. Very little attention has been paid to later steps in the pathway. This project will investigate the regulation of new control points in cholesterol synthesis, which have been largely overlooked in the past.

PROJECT 2
CHOLESTEROL AND CANCER

Cancer is a disease characterised by increased cellular replication and spread beyond the normal location in the body. A hallmark feature of cancer cells is their abnormal metabolism compared to normal cells. Notably, cells need cholesterol to grow and proliferate and mechanisms to accumulate cholesterol are far more common in cancer cells. Our lab discovered a connection between a major player involved in maintaining cholesterol balance in animal cells and a key proliferative pathway that is overactive in many cancers, including prostate cancer. This project investigates novel ways to modulate and decrease cellular cholesterol levels, which may inform the development of new anti-cancer therapies.

METHODS

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

Suggested rerferences (available on request)

- Chua NK, Hart-Smith G, Brown AJ, 2019, 'Non-canonical ubiquitination of the cholesterol-regulated degron of squalene monooxygenase', J. Biol. Chem., vol. 294(20): 8134-8147.
- Brown AJ, Chua NK, Yan N, 2019 'The shape of human squalene epoxidase expands the arsenal against cancer', Nat Comm, vol. 10(1): 888.
- Sharpe LJ, Howe V, Scott NA, Luu W, Phan L, Berk JM, Hochstrasser M, Brown AJ, 2019 'Cholesterol increases protein levels of the E3 ligase MARCH6 and thereby stimulates protein degradation', J. Biol. Chem., vol. 294(7): 2436-2448.
- Sharpe LJ, Cook E, Zelcer N, Brown AJ, 2014, 'The UPS and downs of cholesterol homeostasis', Trends Biochem Sci., vol. 39 (11): 527-35.

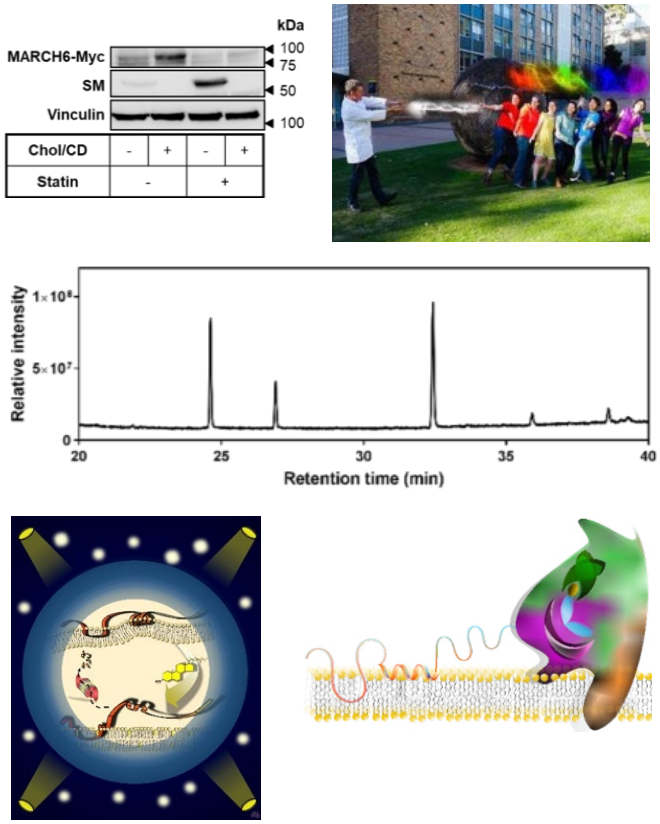

Figure 1: Cholesterol changes the shape of the cholesterol synthesis enzyme SQLE, Chua et al., JBC 2017

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RESEARCH FOCUS

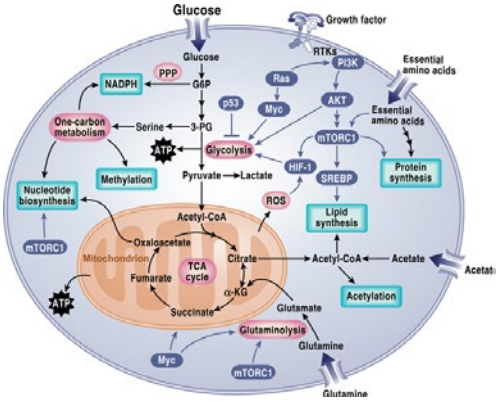
Cancer cells must reprogram their metabolism to facilitate aggressive growth and metastasis. My research is focussed on developing therapeutic strategies to block this metabolic transition and selectively kill cancer cells.

Cancer cells metabolise nutrients differently than non-cancerous cells. This altered metabolism reveals metabolic liabilities that can be targeted for anti-cancer therapy. The first project available in my team centres on developing new drugs that selectively kill cancer cells by targeting their metabolic vulnerabilities.

In recent years obesity has emerged as a major risk factor for many types of cancer, but the mechanism remains unclear. On the one hand obesity could provide access to hormones and nutrients that facilitate cancer metabolism and growth, while on the other hand obesity could have indirect effects on cancer by altering the microbiome. The second project investigates mechanisms linking obesity to cancer initiation or progression.

PROJECT 1
DEVELOPING NEW DRUGS TO SELECTIVELY KILL CANCER CELLS

Cancer cells reprogram their metabolism in order to survive and thrive in our bodies. Therefore, one way to kill cancer cells is to target their Achilles heel- that is, the way they metabolise nutrients. Our lab performed a drug screen to identify novel molecules that disrupt the metabolism of cancer cells by interfering with oxidative metabolism. From this screen we identified an exciting new molecule that kills cancer cells while leaving many 'normal' cells unharmed. By working with medicinal chemists at UNSW, we have developed new and improved molecules based on the structure of the original molecule. However, we need to perform further testing of these molecules to see how they work in vitro (in human cell cultures) and whether they can eradicate cancer in vivo (mouse cancer models). Results from this project could lead to cancer therapies that have less side effects than current chemotherapy agents. These drugs could therefore dramatically improve the quality of life of many cancer patients.



PROJECT 2
INVESTIGATING THE LINKS BETWEEN OBESITY, THE MICROBIOME AND REPRODUCTIVE CANCER

Uterine cancer is one of the most common gynecological cancers and its incidence is on the rise in Australia and other developed countries. This increase in prevalence is likely influenced by the obesity epidemic. Of all cancers, uterine cancer is most strongly linked to obesity. However, it is unclear what factors associated with obesity promote cancer growth. Exciting new research from our lab has shown that the microbiome of the uterus is different in obese vs lean women. Furthermore, the microbiome in the uterus of obese women is similar to women with uterine cancer. We hypothesize that alterations in the microbiome of the uterus promote uterine cancer growth. However, we need to do more research to test this hypothesis. This research project will involve examining the links between the microbiome and uterine health using in vitro (culture of human and bacterial cells) and in vivo (mouse) models. Results from this project could pave the way for new therapies to prevent uterine cancer.

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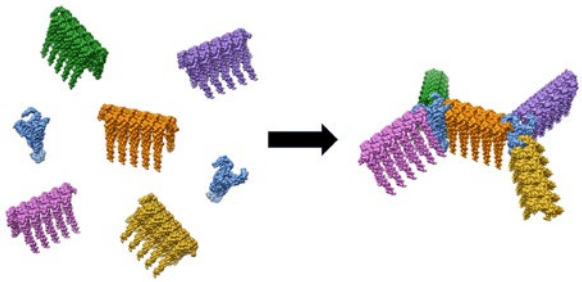
RESEARCH FOCUS

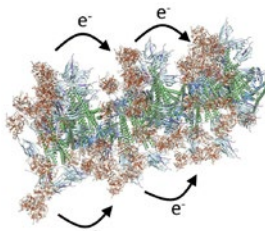
Synthetic biology and bioengineering of protein biomaterials

Suitable for students who have majored in Biotechnology or Molecular Biology

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.

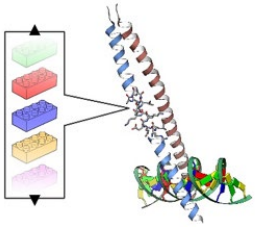


PROJECT 1
CONDUCTIVE PROTEIN NANOWIRES FOR BIOELECTRONICS AND BIOSENSORS



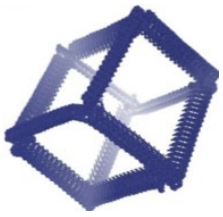
The recent discovery of conductive protein-based nanowires produced by bacteria has potential applications in the development of bioelectronics, biosensors, and bioelectrochemical interfaces. Exploiting this conductivity and the ability of proteins to self-assemble into complex structures may facilitate the fabrication of structured nanoscale devices that can directly interface with biological systems (e.g. enzymes). 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



One of the aims 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 these 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 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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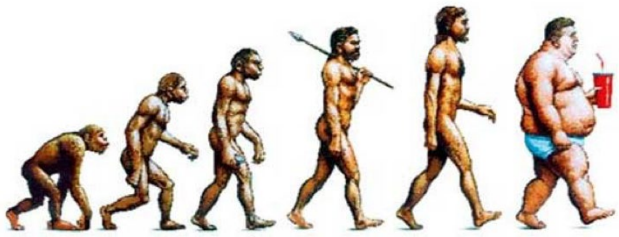
RESEARCH FOCUS

Mechanisms linking altered nutrient metabolism to obesity, cancer and diabetes

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

Obesity contributes to the pathogenesis of cancer and diabetes. Research in my lab is focused on two goals. First, we aim to reverse obesity by identifying and testing new drugs that increase energy expenditure. Second, we aim to determine how obesity increases cancer risk and target the relevant pathways required for obesity-related tumourigenesis or progression.

PROJECT 1
INCREASING ENERGY EXPENDITURE FOR THE TREATMENT OF OBESITY



We have performed a chemical library screen and identified molecules that increase energy expenditure. Our lead molecule increases metabolic rate by 30% and promotes fat loss. In collaboration with chemists, we are developing and testing next-generation molecules. We are seeking an honours student to screen new molecules and test the best ones for beneficial effects in cultured cells and mice. Students undertaking this project will learn cellular bioenergetics, mitochondrial function and mouse physiology.

PROJECT 2
IDENTIFYING NEW DRUG TARGETS FOR THE TREATMENT OF OBESITY-RELATED CANCERS

Genetic analysis studies recently performed by our collaborators within BABS have identified several protein-coding and non-coding genes that are abnormally expressed in cancer tissue compared to non-cancer tissue. Some genes have been linked to other types of cancer, while others are completely new and we have no idea what they do or why they are alternately regulated in cancer. Honours student projects will involve validating differentially expressed genes by qPCR and determining their functional significance in cell growth and survival by knocking down or over-expressing the genes in cancer cells and non-cancer cells. Genes that facilitate cancer cell growth or survival represent potential new drug targets for anti-cancer therapy. Students undertaking this project will learn cancer cell biology, molecular biology, tumour metabolism, and gene editing.

References

- Beth Caruana and Kyle Hoehn. Characterization of Glucose Transporter 6 in Lipopolysaccharide-Induced Bone Marrow-Derived Macrophage Function. Journal of Immunology. Mar 2019; 202(6):1826-1832.
- Frances Byrne and Kyle Hoehn. Serial MRI Imaging Reveals Minimal Impact of Ketogenic Diet on Established Liver Tumor Growth. Cancers. Sep 2018; 10(9).
- Marin Nelson and Kyle Hoehn. Inhibition of hepatic lipogenesis enhances liver tumorigenesis by increasing antioxidant defense and promoting cell survival. Nature Communications. Mar 2017; 8:14689.
- Brandon Kenwood and Kyle Hoehn. Identification of a Novel Mitochondrial Uncoupler that Does Not Depolarize the Plasma Membrane. Molecular Metabolism. Nov 2014; 3(2):114-23.
- Daeho Park, Kyle Hoehn, and Kodi Ravichandaran. Continued clearance of apoptotic cells critically depends on the phagocyte Ucp2 protein. Nature. Aug 2011; 477(7363):220-4.

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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

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 identify a candidate reductive dehalogenase, followed by generating and evaluating a recombinant version of the enzyme.

PROJECT 3
MICROFLUIDICS FOR MAMMALIAN CELL BIOPROCESSING

Cultured mammalian cells produce valuable biopharmaceuticals and potentially provide tissues for autologous transplantation therapies. Perfusion processes are potentially useful approaches to generate high cell density cultures, suitable for industry. This project will examine application of unique microfluidic devices developed by Dr. Majid Warkiani at UTS to facilitate rapid cell separation for application in recombinant protein production processes.

PROJECT 4
BIOREACTORS FOR INVESTIGATING REDUCED BIOFILM FORMATION IN MODIFIED PVC

PVC conduits are widely used for the supply of drinking water. Microbial biofilm formation in water conduits can result in a reduction in drinking water quality; hence, there is a desire to reduce the propensity for biofilm formation by developing “self-cleaning” materials that deter biofilms by chemically-mediated nitric oxide release.

This project will examine the use of newly acquired stirred and drip-film bioreactors to establish freshwater biofilm communities on PVC and then undertake biofilm deterrence experiments on novel PVC materials generated by our collaborators.

PROJECT 5
FUNCTIONALISING OUTER MEMBRANE VESICLES FOR RECOMBINANT EXPRESSION OF MEMBRANE-BOUND PROTEINS

Outer membrane vesicles (OMVs) are “blebbed” from the surface of gram-negative bacteria such as E.coli. Under certain conditions, the rate of blebbing increases. A number of genes have been identified that control blebbing, and hypervesiculating strains have been developed that bleb at higher rates. These hypervesiculating strains provide a potential means to secrete membrane-bound recombinant proteins and create functionalised OMVs with one or more recombinant proteins present in the “blebbed vesicles”. In this project, we are interested in exploiting this property to create functional enzyme cascades in secreted OMVs.

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RESEARCH FOCUS

Gene 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 therapeutics. White adipose tissue can be converted to 'beige' adipose tissue, which burns energy to produce heat rather than energy for the cell. We aim to better understand beige adipose tissue so that this knowledge can be harnessed to reverse obesity.

Currently, our collaborative research group includes 2 Postdoctoral Associates, 6 PhD students and 2 Honours students. Two Honours positions will be available for 2020.

PROJECT 1
CONTROLLING OBESITY: TRANSCRIPTIONAL REGULATION OF ADIPOGENESIS

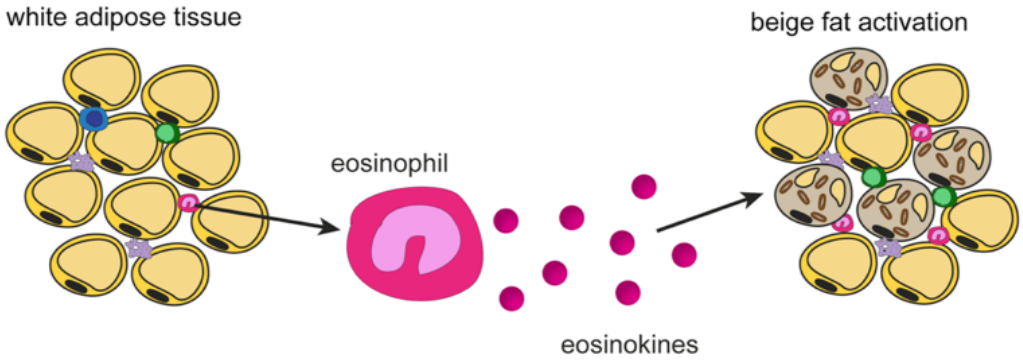
Obesity is currently one of the Western world's greatest medical challenges. In this project, we will investigate the transcriptional control in adipose tissue by identifying the signaling cascades and downstream target genes controlling fat cell development and energy expenditure. We are particularly 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.

Techniques

Our 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

- 'Defining eosinophil function in adiposity and weight loss.' Bioessays, 2018, 40(10):e1800098
- 'Genome Editing of Erythroid Cell Culture Model Systems.' *Methods Mol Biol.*, 2018, 1698:245-257
- 'Direct competition between DNA binding factors highlights the role of Krüppel-like Factor 1 in the erythroid/megakaryocyte switch.' *Scientific Reports*, 2017, 7(1):3137
- 'How does α-actinin-3 deficiency alter muscle function? Mechanistic insights into ACTN3, the 'gene for speed'.' *Biochim Biophys Acta*, 2016, 1863(4):686-693



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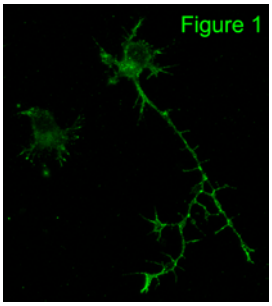
RESEARCH FOCUS

Neurobiology, neuroscience, recognition and cell adhesion in neurons

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

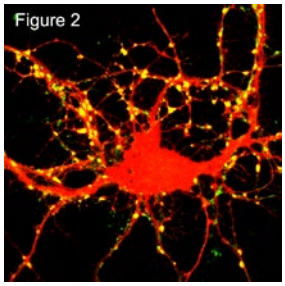
In the brain, information is transmitted, processed and memorised by neurons. To perform these functions, neurons must grow and form networks, in which individual neurons are connected to other neurons by specialised contacts called synapses. Neurons use synapses to communicate with other neurons and 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.

PROJECT 2
SYNAPTIC MECHANISMS OF MEMORY FORMATION AND MAINTENANCE



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). 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.

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 reduction 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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The Whitaker lab has demonstrated the presence of three viruses, HPV, MMTV and EBV, in Australian breast and prostate cancer specimens, suggesting a causal role in initiating carcinogenesis in these tissues. We are now focusing on identifying the mechanisms by which viruses transform cells into cancer cells.

PROJECT 1
EXAMINING CELLULAR CHANGES INDUCED BY VIRUSES

PROJECT 2
TRANSFER OF VIRUS MATERIAL TO NEIGHBOURING CELLS VIA CO-CULTURE AND BY EXOSOMES

PROJECT 3
USE OF PHAGE AS BIOCONTROL OF FOOD POISONING

For these projects, we will use basic microbiology, phage isolation, molecular and cell biology techniques, exosome isolation and transfer, retrovirus infection, Immunohistochemistry, arrays, etc.

PROJECT 4
NOVEL THERAPIES FOR ANGIOSARCOMA

Angiosarcoma, a tumour of the inner lining of the blood vessels, is a rare but often fatal condition with current treatment regimens showing limited efficacy. In dogs, hemangiosarcoma affects up to 20% of certain breeds, and shows highly similar pathology to angiosarcoma. This offers a unique disease model for the development of novel treatments for this condition. This project will use high throughput drug screening and next-generation sequencing technologies, as well as cell health and survival assays, to identify novel therapies for both dogs and humans.

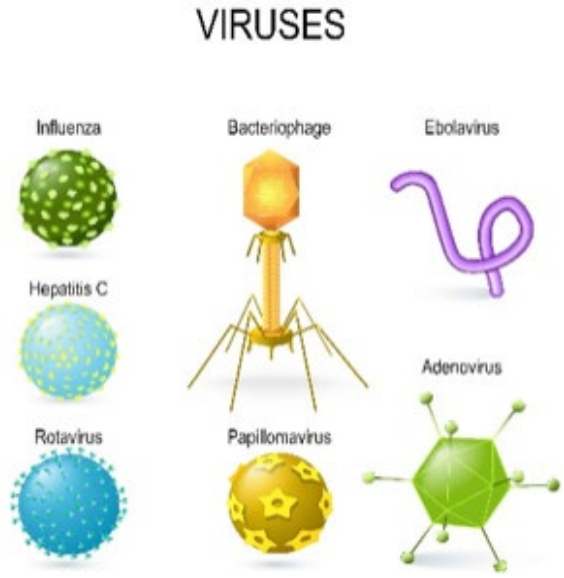
RESEARCH FOCUS

Role of viruses in human cancer; identifying novel chemotherapeutics for the treatment of cancer

Suitable for students who have majored in Molecular Biology, Biotechnology, Genetics or Medical Microbiology & Immunology

References

- Chris Hewson, David Capraro, Jon Burdach, Noel Whitaker and Kevin Morris (2016) Extracellular vesicle associated long non-coding RNAs functionally enhance cell viability. Non-coding RNA Research. Xxx. 1-9 (In Press).
- Lawson JS, Glenn WK, Salyakina D, Clay R, Delprado W, Cheerala B, Tran DD, Ngan CC, Miyauchi S, Karim M, Antonsson A, and Whitaker N J. Human papilloma virus identification in breast cancer patients with previous cervical neoplasia. Front Oncol, 5: 01 Jan 2016. doi.org/10.3389/fonc.2015.00298.
- James Sutherland Lawson, Wendy K Glenn and Noel James Whitaker. Human Papilloma Viruses and Breast Cancer – Assessment of Causality. Front Oncol, 29, 29 September 2016. Doi.org/10.3389/fonc.2016.00207.



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RESEARCH FOCUS

Cellular metabolism of cholesterol and fatty acids, 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 and neurodegenerative disorders.

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

Aberrant distribution of cholesterol causes neurodegenerative diseases such as Alzheimer's disease. 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.
- Du X., Zadoorian A., …, Brown A.J. and Yang H. (2018) Oxysterol-binding protein-related protein 5 (ORP5) promotes cell proliferation by activation of mTORC1 signaling. *J. Biol. Chem.* 293: 3806-3818.

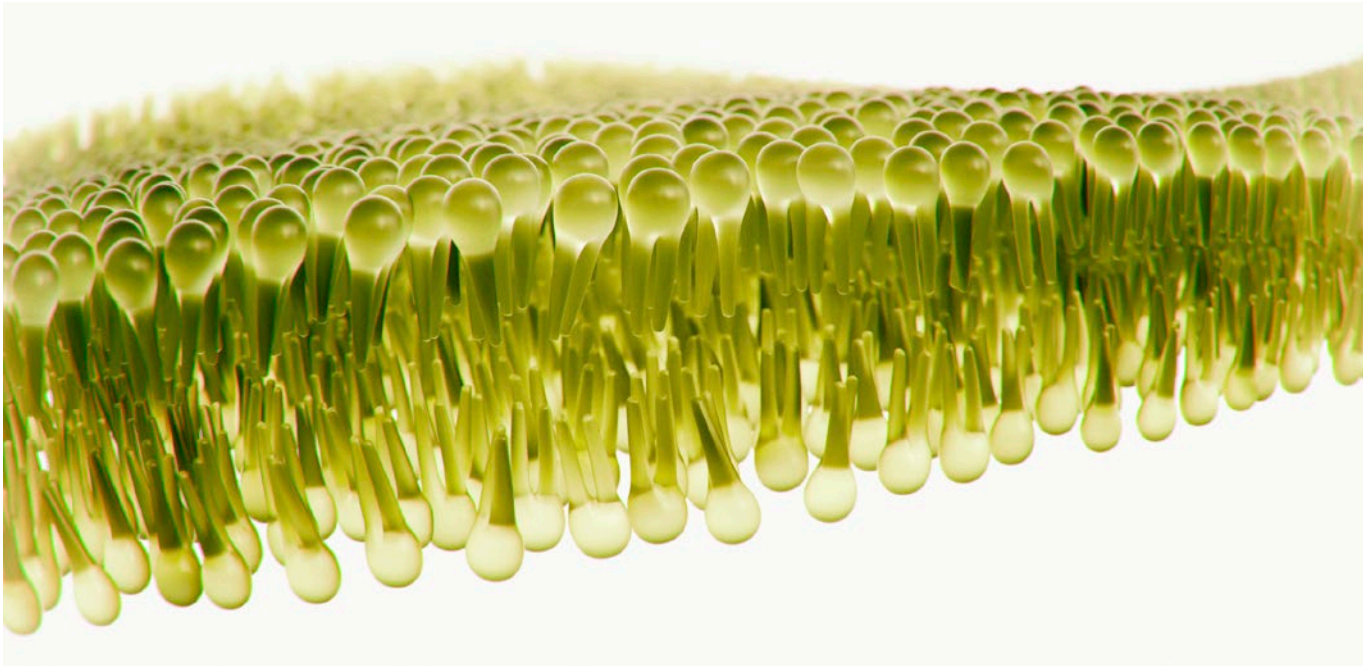
PROJECT 2
SEIPIN, LIPID DROPLETS, ADIPOSE TISSUE DEVELOPMENT AND HUMAN OBESITY

Human obesity is, in essence, the accumulation of lipid droplets, which are storage granules of fat. We have identified many mutants that affect the size and number of lipid droplets, and have also 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 techniques in lipid biochemistry and cell biology.

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.



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 Till Böcking

Single Molecule Science, UNSW School of Medical Sciences

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Research area
Mechanisms of molecular motors; imaging of cellular processes; single molecule biophysics.

A/Professor Antony Cooper

Head, Neuroscience Division, Garvan Institute of Medical Research

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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.

Dr Jennifer Cropley

St Vincent's Clinical School, UNSW Faculty of Medicine

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Research area
Epigenetics, environmental epigenetics, epigenetic inheritance.

Professor Peter Croucher

Garvan Institute of Medical Research

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Research area
Cellular and molecular mechanisms responsible for physiological and pathological regulation of the skeleton.

A/Professor Sally Dunwoodie

Victor Chang Cardiac Research Institute

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Research area
Identifying gene mutations that cause birth defects in humans through whole genome sequencing, bioinformatics, embryology, imaging and CRISPR/TALEN generation of mouse and zebrafish models of disease.

Dr Dan Hesselson

Diabetes and Metabolism Division, Garvan Institute of Medical Research

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Research area
Parkinson's Disease; functional genomics; in vivo drug discovery.

Dr Lawrence Lee

Single Molecule Science, UNSW School of Medical Sciences

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Research area
Synthetic biology.

Professor Bill Rawlinson AM

Director, Serology & Virology Division, SEALS Microbiology, Prince of Wales Hospital

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Research area
Molecular biology of viruses, particularly cytomegalovirus, clinical virology, enteroviruses and diabetes, and respiratory viruses.

Dr Catherine Suter

Victor Chang Cardiac Research Institute

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Research Area
Epigenetic variation and epigenetic inheritance in mammals.

Professor Seán O'Donoghue

BioVis Centre, Garvan Institute of Medical Research

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Research Area
Systems biology, computational biology, bioinformatics.

FREQUENTLY ASKED QUESTIONS

1 Can I start Honours in Term 3?

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

2 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.

3 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.

4 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.

5 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.

6 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.

7 Can I request an external supervisor not on the external supervisor list?

No. Students may only nominate approved BABS external supervisors. If you include any external supervisors on your preference list that are not approved, they will be ignored.

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