UNSW SYDNEY

2023 HIGHER DEGREE RESEARCH (HDR) INFORMATION HANDBOOK

SCHOOL OF BIOTECHNOLOGY AND BIOMOLECULAR SCIENCES (BABS)

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

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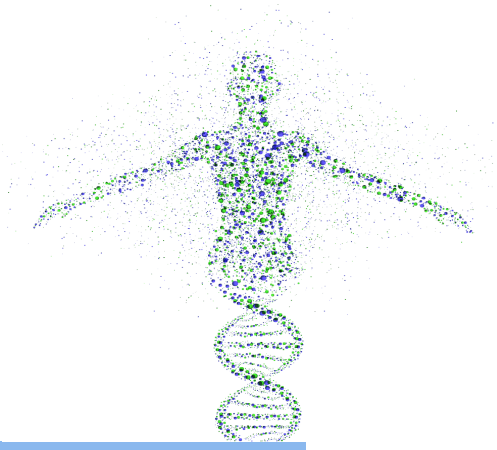


School of Biotechnology and Biomolecular Sciences

Room 520, Level 5 Biological Sciences North Building (D26)

University of New South Wales, Kensington, NSW 2033, Australia

babs-pg@unsw.edu.au

www.babs.unsw.edu.au

WELCOME FROM THE SCHOOL

This handbook provides a guide for students considering undertaking Higher Degree Research (HDR) in the School of Biotechnology and Biomolecular Sciences (BABS) at UNSW Sydney.

BABS is home to a number of active research groups that provide opportunities for postgraduate research students to work towards a PhD degree, Masters by Research or Graduate Diploma. For international students, we also offer a Master of Philosophy.

In BABS HDR programs candidates undertake a full-time research project supervised by a BABS researcher or approved external supervisor in an affiliated institution. HDR 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 candidates, 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 HDR candidates 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 HDR programs 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 candidate's experience is as enjoyable and scientifically stimulating as possible.

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

Professor Shane Grey
Head of School

Associate Professor
Cecile King
PGC - Admissions & Scholarships

Associate Professor
Jai Tree
PGC - Candidature

Dr Michael Janitz
PGC - Thesis

WHY DO A PHD IN BABS?

The Doctoral degree programs within the School of Biotechnology and Biomolecular Sciences (BABS) provide the highest level of training in key areas of scientific research. Students work on an independent research project encompassing the broader interests of one of the research teams within the School. In the early stages of the program, students receive close supervision and guidance in the management of their project. In the later stages, however, students are encouraged to exercise initiative and demonstrate originality. In the last year of the program, the candidate should be able to work independently and be guided rather than directed by the supervisor.

A key benefit of doing a PhD 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 PhD 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

A PhD is also an opportunity for the student to reflect on their future career.

PhD graduates have the opportunity to develop greater competence and confidence in the practical skills and laboratory methods acquired during their Honours year, 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.

A PhD degree requires three to four years full-time study and completion of a written thesis. The length of a doctoral thesis is normally around 100,000 words. The thesis is reviewed by members of the Australian and international scientific academic community. In the course of their research, PhD students must make a distinct contribution to the knowledge within their specific discipline. Ideally, this will result in the publication of original research findings in peer-reviewed journals of international standing.

Who is eligible for PhD?

The minimum entry requirement for a PhD is a 4-year Bachelor's degree with First or Upper Second Class honours; or with the consent of the potential supervisor, a qualification or combination of qualifications considered to be equivalent by the Faculty of Science Higher Degree Committee e.g. completion of a Bachelor degree and substantial laboratory experience.

It is essential for you to have identified a BABS supervisor who has agreed to take you on as a student prior to applying.

Applicants must provide evidence that their English language ability meets the minimum requirements for admission: English language requirements.

Further information can be obtained from the Graduate Research School (GRS).

PhD Program Options

PhD - Biochemistry & Molecular Genetics (1410)
PhD - Bioinformatics (1683)
PhD - Biotechnology (1036)
PhD - Microbiology & Immunology (1440)

FIVE REASONS STUDENTS CHOOSE TO DO A PHD

Biotechnology and Biomolecular Sciences are rapidly growing areas with broad impact. There are many rewarding career paths that require advanced knowledge in life sciences and many reasons that people decide to undertake a PhD within the School of Biotechnology and Biomolecular Sciences. Here's just a few:

Salary

Money can't buy happiness, but it doesn't hurt. UNSW students are among the highest earning undergraduates in Australia [1] and our post-graduate students are the highest earning in the country [2]. The median salary for a UNSW undergraduate student is $77,500 and with post-graduate studies, UNSW students' salary increases to $93,600. A PhD can also open avenues to more opportunities and better career progression.

Employability

UNSW post-graduates have an impressive track record of stepping out of post-graduate degrees and into full-time work. From 2018-2020, 82.5% of UNSW post-graduates research students stepped into full-time employment. Overall students with post-graduate degrees maintained a high employment rate during COVID-19 economic downturn of 2020. A PhD in BABS can help future-proof your career.

Make A Difference

Understanding and harnessing the information encoded within a cell is one of the great challenges of the 21st century. We've already seen how this can change lives (think personalised genomic medicine, CAR-T cells, and CRISPR). Research in BABS seeks to understand diverse aspects of molecular and cellular biology and translate that knowledge into real world solutions. PhD projects in BABS lead to advances in genetics, neurobiology, metabolism, infectious diseases, and environmental sciences. A PhD in BABS gives you to tools to make a difference.

Find The Cutting-edge And Stay There

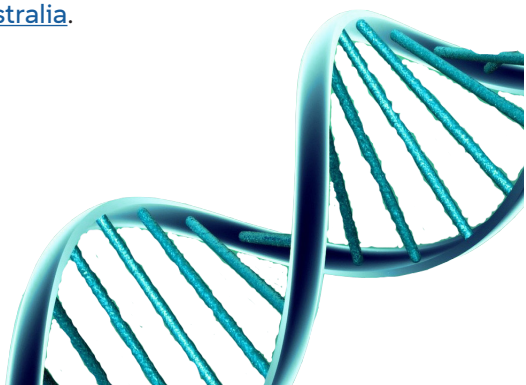
Technology is advancing at an unprecedented pace and high-quality jobs require advanced, specialist knowledge. A PhD in BABS places you at the forefront of the latest advances in life sciences and equips you with the skills to stay there.

Biotechnology And Biomolecular Sciences Are Growth Areas

Investment in biotechnology has grown rapidly for the past decades and continued to grow strongly in 2020 [3]. Investment in biomedical research returns both financial, health, and productivity gains [4] and perhaps unsurprisingly biomedical research in Australia continues to be supported by both the Government and private sector. Several new medical research institutes have recently been created - including the Randwick Health and Innovation Precinct across the road from BABS. Biotechnology and Biomolecular Sciences are areas of strong growth that can provide rewarding and lasting career paths.

Lastly, you might want to read this recent paper on 'Research Culture: Highlighting the positive aspects of being a PhD student'.

1. QILT, Nov 2020, 2020 GOS National Report - Graduate Outcomes Survey: Short-term graduate Outcomes in Australia.
2. Menzies, S, Jan 2019. UNSW among top Australian universities for high salaries.
3. DeFrancesco, L. Financing breaks all records in 2020. *Nature Biotechnology*. 2021. 39, p133.
4. Association of Australian Medical Research Institutes. Oct 2018. Economic impact of Medical Research in Australia.



OTHER HDR OPPORTUNITIES IN BABS

Masters by Research (MSc)

Each Masters program is an advanced area of study where graduates may obtain specialist knowledge in a particular area of science. These research programs focus on training students to be innovative and independent.

The MSc degree is normally two years full-time in duration and students are required to dedicate most of their time to research and the preparation of a Masters thesis. The length of a Masters research thesis normally should not exceed 75,000 words. Once completed, the thesis is examined by members of the Australian and international scientific academic community.

Who is eligible for MSc?

The minimum requirement for admission is a relevant 4-year Bachelor's degree with Honours that includes a substantial research component; or with the consent of the potential supervisor, a qualification or combination of qualifications considered to be equivalent by the Faculty of Science Higher Degree Committee.

It is essential for you to have identified a BABS supervisor who has agreed to take you on as a student prior to applying.

Applicants must provide evidence that their English language ability meets the minimum requirements for admission: English language requirements.

Further information can be obtained from the Graduate Research School (GRS).

MSc Program Options

MSc - Biochemistry & Molecular Genetics (2460)
MSc - Biotechnology (2036)
MSc - Microbiology & Immunology (2490)

Master of Philosophy (MPhil)

The Master of Philosophy (BABS) is offered to international students and is recognised as a postgraduate research degree that sits somewhere between a BSc and a PhD. It is designed to be completed over six terms (full-time), or 1.5 years, during which three subjects of coursework are undertaken and a supervised research project is completed in the supervisor's research laboratory.

The outcomes of the research project are documented in a thesis, which is examined.

This program is intended for international students who do not meet the requirements for an MSc by Research or PhD, or those wishing to develop expertise in an area different from their undergraduate degree. The MPhil should be considered as an alternative to an Honours year for international students.

This qualification allows students to experience modern and sophisticated laboratory techniques that apply to a wide range of biotechnology and molecular biology fields. To allow greater flexibility to pursue a particular area of interest, course electives may be chosen, subject to the approval of the PGC.

Who is eligible for MPhil?

International students with a first class degree or 4-year degree in a relevant discipline.

It is essential for you to have identified a BABS supervisor who has agreed to take you on as a student prior to applying.

Applicants must provide evidence that their English language ability meets the minimum requirements for admission: English language requirements.

Further information can be obtained from the Graduate Research School (GRS).

MPhil Program

MPhil - Science (2475)

Graduate Diploma

The School also offers a Graduate Diploma degree (5304). Note: this is not considered HDR so the How to Apply page and scholarship information in this handbook do not apply.

If you do not possess an Honours degree, this program is recommended as a pathway to gain a qualification for entry into the MSc or PhD programs.

Further information can be obtained from the BABS website.

UNSW SCHOLARSHIPS

UNSW Sydney Raises Stipends for Higher Degree Research Scholarships

UNSW will lift stipends for PhD and other HDR scholarship candidates from 2023, to set the benchmark for living wage stipends in Australia. In 2023, all new scholarships will be offered at the rate of $35,000pa. The rate will further increase to $37,684pa in 2024, which is in line with the current living wage. More information is available here.

International Research Scholarships

UNSW Sydney offers a number of prestigious scholarships to International Higher Degree Researcher including:

- Australian Government Research Training Program (RTP) Scholarship
- University International Postgraduate Award (UIPA)
- Tuition Fee Scholarship (TFS) plus a Research Stipend

Further information including how to apply can be obtained from the Graduate Research School (GRS).

Domestic Research Scholarships

UNSW Sydney assists Domestic Higher Degree Researchers through a range of scholarship schemes including:

- Australian Government Research Training Program (RTP) Scholarship
- University Postgraduate Award (UPA)
- Aboriginal and Torres Strait Islander Research Training Program Scholarships
- Faculty Top Up Scholarships - attached to RTP Scholarship or UPA

Further information including how to apply can be obtained from the Graduate Research School (GRS).

UNSW / Home Country Joint Scholarships

A number of UNSW / Home Country Joint Scholarships have been established to promote international collaboration for international candidates seeking to undertake PhD degree at UNSW including:

- China Scholarship Council (CSC) Scholarship
- UNSW / HEC Pakistan Joint Scholarship
- UNSW / ANID Chile Joint Scholarship
- Vietnam - Vingroup Scholarships
- GOstralia! Higher Degree Research Scholarships

Further information including how to apply can be obtained from the Graduate Research School (GRS).

Other Scholarship Opportunities

- Faculty and Donor Funded Scholarships - Further information including the current range of full or top up scholarships available to candidates can be obtained from the Graduate Research School (GRS).
- Externally Funded Scholarships - Further information including eligibility criteria, funding availability and application processes can be obtained from the Graduate Research School (GRS).

Additional Information

Find out additional information regarding scholarships here.

UNSW SCHOLARSHIPS

HDR Development and Research Training Grant (DRTG)

The DRTG scheme is a centrally funded Grant-in-Aid program that provides 2nd and 3rd year candidates with an opportunity to enhance their candidature experience by providing funding to attend conferences, as well as profile building and skill development activities.

Throughout an individual's candidature, they can apply twice to the DRTG scheme, where the maximum funding being requested is $1,500 per round ($3,000 in total over the two rounds). This funding is a contribution to the total cost of the activities, and may not necessarily fund these activities outright.

Candidates can request funding to support one or more of the five listed activities:

- Registration fees for a virtual conference (international or domestic)
- Registration, travel and/or accommodation fees for a domestic conference
- Registration, travel and/or accommodation fees for international conference
- Professional Development short courses and training opportunities
- Cost of childcare where it allows the candidate to attend one of above approved activity types

Note: This scheme is on offer in 2023. The 2024 scheme is TBC. Further information is available on the UNSW HDR Hub which can only be accessed after enrolment is completed (it is only available to current students).

UNSW PhD Candidate Paid Parental Leave Scholarship

The PhD Candidate Parental Leave Scholarship is open to PhD candidates who have been awarded a scholarship with no parental leave entitlements.

Candidates successful for this scholarship receive paid parental leave for up to 12 weeks equal to the value of their scholarship.

Further information is available on the UNSW HDR Hub which can only be accessed after enrolment is completed (it is only available to current students).

UNSW Science PhD Scholarships

The UNSW Faculty of Science offers a Science PhD Maternity Scholarship for women PhD research students who suspend their enrolment for a session to have a child. They aim to support women in research by bridging the gap and offering financial support during maternity leave.

The UNSW Science PhD Scholarships (UNSW Science PhD Writing Scholarship and UNSW Science PhD Non-Traditional Outputs Scholarship) aims to better prepare Science graduates for the job market. They support Science doctoral candidates during the three-month period between submitting their thesis and receiving the examiners' reports. This support will allow you to focus on the preparation of journal articles or other non-traditional outputs and become career-ready. Note: This scheme was on offer in 2022. The 2023 scheme may be suspended.

Further information including eligibility requirements and how to apply can be obtained from UNSW Science - PhD Maternity Scholarship and PhD scholarships.

BABS SCHOLARSHIPS

The Adrian Lee Travel Scholarship

This Scholarship is a School-funded initiative to provide eligible postgraduate research students with the opportunity to undertake study, learn new techniques, collaborate or explore opportunities for collaboration with other labs, universities or research institutions.

The value of the scholarship is $6,000 maximum, payable in one lump sum. The Scholarship is tenable for one year only (travel must be taken in the year of award).

The scholarship can be used for travel, reagents or project costs, accommodation and other related travel costs.

Further details including the eligibility requirements and application process can be found on the BABS website.

BABS HDR Travel Fund

This scheme supports eligible PhD & MSc students presenting their research at national or international conferences.

The value is $2,000 maximum for international travel and $1,000 maximum for domestic travel (awarded once only during degree).

Further details including the eligibility requirements and application process can be found on the BABS website.

HOW TO APPLY

Ready to apply for a research higher degree program at UNSW? Below outlines the steps you need to follow, including the supporting documents you need to provide, and the key dates for your application.

It is the applicant's responsibility to ensure that their application is submitted in full by the scholarship closing date. All correct and satisfactory documents must be fully submitted with the application, including English translations, Financial Declaration and proof of English. Additional documents can't be added to an application until after the application has been reviewed, which may not occur before application deadlines. Please refer to Step 3 to ensure you have the correct documents before submission.

Step 1: Determine Your Eligibility

There are a number of eligibility requirements you need to ensure you meet prior to applying for a Higher Research Degree. See here.

Step 2: Find a Supervisor and Prepare Your Research Description

Finding a supervisor with compatible research interests and working styles is critical to your success as a HDR candidate. Information on HDR supervisors and research areas can be found in this booklet or on the BABS website.

Once you have decided which supervisor 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 available projects before submitting your application. In your email, please ensure that you:

a. Identify which research area you are interested in, and why
b. Indicate which term you intend on commencing (Term 1, 2 or 3)
c. Advise your availability times for an interview
d. Attach a copy of your CV and academic transcript
e. Confirm you have available funding to cover both living expenses and the tuition fees
f. Indicate if you have appropriate visa status

More advice and resources for finding a supervisor is available here.

Step 3: Prepare Your Supporting Documentation

There are a number of supporting documents that you are required to submit with your application. Full details are available here.

Step 4: English Translations of Documents

Full details are available here.

Step 5: Meet the UNSW English Language Requirements

Full details are available here.

Step 6: Submit an Application

Once you have secured a supervisor, held your interview, developed a research description, and prepared your supporting documents, you are ready to lodge your application here. Only full applications (i.e. with all required documents) will be processed for assessment.

If you wish to be considered for a scholarship, simply indicate this on the application form and select the applicable scholarship round for your preferred term start date. For more information on applying for a scholarship, please visit Graduate Research Scholarships.

BABS program codes can be found in this handbook or on the BABS website. You can confirm the correct program code with your supervisor.

Application deadlines can be found online at Key Dates.

Further details about after you submit an application, receiving an offer and responding to an offer are available here.

BABS HDR inquiries

BABS HDR Support Officer, BABS School Office
Room 520, Biological Sciences Building D26
T +61 (0)2 9065 9717
E babs-pg@unsw.edu.au

RESEARCH SUPERVISORS -

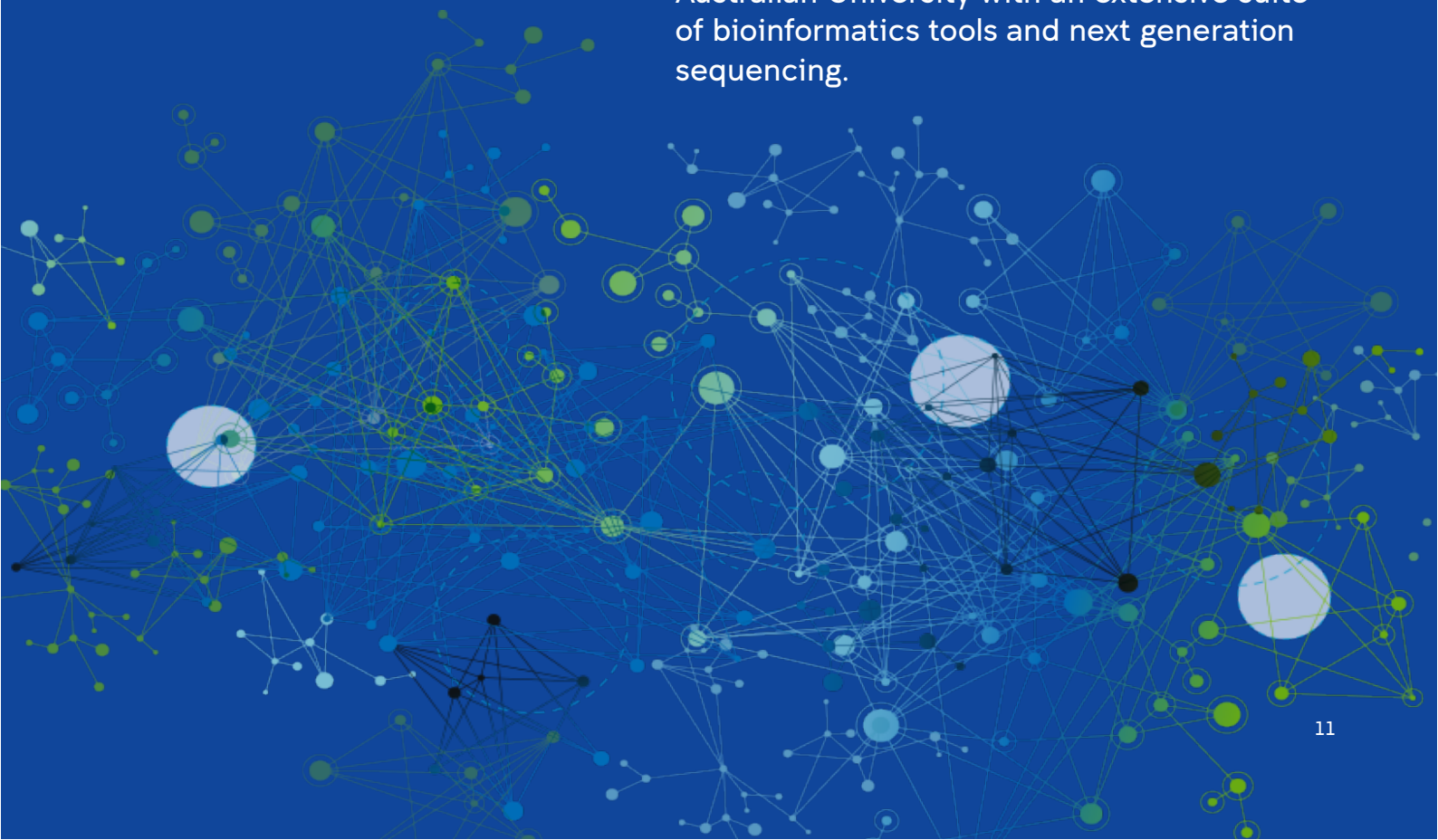
GENOMICS AND BIOINFORMATICS

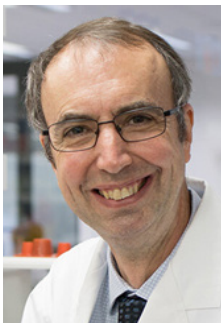
CLUSTER STRENGTHS:

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

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

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





Professor Merlin Crossley
DEPUTY VICE CHANCELOR ACADEMIC AND STUDENT LIFE
Chancellery Building
E m.crossley@unsw.edu.au
research.unsw.edu.au/people/professor-merlin-crossley

RESEARCH FOCUS

Transcription factors and gene regulation in blood cells.

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 a lab manager, 7 PhD students and 2 Honours students.

RESEARCH GOALS

- Fundamental mechanisms of gene regulation
- Epigenetics
- Artificial DNA-binding proteins
- Blood development
- Haemophilia
- Sickle cell anaemia and thalassaemia

RESEARCH IN DETAIL

We are interested in understanding the fundamental molecular mechanisms by which genes are controlled. Ultimately we hope to treat chronic diseases, such as sickle cell anaemia, by turning on beneficial genes or turning off harmful genes.

BIOGRAPHY

Merlin Crossley is Deputy Vice-Chancellor (Academic and Student Life) at UNSW and Professor of Molecular Biology. He has also worked or studied at the Universities of Melbourne, Oxford, Harvard and Sydney. He has been recognized by numerous awards, including a Rhodes Scholarship, the Australian Academy of Science's Gottschalk Medal and the Australian Society for Biochemistry and Molecular Biology's Lemberg Medal. He has made significant contributions to academic administration, serving as Dean at UNSW, and Acting Deputy Vice-Chancellor Research at the University of Sydney.

RECENT PUBLICATIONS

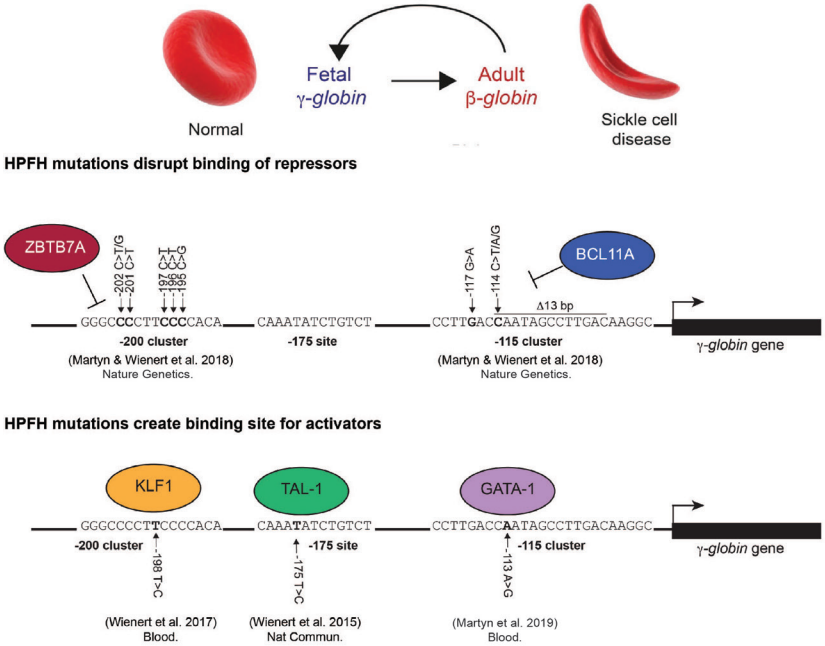
'Disrupting the adult globin promoter alleviates promoter competition and reactivates fetal globin gene expression.' *Blood*, 2022, 139(14):2107-2118

'Methylation of a CGATA Element Inhibits Binding and Regulation by GATA-1', *Nature Communications*, 2020, 11(1):2560

'Natural regulatory mutations elevate the fetal globin gene via disruption of BCL11A or ZBTB7A binding.' *Nature Genetics*, 2018 50(4):498-503

'Transcription factors LRF and BCL11A independently repress expression of fetal hemoglobin', *Science*, 2016, 351(6270):285-9

'Directing an artificial zinc finger protein to new targets by fusion to a non-DNA-binding domain', *Nucleic Acids Research*, 2016, 44(7):3118-30



Dr Michael Janitz
SENIOR LECTURER
Room 3106, Level 3 West
Bioscience South Building E26
E m.janitz@unsw.edu.au
babs.unsw.edu.au/michael-janitz

RESEARCH FOCUS

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

SCIENTIFIC INTEREST

Michael is an internationally recognised expert in the field of transcriptomics, next-generation sequencing technologies and bioinformatics. His current scientific interest focuses on investigations of gene expression and alternative splicing patterns in distinct structures and cell types of the healthy human brain and perturbation of transcriptome profiles during the onset and progression of neurological disorders including multiple system atrophy, epilepsy, amyotrophic lateral sclerosis and chronic fatigue syndrome. Michael is also interested in exploration of cancer-specific alterations in transcriptome profiles towards identification of novel biomarkers such as circular and non-protein coding RNAs.

RESEARCH CONTRIBUTIONS

During his PhD studies and subsequently as a postdoc at the German Centre for Rheumatism Research, Michael specialised in investigating the influence of the sequence polymorphism within the promoter regions of MHC class II genes in several inbred mice strains (Janitz et al. 1997; Janitz et al. 1998; Cowell et al. 1998).

Joining the Max Planck Institute for Molecular Genetics (MPIMG) converged with Michael's growing interest in studying transcription at the genome-wide level. Amongst others, he was involved in collaborative projects to characterise cDNA sequences on the level of the whole transcriptome in mice T helper cells and bovine brain (Gutjahr et al. 2005; Jann et al. 2006), respectively.

While at the MPIMG, Michael and his research group focused on developing a transfected-cell array as a high-throughput genomic tool for functional analysis of genes and their products (Vanhecke and Janitz 2004). This resulted in application of the cell arrays for subcellular protein localisation studies (Hu et al. 2006; Hu et al. 2009; Hu et al. 2010), protein-protein interaction screens (Fiebitz et al. 2008), and functional promoter analysis (Cheng et al. 2010). In addition, with collaborative partners in national and European Community research programs, he applied gene expression profiling studies to identify the genes involved in T helper lymphocytes type 1 immune response (Niesner et al. 2008) and differentiation of murine palatal development (Nogai et al. 2008). His research group also developed miniaturised microarray platforms for DNA hybridization studies using PNA- (Bauer et al. 2004) and LNA-modified oligonucleotide probes (Guerasimova et al. 2006; Liu et al. 2006 and 2007), thus contributing to more efficient exploration of the genome structure and function.

CURRENT RESEARCH

Since his appointment at UNSW Michael has been focused on exploration of different segments of human and mouse transcriptome using combination of Illumina and nanopore DNA and RNA sequencing as well as unique analytical pipeline combining in-house and publicly available bioinformatics tools. He and his team provided first insights into non-protein coding transcriptome of different regions of the human cortex, both in health (Mills et al. 2013; Mills et al. 2015a; Mills et al. 2015b; Bliim et al. 2019) and neurological diseases such as Alzheimer's disease (Twine et al. 2011; Mills et al. 2013; Mills et al. 2014), multiple system atrophy (MSA)(Mills et al. 2015c; Mills et al. 2016) and epilepsy (Mills et al. 2020) as well as cancer (Takenaka et al. 2016; Chen et al. 2017a). His recent research has been concentrated on circular RNAs (circRNAs) genome-wide expression patterns in the normal human (Chen et al. 2019) and mouse brain (Chen et al. 2018) as well as MSA (Chen et al. 2016) and endometrial cancer (Chen et al. 2017b).

Current research projects aim at understanding of circRNA-miRNA-mRNA networks in epilepsy and amyotrophic lateral sclerosis as well as gynaecological malignancies. Another emerging avenue of Michael's research is exploration of RNA post-transcriptional modifications in healthy human tissues and cancer using nanopore direct RNA sequencing. Michael's quest for the discovery of circRNAs, which might serve as molecular biomarker for MSA and endometrial cancer, constitutes another important element of his research program.

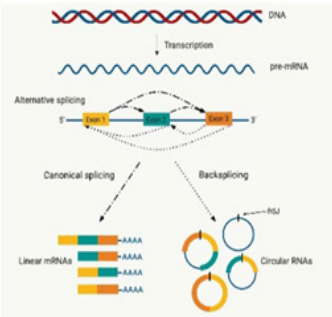


Figure 1. The formation of linear mRNAs and circular RNAs through canonical splicing and backsplicing, respectively. The mechanism of backsplicing leads to covalent linkage of the downstream 3'-end of a pre-mRNA sequence to an upstream 5'-end of the pre-mRNA strand. This process leads to generation of 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. 2020).

Associate Professor Cecile King
Room 3108, Level 3 East
Bioscience South Building E26
E c.king@unsw.edu.au
babs.unsw.edu.au/cecile-king

RESEARCH FOCUS

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

RESEARCH PROGRAM

One of the most intriguing aspects of the immune system is its ability to react to foreign invaders, but not to self. To distinguish healthy cells (self) from infected cells or pathogens, the immune system utilizes multiple receptors and signalling pathways that enable specific recognition of proteins and nucleic acids. Recognition of foreign RNA occurs inside cells and depends upon unique features of pathogen RNA that allow our RNA sensors to see it as foreign. However, for some people, the immune system reacts inappropriately to self-RNA and this can trigger autoimmunity.

The achievement of self-tolerance is even more impressive when we consider that we are colonized by multiple microbial species that are important for our health, and our genomes harbour an abundance of retrovirally sourced nucleic acid acquired from past encounters with retroviruses, known as retroelements. Whilst a challenge for self-tolerance, the retention of retroelements in the genome has been shown to serve multiple regulatory functions that influence the transcription of protein coding genes. Our own work has shown that retroelements can function to neutralise the deleterious effects of duplicated genes in immune gene families, favouring host survival during virus infection.

We are employing both an inside and outside approach to study RNA in the immune system-by studying how the immune system senses RNA during immune responses and how retroelement RNA's regulate immune responses.

Project 1: The role of retroelements in regulation of immune responses. This project will take a genome-wide approach to analyses the role of retroelements in the immune system and their relationship with immune genes families that have arisen by gene duplication. The project will be jointly supervised by Professor Marcel Dinger (babs.unsw.edu.au/marcel-dinger).

Project 2: RNA sensing in health and disease. This project will probe the underlying mechanisms of RNA sensing by the immune system and how autoimmune disease associated mutations in RNA recognition pathways influence immune responses.

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

BIOGRAPHY

Associate Professor Cecile King joined the School of Biotechnology and Biomolecular Sciences at the University of New South Wales Sydney in 2021. Cecile received her Ph.D. in Immunology from the University of Western Australia and completed her postdoctoral training at the Scripps Research Institute, La Jolla, USA. She joined the faculty of the Garvan Institute for Medical Research, Sydney, Australia in 2005, where she established her independent research program. Cecile's research has made important contributions to our understanding of T cell subsets and cytokines in adaptive immune responses and autoimmunity. Cecile's current research focus is RNA at the immune interface: Understanding both immune recognition of RNA and immune regulation by RNA.

Contact Cecile about research supervision opportunities: c.king@unsw.edu.au

Professor John Mattick
Room 3111, Level 3 East
Bioscience South Building E26
E j.mattick@unsw.edu.au
babs.unsw.edu.au/john-mattick

RESEARCH FOCUS

The role of the noncoding genome in regulating human development and cognition.

The human genome contains just 20,000 protein-coding genes, similar in number and with largely the same functions as those in other animals, including tiny nematode worms s that have only 1,000 cells. By contrast, the extent of non-protein-coding DNA increases with increasing developmental complexity, reaching 98.7% in humans. Moreover, these noncoding sequences, previously though to be junk, are differentially and dynamically transcribed to produce tens if not hundreds of thousands of small and long non-protein-coding RNAs that are expressed intronically, intergenically and antisense to protein-coding genes.

Most noncoding RNAs exhibit highly specific expression patterns and subcellular locations. Many have evolved rapidly under positive selection for adaptive radiation, and increasing numbers have been shown to have key roles in development, brain function, cancer and other diseases. They function at many different levels of gene expression and cell biology, including translational control, formation of subcellular (phase-separated) domains, and guidance of the epigenetic processes and chromatin dynamics that underpin development, brain function and physiological adaptation. Plasticity on these regulatory circuits has been superimposed by RNA editing, RNA modification and retrotransposon mobilization, especially in primates.

The challenge now is to determine the structure-function relationships of these RNAs and their mechanisms of action, as well as their place in the decisional hierarchies that control human development, cognition and disease susceptibility.

RESEARCH AREAS

- The structure-function relationships in regulatory RNAs
- The function of ultraconserved sequences in the human genome
- The roles of long noncoding RNAs and transposable elements in human development and cognition
- The roles of noncoding RNAs in complex diseases
- The roles of RNA editing and modification in brain function and plasticity
- The evolution of complex organisms

BIOGRAPHY

Professor Mattick was previously the Director of the Institute for Molecular Bioscience at the University of Queensland, the Australian Genome Research Facility and the Garvan Institute of Medical Research. He is a Fellow of the Australian Academy of Science, the Australian Academy of Technology & Engineering and the Australian Academy of Health & Medical Sciences. He is also an Associate Member of the European Molecular Biology Organisation.

Professor Mattick is internationally recognised for having pioneered a new understanding of the information content and function of the genome in humans and other developmentally complex organisms. has published over 300 research articles and reviews, which have been cited over 78,000 times. His work has received editorial coverage in *Nature, Science, Scientific American, New Scientist* and *The New York Times*, among others. It has also been highlighted in two books: *The Deeper Genome* by John Parrington and *Promoting the Planck Club* by Don Braben. He was listed among the top 1% highly cited researchers 2018, 2019 and 2020, and ranked in the top 1000 scientists globally in 2019.

Professor Mattick's honours and awards include appointment as an Officer in the Order of Australia, the inaugural Gutenberg Professorship at the University of Strasbourg, Honorary Fellowship of the Royal College of Pathologists of Australasia, the Australian Government Centenary Medal, the Australian Society for Biochemistry and Molecular Biology Lemberg Medal, the Advance Global Impact Award, the International Union of Biochemistry and Molecular Biology Medal, the University of Texas MD Anderson Cancer Center Bertner Award for Distinguished Contributions to Cancer Research and the Human Genome Organisation Chen Medal for Distinguished Achievement in Human Genetics and Genomic Research.

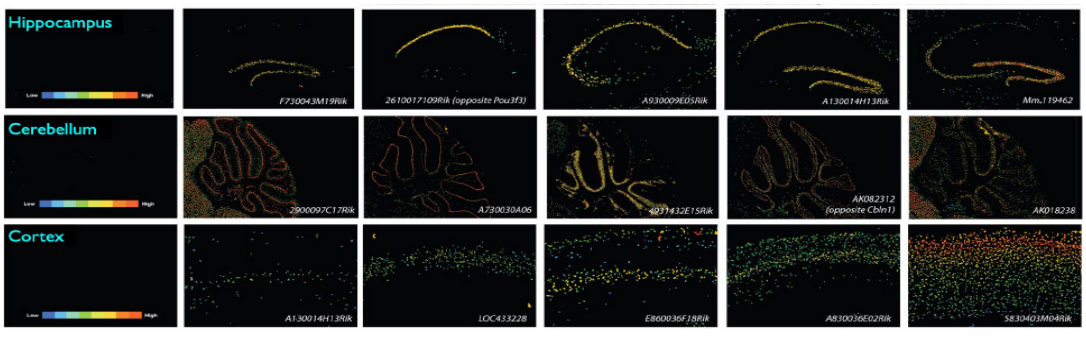


Figure: Images of the restricted expression of noncoding RNAs in the brain.

Dr Emily Oates
SENIOR LECTURER
Room 320C, Level 3
Biological Sciences North Building D26
E e.oates@unsw.edu.au
babs.unsw.edu.au/emily-oates

RESEARCH FOCUS

Human neuromuscular disease gene discovery, the clinical and genetic characterisation of new and emerging neuromuscular disorders, disease-related pharmacogenomics, muscle transcriptomics, clinical severity prediction, genetic treatment development.

Our main area of research interest is the discovery of new genes responsible for congenital and childhood-hood onset genetic muscle conditions. This group of disorders causes significant physical disability and sometimes early death.
Around half of all individuals with one of these conditions still do not have a genetic diagnosis. This adversely impacts their clinical care and the care of their family. In many cases a genetic diagnosis has not been established because the causative gene is not yet known to be a disease-causing gene.
Another significant challenge is that there are no available treatments to prevent, halt, or slow the progression of most congenital and childhood-onset muscle diseases - even when the genetic basis of the disease is known.

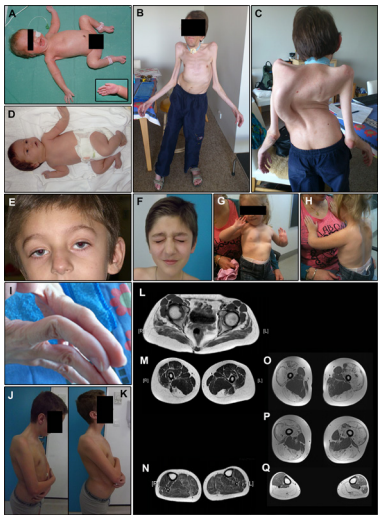
Our research is focused on the discovery of new childhood-onset neuromuscular disease genes, and the analysis of the functional and clinical impacts of disease-causing variants within these genes using state-of-the-art phenotyping, cell and tissue-based analyses, DNA and RNA sequencing and bioinformatic approaches. We use this information to increase genetic diagnosis rates for affected individuals and their families, and to advance our understanding of the clinical characteristics, natural history, and underlying pathogenesis of these disorders. We also have emerging interests in disease-related pharmacogenomics, muscle transcriptomics, clinical severity prediction and the development of new genetic treatments using insights gained through the detailed analysis of the genetic basis of muscle disorders.

BIOGRAPHY

Dr Emily Oates is a head of the UNSW Medical Genomics Group, a neurogenetics consultant for the Sydney Children's Hospital Network, and senior lecturer in medical genomics. Following paediatric physician training she completed specialist clinical genetics training, a neurogenetics-focused PhD and postdoctoral studies in both Australia and London, UK (Great Ormond Street Hopital). She has 14 years of clinical experience in the diagnosis and management of infants and children with neuromuscular disorders. She also has extensive expertise in the clinical characterisation of new neuromuscular disorders and the analysis of human genomic data for diagnostic and gene discovery purposes. She sees patients weekly in the Sydney Children's Hospital Neuromuscular clinic. Many of her patients are enrolled in her research projects. Dr Oates recently completed an NHMRC Neil Hamilton Fairley Early Career Fellowship. This fellowship was focused on harnessing state-of-the-art massively parallel DNA and RNA sequencing technologies to improve genetic diagnosis rates for patients with neuromuscular disorders and to identify new disease-causing genes. During her PhD and ECR fellowship she contributed to the identification of multiple new disorders including *BICD2*-SMA and *SCN4*–myopathy. She also authored multiple peer reviewed journal articles, including a large international publication aimed at comprehensively characterising the genetic and clinical features of the largest congenital (recessive) titinopathy cohort ever described at that time (84 authors: top 10 most downloaded 2018-2019 *Annals of Neurology* papers). Recessive titinopathy is a significant ongoing clinical and research interest for Dr Oates and her team.

Dr Oates is also lead investigator for a new (2022) Medical Research Future Fund (MRFF) grant: 'Advancing congenital and childhood-onset muscle disease diagnosis and treatment - a cross- disciplinary Australian collaboration'. This grant will fund the sequencing, bioinformatic analysis and functional validation of potential disease-causing variants identified within the trio WGS dataset of 100 Australian families impacted by neuromuscular disease who remain without a genetic diagnosis following best practice clinical genetic testing. The grant is also funding the development and testing of treatments targeting recessive titinopathy.

Dr Oates' UNSW Medical Genomics Group also has strong ongoing research collaborations with the Sydney Children's Hospitals Network, the Garvan Institute, the Victor Chang Cardiac Research Institute, as well as Sydney University, University of Western Australia, Murdoch University and Monash University. Her international collaborators include the Dubowitz Neuromuscular Centre (Great Ormond Steet Hospital/ University College London UK), Newcastle University (UK), The Broad Institute (USA) and NIH (USA).



Clinical features of congenital titinopathy. Figure 2: Oates et. al. Congenital Titinopathy: Comprehensive characterization and pathogenic insights. Annals of Neurology 2018 Jun;83(6):1105-1124

Dr Fatemeh Vafaee
SENIOR LECTURER
Room 2106, Level 2 West
Bioscience South Building E26
E f.vafaee@unsw.edu.au
www.vafaeelab.com
babs.unsw.edu.au/fatemeh-vafaee

RESEARCH FOCUS

Computational Biomedicine, Systems Biology, Bioinformatics.

CURRENT APPOINTMENT:

- 2021 - Present: Deputy Director, UNSW Data Science Hub (uDASH), UNSW
- 2020 - Present: Theme Leader, Health Data Science, uDASH, UNSW
- 2017 - Present: Senior Lecturer, School of BABS, UNSW Sydney

BRIEF BIO AND RESEARCH CONTRIBUTION

Dr Vafaee is a Senior Lecturer in Computational Biomedicine and Bioinformatics since 2017. She received her PhD in Artificial Intelligence from the School of Computer Science at the *University of Illinois at Chicago*, USA (2011) followed by 2 multidisciplinary postdoctoral fellowships on computational biomedicine at the *University of Toronto*, University Health Network (2011 – 2012), and at the *University of Sydney*, Charles Perkins Centre (2013 – 2017).

Dr Vafaee has launched (2017) and leads **AI-enhanced Biomedicine Laboratory** at UNSW (www.VafaeeLab.com) which currently holds 10 members collaboratively working on deploying advanced AI techniques to address a variety of biomedical pressing problems. Relying on multidisciplinary expertise and cross-faculty collaborations, Dr Vafaee and her team are developing advanced machine-learning methods and deep-learning models that leverage large omics data to find hidden structures within them, account for complex interactions among the measurements, integrate heterogeneous data and make accurate predictions in different biomedical applications ranging from **single-cell sequencing** analysis and multi-omics **biomarker discovery** to disease **functional genomics** and **drug repositioning**. Dr Vafaee's research has been featured in the Faculty of Science Capability Statement in Health Science and UNSW Capability Statement in Biomedical Research.

AREAS OF RESEARCH PROJECTS

1) Minimally invasive biomarker discovery for personalised medicine and precision therapy: Recent advances in high-throughput technologies have provided a wealth of genomics, transcriptomics, and proteomics data to decipher disease mechanisms in a holistic and integrative manner. Such a plethora of -omics data has opened new avenues for translational medical research and has particularly facilitated the discovery of novel biomarkers for complex diseases such as cancers. My research lab – in close collaboration with experimentalists, clinicians, and oncologists – is adopting an innovative multi-disciplinary approach to tackle one of the biggest challenges of personalised cancer medicine, that is to to identify *robust and reproducible biomarkers in a minimally invasive way*. We are integrating multiple data sources, network and temporal information using advanced machine learning approaches to better understand the molecular complexity underpinning pathogenesis and to identify novel, precise and reproducible blood-based biomarkers for disease early detection, diagnosis, prognosis and drug responses paving the way for personalised medicine. Examples of publications: (Ebrahimkhani et al, *Molecular Neurobiology*, 2020), (Colvin et al. *Cancer Science*, 2020), (Vafaee et al, *Systems Biology and Applications*, 2018), (Ebrahimkhani et al, *Precision Oncology*, 2018)

2) Single-cell sequencing data analysis and integration: Cellular heterogeneity is one of the main clinical drivers of the current inefficiency in treating cancer and other complex diseases as molecular-based prescriptions or personalised medicine have often relied on *bulk pro/filing* of cell populations, masking intercellular variations that are functionally and clinically important. In recent years, however, there has been an increasing effort in shifting the focus from bulk to *single-cell profiling*. Single-cell sequencing will have a major global impact on the precision medicine through detecting rare disease-associated cells and identifying cell-type-specific biomarkers and therapeutic targets. Single cells, however, make 'big data', provoking substantial analytical challenges to decipher underlying biological and clinical insights. Hence, there is an emerging demand for scalable yet accurate analysis pipelines for rapidly increasing single-cell sequencing data and my research program is focused (during the last 18 months) to contribute to this significant field. Examples of publications: (Koch et al, Briefings in Bioinformatics, 2021), (Zandavi and Vafaee, NeurIPS 2021, under-review)

3) Computational drug repositioning and network pharmacology: Repositioning existing drugs for new indications is an innovative drug development strategy offering the possibility of reduced cost, time and risk as several phases of *de-novo* drug discovery can be bypassed for repositioning candidates. Biopharmaceutical companies have recognised advantages of repositioning, and investment in the area is dramatically increasing. With the rapid advancement of high-throughput technologies and the explosion of various biological and medical data, computational drug repositioning has become an increasingly powerful approach to systematically identify potential repositioning candidates. My lab is the only group at UNSW, and one of the few across Australia, advancing the field of computational drug repositioning. We are developing computational tools and databases which integrate massive amounts of biological, pharmacological and biomedical information related to compounds into advanced machine learning or network-based models to predict accurate repositioning candidates. Examples of publications: (Azad et al, Briefings in Bioinformatics, 2020), (Azad et al, Patterns, 2021)

Associate Professor Irina Voineagu
ARC FUTURE FELLOW
Room 3107, Level 3 West
Bioscience South Building E26
E i.voineagu@unsw.edu.au
babs.unsw.edu.au/irina-voineagu

RESEARCH FOCUS

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

RESEARCH PROGRAM

Broadly, my research interests are in the area of molecular genetic mechanisms underlying human brain disorders. My PhD work demonstrated that unstable DNA repeats block replication fork progression in bacteria, yeast and mammalian cells by forming DNA-hairpins on the lagging strand (Voineagu et al. PNAS 2008), and investigated for the first time the cellular checkpoint responses to replication fork arrest at CGG repeats. This work led to a novel model of chromosomal fragility at CGG repeat sequences (Voineagu et al. Nature Struct. Mol. Biol 2009). For postdoctoral research, I joined the Neurogenetics Department at UCLA, to investigate the molecular mechanisms of autism and intellectual disability, using transcriptome methods. My postdoctoral work led to the identification of a novel gene implicated in X-linked intellectual disability (Voineagu et al., Mol. Psychiatry 2011) and the characterisation of shared molecular pathways in autism post-mortem brain tissue (Voineagu et al. Nature 2011). Currently, my group's research concentrates on the molecular genetic mechanisms underlying normal brain function and their perturbation in neurodevelopmental disorders, using a combination of functional genomic studies in human brain tissue and neuronal cell culture systems.

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

SELECTED PUBLICATIONS

» Won H, de la Torre-Ubieta L, Stein JL, Parikshak NN, Huang J, Opland CK, Gandal MJ, Sutton GJ, Hormozdiari F, Lu D, Lee C, Eskin E, Voineagu I, Ernst J, Geschwind DH (2016). Chromosome conformation elucidates regulatory relationships in developing human brain. *Nature* 538(7626):523-527.

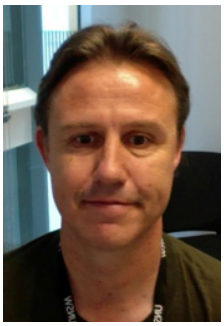
» Yao P, Lin P, Gokoolparsadh A, Assareh A, Thang MW, Voineagu I (2015). Coexpression networks identify brain region-specific enhancer RNAs in the human brain. *Nature Neuroscience* 18(8):1168-74.

» Voineagu I, Huang L, Winden K, Lazaro M, Haan E, Nelson J, McGaughran J, Nguyen L, Friend K, Hackett A, Field M, Gecz J, Geschwind DH (2012). CCDC22: a novel candidate gene for syndromic X-linked intellectual disability. *Molecular Psychiatry* 17(1):4-7.

» Voineagu I, Wang X, Johnston P, Lowe JK, Tian Y, Horvath S, Mill J, Cantor RM, Blencowe BJ, Geschwind DH (2011). Transcriptomic analysis of autistic brain reveals convergent molecular pathology. *Nature* 474(7351):380-4.

» Voineagu I, Surka CF, Shishkin AA, Krasilnikova MM, Mirkin SM (2009). Replisome stalling and stabilization at CGG repeats, which are responsible for chromosomal fragility. Nature Structural and Molecular Biology 16(2):226-8.

» Voineagu I, Narayanan V, Lobachev KS, Mirkin SM (2008). Replication stalling at unstable inverted repeats: Interplay between DNA hairpins and fork stabilizing proteins. *Proc Natl Acad Sci U S A* 105(29):9936-41.



Associate Professor Paul Waters
Room 3110, Level 3 East
Bioscience South Building E26
E p.waters@unsw.edu.au
babs.unsw.edu.au/paul-waters

RESEARCH FOCUS

Sex chromosome structure, function, regulation and evolution.

My central area of expertise is sex chromosome biology and evolution, with a focus on epigenetic regulation of the X chromosome. In more recent years, I have also worked on hibernation in bearded dragons.

RESEARCH PROGRAM

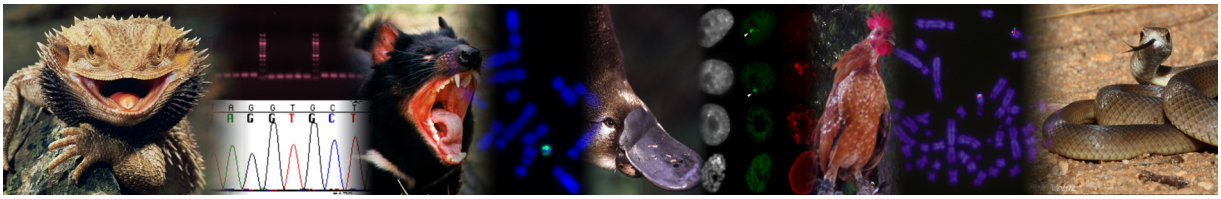
We use various molecular and bioinformatic methods to examining genome biology in diverse model species, unlocks answers about the evolution of complexities within our own genomes. The lab focuses on better understanding the epigenetic regulation of transcription in distantly related vertebrate representatives, specifically focussing on sex chromosomes. The ultimate goal is to understand how complex epigenetic silencing mechanisms evolved. We use eutherian, marsupial, monotreme and bird/ reptile models. Representatives from these groups each have different (sometimes weird and wonderful) sex determining mechanisms and sex chromosome systems.

We have a keen interest in X chromosome inactivation and meiotic sex chromosome inactivation in marsupial models. We also have particular interest in dosage compensation of the strange sex chromosomes of platypus, which have 5 X chromosomes and 5 Y chromosomes! We also study the Australian central bearded dragon, which are unusual in that they have both genetic and environmental sex determination. We also have a lot of interest in 3D genome structure, especially in the transmissible Tasmanian devil facial tumour.

Click here for a full list of publications.

SUPERVISION

PhD, MSc, Honours, and 3rd year Undergraduate projects in Epigenetics and Molecular Biology are available in the lab.



Associate Professor Robert Weatheritt

Lab Head (Neurotranscriptomics),
Garvan Institute of Medical Research,
384 Victoria Street, Darlinghurst
E r.weatheritt@unsw.edu.au
unsw.edu.au/staff/robert-weatheritt

RESEARCH FOCUS

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

RESEARCH PROGRAM

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

RESEARCH PROJECTS

Project 1: Alternative splicing and membraneless organelles in neuronal differentiation. This project will investigate the role of RNA in regulating the function of membraneless organelles and its role in controlling neuronal differentiation, as well as its implications on neurodevelopmental disorders.

Project 2: Membraneless organelles and chemoresistance. This project will aim to understand the role of stress granules and P-bodies in chemoresistance.

Project 3: Developing deep learning algorithms to discern impact of epitranscriptomic modifications on the genome. This project will develop algorithms to understand the genetic code controlling RNA modifications identified by nanopore long-read data.

BIOGRAPHY

Associate Professor Weatheritt is an EMBL Australia group leader and an ARC Future Fellow. Robert received his PhD from the European Molecular Biology Laboratory in Heidelberg, Germany. He completed his postdoctoral training in Cambridge and Toronto before beginning his lab at the Garvan Institute in 2018. Since 2022, Robert has a joint appointment at School of Biotechnology and Biomolecular Sciences.

Contact Robert about research supervision opportunities at: r.weatheritt@unsw.edu.au

RELEVANT RECENT PUBLICATIONS

Evolution of splicing:

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

Membraneless organelles:

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

Splicing and neuroscience:

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

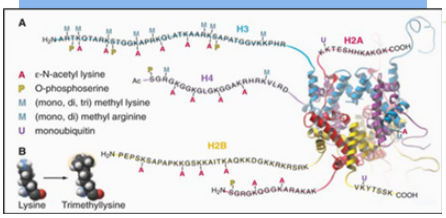
Splicing algorithms:

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

Professor Marc Wilkins
Room 2112, Level 2 East
Bioscience South Building E26
E marc.wilkins@unsw.edu.au
babs.unsw.edu.au/marc-wilkins

RESEARCH FOCUS

Discovery and functional characterisation of intracellular networks.



RESEARCH
My research questions are centred around proteomics.

1. What is the regulatory network of histone methylation?
Histone methylation is a crucial process that affects the compaction and relaxation of chromatin, and thus gene expression in the cell. The sites of histone methylation are understood and the enzymes responsible are known, at least in the model system of yeast. However we know little about how the four 'writer' enzymes and the four 'eraser' enzymes are actually regulated and how they work as a single integrated system. We are exploring:

- Are the histone methyltransferases and demethylases phosphorylated?
- If phosphorylation on these enzymes affect their activity and if so, how?
- What kinases are responsible for this phosphorylation?
- Do the modification of writer and eraser enzyme control where they act, on chromatin in the genome?

We aim to connect the cell's signalling system with its histone-based system of gene regulation in this project.

The project is supported by ARC Discovery Project grant 2020: The Regulatory Network of Histone Methylating and Demethylating Enzymes.

Recent papers on protein methylation:

- Characterization of Protein Methyltransferases Rkm1, Rkm4, Efm4, Efm7, Set5 and Hmt1 Reveals Extensive Post-Translational Modification. Winter DL, Hart-Smith G, Wilkins MR. *J Mol Biol.* 2018 430(1):102-118.
- Methylation of Elongation Factor 1A: Where, Who, and Why? Hamey JJ, Wilkins MR. *Trends Biochem Sci.* 2018 43(3):211-223.
- METTL21B Is a Novel Human Lysine Methyltransferase of Translation Elongation Factor 1A: Discovery by CRISPR/Cas9 Knockout. Hamey JJ, Wienert B, Quinlan KGR, Wilkins MR. *Mol Cell Proteomics.* 2017 Dec;16(12):2229-2242.

2. How do cells make decisions via protein interaction networks?
Cells use protein post-translational modifications as an 'information management' and 'status management' system. Yet how this information is integrated, to make actual decisions inside networks, is poorly understood.

We are exploring:

- How often are two post-translational modifications found next to each other in the proteome? Especially methylation, phosphorylation and acetylation?
- For modifications that are nearby, what is their 'logic' - do they block each other? Is one required before the other?
- Do nearby modifications form small 'decision making modules' in interaction networks?
- Do nearby modifications change the interaction choice of a protein? Or change its localisation in the cell?

The project is supported by ARC Discovery Project grant 2017: The discovery of decision-making modules in protein interaction networks.

Recent papers on crosstalk of post-translational modifications:

- Crosstalk of Phosphorylation and Arginine Methylation in Disordered SRGG Repeats of Saccharomyces cerevisiae Fibrillarin and Its Association with Nucleolar Localization. Smith DL, Erce MA, Lai YW, Tomasetig F, Hart-Smith G, Hamey JJ, Wilkins MR. *J Mol Biol.* 2020 432(2):448-466.
- Knockout of the Hmt1p Arginine Methyltransferase in Saccharomyces cerevisiae Leads to the Dysregulation of Phosphate-associated Genes and Processes. Chia SZ, Lai YW, Yagoub D, Lev S, Hamey JJ, Pang CNI, Desmarini D, Chen Z, Djordjevic JT, Erce MA, Hart-Smith G, Wilkins MR. *Mol Cell Proteomics.* 2018 17(12): 2462-2479.

3. How is the protein interactome regulated?
Recent, breakthroughs in crosslinking mass spectrometry (XL-MS) have made it possible to measure thousands of protein-protein interactions in a single sample. These generate a 'protein interactome' which reflects the biological state of a system, at a point in time. Use of heavy isotope-based techniques with XL-MS allows 'protein interactomes' to then be compared. We are exploring:

- The optimisation of techniques for XL-MS.
- The roles of gene expression and protein post-translational modifications in the regulation of the protein interactome.
- The role of alternate splicing of mRNA and resulting isoforms in regulating the protein interactome.

Recent papers on crosslinking mass spectrometry:

- Cross-linking Mass Spectrometry Analysis of the Yeast Nucleus Reveals Extensive Protein-Protein Interactions Not Detected by Systematic Two-Hybrid or Affinity Purification-Mass Spectrometry. Bartolec TK, Smith DL, Pang CNI, Xu YD, Hamey JJ, Wilkins MR. *Anal Chem.* 2020 92(2):1874-1882.
- Characterization of the Interaction between Arginine Methyltransferase Hmt1 and Its Substrate Npl3: Use of Multiple Cross-Linkers, Mass Spectrometric Approaches, and Software Platforms. Smith DL, Götze M, Bartolec TK, Hart-Smith G, Wilkins MR. *Anal Chem.* 2018 90(15):9101-9108.

Dr Emily Wong
SENIOR RESEARCH FELLOW
Head of Regulatory Systems, Victor Chang Cardiac Research Institutes
405 Liverpool Street, Darlinghurst
E e.wong@victorchang.edu.au
unsw.edu.au/staff/emily-wong

RESEARCH FOCUS

How sequences specify phenotypes by deciphering gene regulation.

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

BIOGRAPHY

Dr Emily Wong received her Masters and PhD from the University of Sydney in Bioinformatics and Computational Genomics. She was an EMBO postdoctoral fellow at the European Molecular Biology Laboratory–European Bioinformatics Institute (EMBL-EBI) at the Wellcome Trust Genome Campus, Cambridge, UK. There, she studied the regulatory evolution of mammalian tissues. In 2016, She returned to Australia as an Australian Research Council Discovery Early Career Fellow to the University of Queensland where she worked on genomic control during development.

Emily is part of UNSW and the Victor Chang Cardiac Research Institute. Her research seeks to tie together genetic and molecular understanding to decipher the rules controlling cell and trait diversity. She uses new cross-disciplinary approaches integrating big data with in vivo experiments. Her work leverages the power of comparative genomics to understand how traits are encoded in our genomes and how regulatory systems are disrupted in disease.

RECENT PUBLICATIONS

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

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

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

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

RESEARCH SUPERVISORS -

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.

Associate Professor Brendan Burns
Room 4101, Level 4 West
Bioscience South Building E26
E brendan.burns@unsw.edu.au
theburnslab.com
babs.unsw.edu.au/brendan-burns

RESEARCH FOCUS

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

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

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

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

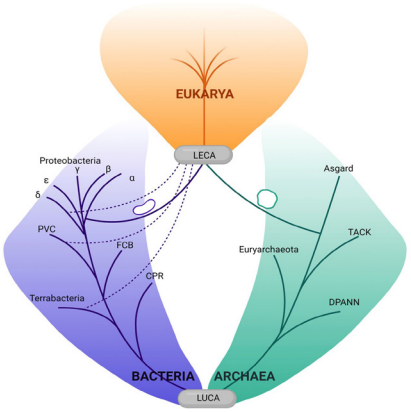
In particular, we are pursuing the role of 'microbial dark matter' in these systems including the enigmatic group of Asgard archaea. We aim to break down the traditional distinctions between prokaryotic and eukaryotic life using the Asgardians as a 'missing link'.

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

Specific project areas include:

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

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



Dr Natalia Castaño-Rodríguez
CANCER INSTITUTE NSW FELLOW AND UNSW SCIENTIA FELLOW / SENIOR LECTURER

Room 420E, Level 4
Biological Sciences Building North D26
E n.castanorodriguez@unsw.edu.au
babs.unsw.edu.au/natalia-castano-rodriguez

RESEARCH FOCUS

Gastrointestinal disease.

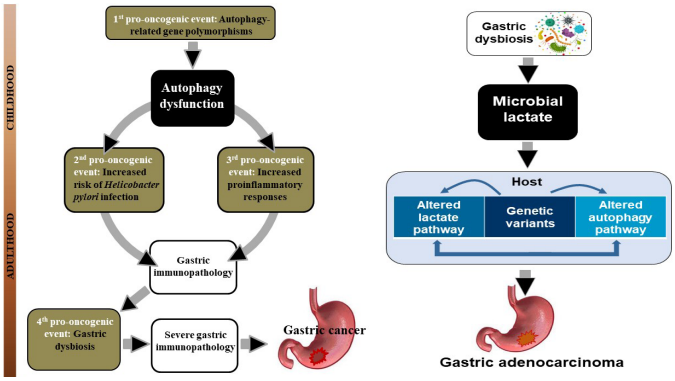
BIOGRAPHY AND RESEARCH CONTRIBUTION

Dr Natalia Castaño Rodríguez is a WSTEM Early Career Researcher, who has worked in the fields of molecular biology, microbiology, biostatistics and bioinformatics related to immunogenetics and genetics of cancer for the past 12 years. She currently leads a research group composed of higher degree research and Honours students, all dedicated to investigate the interplay between host immunogenetic factors and gastrointestinal dysbiosis in gastrointestinal carcinogenesis (mainly stomach cancer) and other chronic inflammatory conditions (mainly inflammatory bowel diseases).

Prior to moving to Australia, Natalia undertook research trainee fellowships in Colombia (Biological Research Corporation (CIB), Medellín, Colombia) and Mexico (Occidental Biomedical Research Centre (CIBO), Guadalajara, Mexico), where she acquired skills in the areas of human genetics and autoimmunity.

Following the completion of her MD degree, Natalia funded her postgraduate studies with competitive scholarships from Colombia and Australia (COLFUTURO Scholarship and UNSW University International Postgraduate Award) to investigate the role of innate immunity in stomach cancer. After a stint as a research associate in the *Helicobacter* and *Campylobacter* laboratory at UNSW, she was then awarded an Early Career Fellowship by the National Health and Medical Research Council (NHMRC) to expand her work on the role of immunogenetics, particularly related to pattern recognition receptors and the autophagy pathway, in *Helicobacter pylori*-related stomach cancer (May 2016- April 2020). During this time, she further funded her research with a Cancer Australia Priority-driven Collaborative Cancer Research Scheme (PdCCRS) Young Investigator grant (2017) as well as a Gastroenterological Society of Australia Project Grant (2019) to investigate the contribution of dysregulated autophagy to carcinogenesis in the stomach. Having established herself as an emerging leader in the field of immunogenetics in cancer, Natalia recently secured a Cancer Institute NSW ECF (2020-2023) as well as a UNSW Scientia Fellowship (2020-2024).

If you would like to learn more about Natalia and her research, please read these layperson articles published in Nature Communications Biology, Can Too Foundation and Medscape. A full list of Natalia's scientific publications can also be found here.



RESEARCH PROGRAM

Stomach cancer is the 5th most common cancer and the 3rd leading cause of cancer-related mortality worldwide, with incidence rates particularly high in East Asia and South America. Notably, stomach cancer incidence is equally high in Indigenous Australians while the incidence in non-Indigenous Australians will increase due to an ageing population and high influx of migrants from East Asia and South America, placing stomach cancer as a research priority in our nation. While *Helicobacter pylori* is a fundamental risk factor, stomach cancer aetiology involves the combined effects of microbial, host and environmental factors. This is evidenced by the fact that only 1-3% of *H. pylori* infected people develop stomach cancer, and that progression to stomach cancer in some subjects occurs even after eradication of the bacterium. Natalia proposes a synergistic interaction between innate immunity (mainly pattern recognition receptors (PRRs) and autophagy), *H. pylori* infection and gastric dysbiosis in stomach cancer. Based on this hypothesis, her research program can be divided into the following arms: 1) Autophagy in gastric carcinogenesis, 2) The role of the gastric microbiome (*H. pylori* and non-*H. pylori* taxa) in gastric carcinogenesis, 3) The role of microbial metabolites in gastric carcinogenesis, and 4) Pattern recognition receptors in gastric carcinogenesis.

AREAS OF SUPERVISION

Natalia is interested in supervising both Honours and HDR (Masters and PhD) students in the areas of immunology, genetics and microbiology. If you are interested, please contact her via email describing why you would like to undertake a degree in her lab.

Associate Professor Belinda Ferrari
ARC FUTURE FELLOW
Room 4104, Level 4 West
Bioscience South Building E26
E b.ferrari@unsw.edu.au
babs.unsw.edu.au/belinda-ferrari

RESEARCH FOCUS

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

RESEARCH GOALS

- Determine the resilience of Antarctic soil microbial communities to global change
- Determine the global significance of atmospheric chemosynthesis
- To develop novel cultivation approaches for yet-to-be cultured bacteria and fungi
- Develop new approaches for modelling environmental drivers of soil microbial communities
- Develop site-specific ecotoxicity assessments using microbes as indicators of soil health
- To isolate and characterise cold-adapted hydrocarbon degrading fungi and bacteria

RESEARCH IN DETAIL

I have built up strong partnerships across both the Biotechnology industry and government bodies in Australia. My research has real-world applications, driving remediation targets, guideline derivation and conservation efforts in Antarctica.

In Antarctic soils, microbes are the most dominant lifeform and thus they drive geochemical processes, particularly carbon and nitrogen cycling. My research is aimed at unravelling the breadth of microbial diversity and their functioning in soil. My team focuses on microbial dark matter, that is bacteria, archaea and fungi that are yet-to-be cultured or characterised. By integrating single-cell with genomics and new multivariate analyses, my group is exploring the ecology of microbes in both pristine and contaminated soils.

Through collaboration with the Australian Antarctic Division, we are using molecular tools to evaluate soil health in response to both natural and man-made disturbances, from hydrocarbon contamination through to climate induced change. My research is world-class, and of high impact, with our recent discovery of Antarctica bacteria surviving by literally living on air published in the journal Nature. My research is challenging our understanding of the nutritional limits required to support life and opens the possibility for life elsewhere.

Please see Ferrarilab.org for more details including information on our recent expedition to the Windmill Islands, east Antarctica.

I am a supportive, approachable superviser with my team being comprised of a high number of PhD and Honours students

- Uncovering the diversity of novel secondary metabolites in polar soils - Nicole Benaud, PhD; Completed 2020
- Residual toxicity and bioremediation of soils at Casey station, Antarctica - Sarita Pudasaini, PhD; Completed 2020
- Isolation and characterisation of *Candidatus Dormibacteraeota* (AD3) in Antarctic soil - Kate Montgomery, PhD
- Microbial diversity and drivers of community assembly across east Antarctica - Eden Zhang, PhD
- Mapping the global significance of atmospheric chemosynthesis - Angelique Ray, PhD
- Microbial community shifts after a decade of change in the Windmill Islands, east Antarctica - Sin Yin Wong, PhD
- Microbial bioactives and elucidating their role in Antarctica - Carolina Gutiérrez-Chávez, PhD
- Cultivation and characterisation of ammonia oxidising Archaea from Antarctic Enrichments – Devan Chelliah, PhD
- Ecotoxicity assessments of aged hydrocarbon contaminated soils at Casey station - Jessica Dai, Honours
- Can *Candidatus Eremiobacterota* be cultivated? - Dana Tribbia, Honours

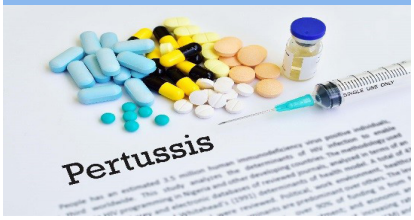
Figure 1. Mitchell Peninsula, Antarctica; a nutrient-limited desert that hosts a unique microbial community that uses trace gases to survive.

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

Professor Ruiting Lan
Room 3115, Level 3 East
Bioscience South Building E26
E r.lan@unsw.edu.au
babs.unsw.edu.au/ruiting-lan

RESEARCH FOCUS

Genomics and molecular evolution of bacterial pathogens.



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 work on a number of bacterial pathogens including *Bordetella pertussis, Salmonella, Shigella* and *Vibrio cholerae*. 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. These studies are significant in designing strategies that will be effective in preventing the emergence and spread of pathogens.

RESEARCH PROGRAM

Evolution and virulence of respiratory tract pathogen *B. pertussis*

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 and the second from 2014 to 2017 with 20,000 cases at its peak. Recent pertussis epidemics have also been observed in other countries with high vaccine coverage and several causes have been suggested for the resurgence of pertussis. Our research has provided strong evidence that adaptation of *B. pertussis* in response to selection pressure from pertussis vaccines has contributed to the pertussis resurgence. In this program we aim to understand how *B. pertussis* involve under the selection pressure of vaccines and antibiotics. We also aim to understand the virulence and pathobiology of *B. pertussis* using both genomic and proteomic approaches to improve the current vaccine.

Genomic epidemiology, surveillance, and evolution of bacterial pathogens

The effectiveness of public health interventions for infectious disease control is limited by the low resolution of current surveillance methods and a limited understanding of pathogen evolution. Both can be radically improved by whole genome sequencing (WGS), which enables the identification of outbreak cases, detection and tracking of emerging epidemic clones and elucidation of the factors that contributed to their emergence and spread. This research program aims to develop novel methods and solutions to enhance infection control and prevention through genomics guided surveillance.

We pioneered a new approach for genomic surveillance of *Salmonella* Typhimurium. We have developed multi-level genome typing (MGT), using multiple, sequential multilocus sequence typing (MLST) schemes of increasing size that allow examination of genetic relatedness at resolutions from seven gene MLST to core genome (cg) MLST. MGT provides the best means to identify strains and genome types at a resolution appropriate to the needs of short and long term epidemiology. We implemented this system for STM to demonstrate its utility and an online MGT database (http://mgtdb.unsw.edu.au) for public health applications. We aim to apply similar approaches to other bacterial pathogens for outbreak detection and epidemiological surveillance for better control of outbreaks, disease spread and antibiotic resistance. We also aim to understand pathogen evolution and adaptation through novel bioinformatic and genomic analyses.

ABOUT THE LAB HEAD

I am a Professor of Medical Microbiology in the School of Biotechnology and Biomolecular Sciences at UNSW Sydney where I teach medical microbiology to science and medical students. I grew up in the southeast countryside of China and did my undergraduate degree in China. I moved to Australia in 1986. I completed my PhD at University of Sydney in 1992 and did my postdoctoral training also at the University of Sydney. I was appointed as a Senior Lecturer at UNSW in 2002 and promoted to Professor in 2018. I have published over 190 papers with >10,000 citations (Google scholar). I invented the core genome concept which is central to the understanding of bacterial evolution.

ABOUT THE LAB

Our research group currently has 1 postdoctoral associate, 1 Bioinformatician, 6 PhD students and 2 honours students. Our Lab is known for its collaborative and supportive research environment that encourages innovation and creativity to unlock each student's potential. We welcome students from around the world with academic backgrounds in microbiology, genetics, bioinformatics, and related disciplines.

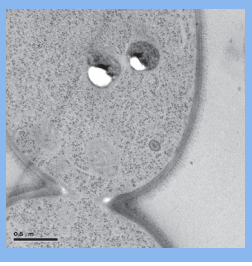
Our past and present students came from around the world and our graduates have gone on to successful careers including university professors, senior scientists, and laboratory heads.

For more information about us please visit our lab website http://www.lanlab.unsw.edu.au.

Dr Megan Lenardon
SENIOR LECTURER
Room 4103, Level 4 West
Biosciences South Building (E26)
E m.lenardon@unsw.edu.au
research.unsw.edu.au/people/dr-megan-denise-lenardon

RESEARCH FOCUS

Fungal infections of humans.



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

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

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

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

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

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

REFERENCES

1. Ricci et al. (2021). Human gut bifidobacteria inhibit the growth of the opportunistic fungal pathogen *Candida albicans*. Preprint on bioRxiv https://doi.org/10.1101/2021.12.21.473717.
2. Lenardon et al. (2020) Scalar nanostructure of the *Candida albicans* cell wall; a molecular, cellular and ultrastructural analysis and interpretation. *The Cell Surface* 6C:100047
3. Schaefer et al. (2021) Rational design of an antifungal polyacrylamide library with reduced host cell toxicity. *ACS Applied Materials & Interfaces*: 13(23):27430-27444.

Professor Mark Tanaka
Room 2111, Level 2 East
Bioscience South Building E26
E m.tanaka@unsw.edu.au
www.unsw.edu.au/staff/mark-tanaka

RESEARCH FOCUS

Evolution of pathogens: computational biology and mathematical modelling.

RESEARCH AREAS

In our group we are interested in understanding how microbes evolve. We use mathematical, statistical and computational methods to model the population dynamics of pathogens and other microorganisms and to analyse genetic data. Recent research areas include the dynamics of gut microbial organisms, microbial niche construction, the evolution of pathogens across multiple scales, the role of cultural evolution in pathogen evolution, and the extinction of asexual populations. The following are some current questions.

How old is a pathogen? Genomes contain information about the history of a species. For example, when free-living bacteria turn into pathogens they undergo reductive evolution and relaxed selection on some genes which then become pseudogenes. One way to infer the age of a pathogen is by studying patterns of molecular evolution in genes and pseudogenes; this was done to estimate the age of leprosy, for instance. This project aims to refine the methodology for this estimation procedure and to apply it to a variety of bacterial pathogens.

How do technology and culture influence the transmission of infectious diseases? Technological advances have opened many opportunities for economic development but they have simultaneously altered the way we interact with the environment. For instance, we have increased contact with wildlife and potentially raised the risk of zoonoses. This project aims to study how the dynamics of human cultural practices contribute to this risk.

How do pathogens adapt or go extinct? When pathogens spread in host populations during epidemics, their population sizes expand and contract. They may go extinct after the contraction or cause further outbreaks. Such population dynamics can be captured by mathematical models. Although these models have been well studied it is less clear how evolution occurs in oscillating populations. While population genetic models have been well-studied, they focus on constant population sizes. This project aims to predict the trajectories and consequences of new mutations in oscillating pathogen populations.

For more information about us please visit our lab website: www.tanakalab.unsw.edu.au

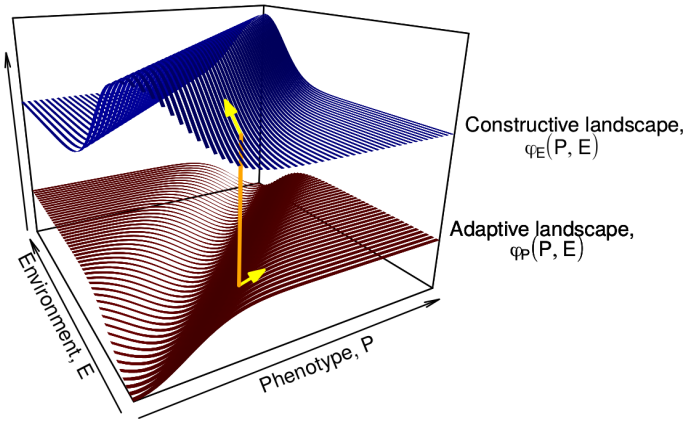


Figure: The Dual Landscape model of adaptation and niche construction. Adaptive landscape (lower surface) and constructive landscape (upper surface). Vectors show partial change in the directions of the phenotype *P* on the lower landscape and the environment *E* on the upper landscape. The pole connecting the two vectors shows that they are located at corresponding positions in the *P-E* space.

Associate Professor Jai Tree
Room 3113, Level 3 East
Bioscience South Building E26
E j.tree@unsw.edu.au
babs.unsw.edu.au/jai-tree

RESEARCH FOCUS

Gene regulation in bacterial pathogens.

RESEARCH PROGRAM

The lab is interested in how bacteria regulate gene expression with a focus on understanding the contribution of non-coding RNAs. It is now apparent that the genomes of all organisms are transcribed into an array of regulatory non-coding RNAs (ncRNAs) and bacterial pathogens have not escaped the ncRNA revolution. Our major challenge now is to understand the functions of these RNA species and high throughput sequencing technologies and bioinformatics are providing the tools that will allow us to address these questions.

Regulatory RNAs and pathogenesis

Our model system is the human pathogen, enterohaemorrhagic E. coli O157 (EHEC), that causes disease ranging from gastroenteritis to life treating haemolytic uremic syndrome. The later is caused by release of Shiga toxins that are expressed from bacteriophage (bacterial viruses) that have inserted into the bacterial genome. We have recently identified large numbers of non-coding RNAs that are encoded in EHEC and are seeking to identify those that regulate virulence. We anticipate that by understanding how bacteria employ ncRNAs to control gene expression and respond to stress we will be able to design interventions that limit bacterial pathogenesis and dissemination.

Regulatory RNAs and antibiotic resistance

Non-coding RNAs play prominent roles in controlling the composition of the bacterial cell wall and membranes. A number of ncRNAs have been shown to control intrinsic antibiotic resistance in bacterial pathogens with 'urgent' or 'serious' levels of antimicrobial resistance. Non-coding RNAs contribute to antibiotic resistance in Methicillin-resistant Staphylococcus aureus (MRSA, designated a 'serious' threat) and we are using high-through put sequencing technologies, bioinformatics, and molecular biology to identify key ncRNAs that mediate antibiotic resistance in MRSA.

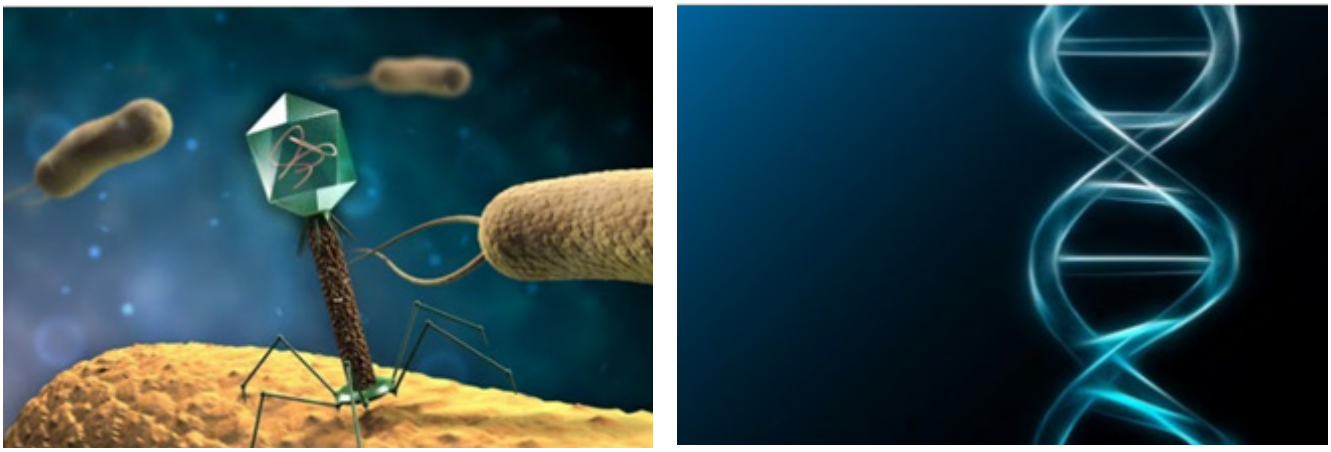
More information on the lab's research can be found on the Tree Lab website.

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

SUPERVISION

PhD, Honours, and 3rd year Undergraduate projects in Molecular Biology and Microbiology are available in the lab.

Current Lab members:
Dr Daniel Mediati (Post-doctoral researcher)
Dr Brandon Sy (Post-docotral researcher)
Dr Ignatius Pang (Post-doctoral researcher)
Winton Wu (PhD student)
Sylvania Wu (PhD student)
Daniel Neville (Honours student)

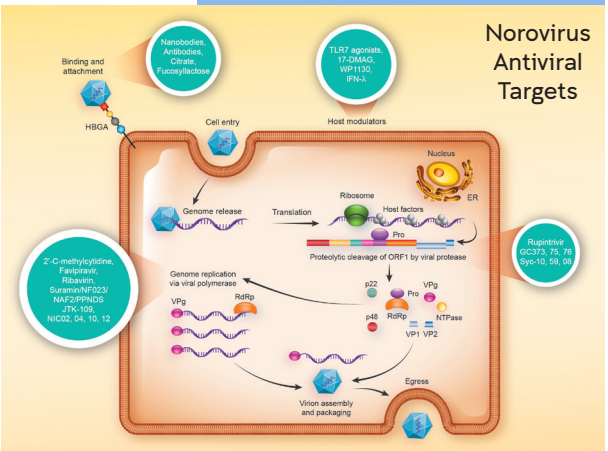


Bacteriophage are common vectors for transferring virulence genes between bacteria.

Professor Peter White
Room 3112, Level 3 East
Bioscience South Building E26
E p.white@unsw.edu.au
unsw.edu.au/staff/peter-white1
whitelab.unsw.edu.au

RESEARCH FOCUS

Molecular virology.



RESEARCH AREAS

Viral infections are a major global health threat and burden. Unless we understand the mechanisms, patterns, and consequences of their rapid evolution, we will not be able to build rational strategies for controlling their spread. Our research encompasses molecular virology, viral discovery, molecular surveillance, drug discovery, host-virus evolution and tickborne disease to better understand what makes a successful virus. We use a multi-disciplinary approach in our projects, combining wet-lab molecular biology and microbiology techniques with computational analysis and bioinformatics.

SPECIFIC PROJECTS

Our research revolves around four main areas.

Molecular epidemiology of human enteric viruses

All human pathogens regularly circulate within the community, genetically evolve and emerge to cause outbreaks. Norovirus, a leading cause of acute gastroenteritis worldwide, it regularly attacks cruise ship, aged-care centres, hospitals, and childcare. Pandemic strains can take this to a global scale with hundreds of millions of cases of acute gastroenteritis yearly when a pandemic strain strikes, as in 2013, caused by the Sydney 2012 norovirus which was discovered by our group at UNSW.
In our research we use a combination of clinical and wastewater samples to monitor the evolution of norovirus strains over time, identify recombination events and antigenic shift, and link these molecular changes to epidemiological data. We also conduct similar monitoring on human adenovirus and SARS-CoV-2.

Viral discovery

Over 70% of pandemics are caused by zoonotic viruses; HIV, SARS-CoV-2, and Zika virus are some examples from recent years. Using a combination of RNA-sequencing and bioinformatics, we discover viruses in a range of animals including bats and ticks. We also aim to discover viruses in vulnerable and endangered populations to aid in the detection and management of future viral outbreaks.

Endogenous viral elements in host genomes (paleovirology)

Endogenous viral elements (EVEs) are viral "fossils" inside host DNA. These fossils can be used to study ancient viruses and understand virus evolution over millions of years. We study the prevalence and diversity of EVEs throughout vertebrates and invertebrates to better understand the age and genetic evolution of viral families. In addition, we have evidence that EVEs contribute to cellular function and therefore they can protect cells from infection.

Antiviral discovery

Our research focusses on the development and repurposing of small compound antivirals, including non-nucleoside polymerase inhibitors, TLR7 agonists, and nucleoside analogues for the treatment of infections against positive sense RNA viruses, including norovirus, hepatitis C virus, feline calicivirus and hepatitis E virus. We explore our best antiviral candidates through high-throughput and *in silco* screening, using our cutting-edge enzyme, viral replicons and infection cell-culture based systems.

BIOGRAPHY

After undergraduate studies in Biotechnology from King's College London, Peter completed a PhD at University College, London in bacterial microbiology and molecular biology. In 1996, he started a period of Postdoctoral research at Macquarie University, Sydney, as a recipient of a Royal Society Fellowship to study antibiotic resistance in Gram-negative bacteria. Then in 1998, he joined the Virology Division, Prince of Wales Hospital as Hepatitis Group Leader until 2002, and worked on both HCV and norovirus. In January 2003, he was appointed an academic at UNSW, Sydney and established a molecular microbiology research group and laboratory within the School of Biotechnology and Biomolecular Sciences (BABS). Peter is also the course Coordinator for the third-year course Viruses and Disease (MICR3061), and he lectures and tutors 2nd and 3rd year science students, as well as medical students at UNSW.

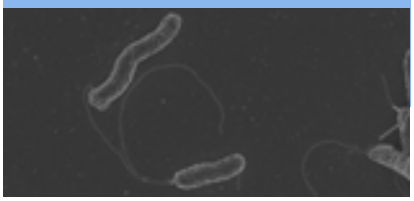
Viral Discovery in Ancient Fish

Associate Professor Li Zhang

Room 4106, Level 4 West
Bioscience South Building E26
E l.zhang@unsw.edu.au
babs.unsw.edu.au/li-zhang

RESEARCH FOCUS

Campylobacter, Aeromonas 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, metagenomic analysis, molecular diagnosis of bacterial infection, antibiotics, vaccines for mucosal associated bacteria, or cancer immunotherapy-associated gut microbes.

PROJECTS ON *CAMPYLOBACTER CONCISUS* AND *AEROMONAS* SPECIES

Campylobacter concisus is an oral bacterium that may cause enteric diseases. We found that *C. concisus* strains carrie pICON plasmid and pSma1 plasmid are associated with severe Crohn's disease and ulcerative colitis (two major forms of inflammatory bowel disease). *Aeromonas* species are important pathogens of fish, they also cause several human diseases. We recently found that *Aeromonas* species are the third most common enteric pathogens in Australia. Research projects on *Campylobacter* and *Aeromonas* species examine bacterial genomes, virulence factors, bacterial interaction with host immune system, and molecular diagnostic methods.

PROJECTS ON PRECISION ANTIBIOTICS AND VACCINES

Research projects in antibiotic area aim to develop precision antibiotics to specifically eradicate or inhibit individual bacterial species without affecting the balance of gut microbiota. Precision antibiotics may also be used to treat antibiotic resistant pathogenic bacterial species. We are also interested in identifying bacterial components that can be used as vaccines to control mucosa-associated bacterial pathogens.

PROJECTS ON CANCER IMMUNOTHERAPY-ASSOCIATED GUT MICROBES

Blockade of immune checkpoint proteins is a type of cancer therapy. Recent studies found that some bacterial species in the gastrointestinal tract may affect the efficacy of immune checkpoint blockade therapy. Projects in this area investigate the mechanisms by which gut bacterial species affecting cancer immunotherapy, aiming to provide additional strategies to improve cancer immunotherapy efficacy.

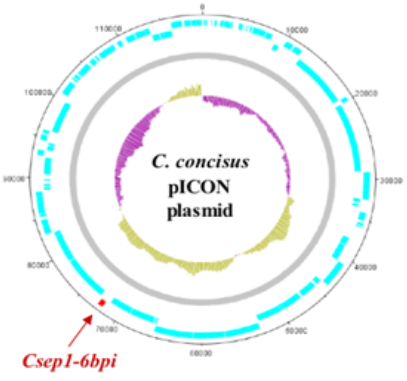


Figure 1. Circularised diagram of the pICON plasmid in *C. concisus* strain P2CDO4. (doi:10.1038/s41426-018-0065-6)

BIOGRAPHY

Associate Professor Li Zhang received MBBS degree from Fudan University in Shanghai, China and PhD degree from the University of Cambridge in the UK. A/Prof Zhang was a clinician at the China-Japan Friendship Hospital in Beijing prior to her PhD study. She worked as a postdoctoral fellow at the Institute of Molecular and Cell Biology in National University of Singapore before joining the University of New South Wales.

RESEARCH

A/Prof Zhang's group investigates bacterial species that cause or prevent inflammatory diseases and cancers of the gastrointestinal tract. They study bacterial genomes, bacterial virulence factors, interactions of bacterial pathogens and gut microbiome with the immune system, and novel methods to modify gut and oral microbiome. A/Prof Zhang's earlier research was on autoimmune diseases.

A/Prof Li Zhang is a pioneering researcher in the field of human hosted *Campylobacter* species and inflammatory bowel disease (IBD). She hypothesized that some strains of *C. concisus*, a bacterium that usually colonises the human oral cavity, have enteric pathogenicity and are the initiator of a subgroup of human IBD. Research in A/Prof Zhang's group has provided critical information to this research field, including disease associations, *C. concisus* natural colonisation site, *C. concisus* metabolic pathways and *C. concisus* genomic features associated with severe IBD.

Aeromonas species are important pathogens of fish and emerging human pathogens. A/Prof Zhang group recently reported that *Aeromonas* species are the third most common gastrointestinal bacterial pathogens in Australia, following *Campylobacter* and *Salmonella* species. They are currently examining the pathogenic mechanisms of *Aeromonas* species in causing human diseases.

Evidence shows that bacterial species in the gastrointestinal interesting tract affecting cancer immunotherapy A/Prof Zhang group investigates the mechanisms by which gut bacterial species affecting cancer immunotherapy. They also develop precision antibiotics to modify gut microbiota, aiming to provide additional strategies to improve cancer immunotherapy efficacy.

For other details about research in A/Prof Zhang group and their publications, please visit:

- research.unsw.edu.au/people/associate-professor-li-zhang
- scholar.google.com.au/citations?user=gddDrbMAAAAJ&hl=en

RESEARCH SUPERVISORS -

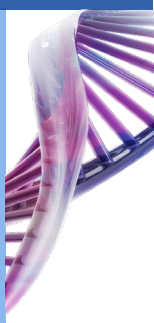
MOLECULAR AND CELL BIOLOGY

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.



RESEARCH FOCUS

Evolutionary Biophysics
Synthetic Biology
Super resolution microscopy

Dr Matthew Baker
SCIENTIA SENIOR LECTURER
Room 301A, Level 3 East
Biosciences North Building D26
E matthew.baker@unsw.edu.au
babs.unsw.edu.au/matthew-baker
https://linktr.ee/phatmattbaker

My research group currently focuses on three streams of research:

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

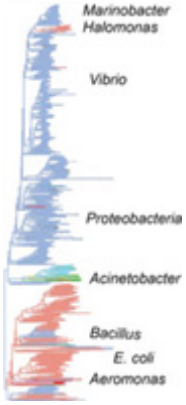
PROJECT 1 - EVOLUTION ACROSS INTERFACES

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

PROJECT 2 - ANCESTRAL RECONSTRUCTION OF THE BACTERIAL FLAGELLAR ROTOR

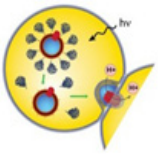
We recreate microbial 'Jurassic Parks' by resurrecting ancient flagellar motor componentry in contemporary hosts and measuring how well they work. This allows us to create ancient motors that have never existed in the present day to synthesise and evolve new motors as well as to learn about the process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

PROJECT 3 - ORIGINS OF MOTILITY



The evolutionary origins of the bacterial flagellum have been a subject of scientific and public controversy – how can evolution produce such a complex system? We believe we can make progress on the issue by updating old phylogenetic work with new datasets and improved models, and combining this with experimental evolution work being done in our labs. The project will be to assemble a well- organized database of flagellar proteins and explore sequenced bacterial genomes with genome browsers and similarity searches. The student will identify flagellar proteins and their evolutionary relatives, including recording their position in the genome. The student will also plan and conduct phylogenetic analyses, and then use synthetic biology to recreate these ancestors in a contemporary microbial 'Jurassic Park'.

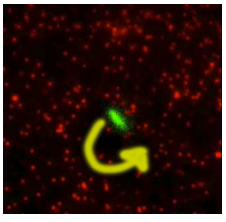
PROJECT 4 - REGULATION OF MEMBRANE PROTEIN INSERTION IN ARTIFICIAL BILAYERS USING DNA ORIGAMI



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

PROJECT 5 - APPLICATIONS OF FLAGELLAR MOTOR TO FLUID FLOWS

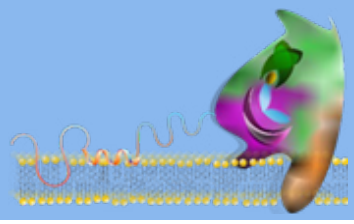
We utilise the high efficiency and self assembly of the flagellar motor to drive rotation of cells on patterned surfaces to control mixing and fluid flows in microfluidics. We have projects involving designing and building new devices to apply the flagellar motor onto other things. This would suit someone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



Professor Andrew Brown
Room 3103, Level 3 West
Bioscience South Building E26
E aj.brown@unsw.edu.au
babs.unsw.edu.au/andrew-brown

RESEARCH FOCUS

Controlling cellular cholesterol.



RESEARCH

"I <3 Cholesterol, but my <3 doesn't"

However, there's much much more to cholesterol than that. We study how we and our cells balance this Jekyll/Hyde molecule.

Cholesterol is notorious in human health and disease. It is both vital and lethal, depending on its levels, which are determined by several factors, including cholesterol synthesis. For the past decade, my lab has focused on investigating the control of cholesterol synthesis. We have made major progress, uncovering novel modes of regulation of enzymes beyond the best known and most intensively studied enzyme (HMGCR, target of the statin class of drugs). Notably, we discovered an important control point later in the pathway (squalene monooxygenase or epoxidase, SQLE), which has recently become the subject of intense interest as an oncogene and therapeutic target in several cancers.

RESEARCH GOALS

- To discover new factors in achieving cholesterol balance in cells
- To identify links between cholesterol and cancer

SPECIFIC PROJECTS

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 achieving cholesterol balance
An imbalance of cholesterol plays a role in numerous diseases. Therefore, knowing precisely how cells regulate their cholesterol levels is central to understanding the development of these diseases, and to identify possible new treatments. Only one of the 20+ enzymes involved in cholesterol biosynthesis is targeted clinically (by statins). The statin class of drugs, worth >$30 billion a year, inhibit a very early step in cholesterol synthesis and have been effective in treating heart disease, but are not without their side effects. 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. 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. 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 ROUTINELY USED IN THE LAB

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

SUPERVISION OPPORTUNITIES/AREAS

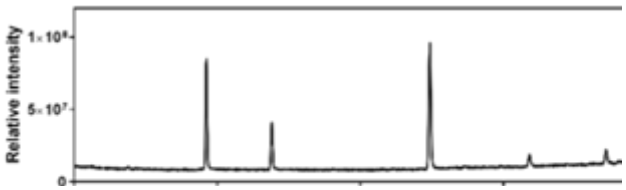
Our lab provides a nurturing, supportive and stimulating research environment for students.

I have supervised 26 Honours students and all have received first class honours; 15 have gone on to do a PhD with me. Seven of my Honours students have received University medals (top of their cohort).

I have supervised 10 PhD students and all obtained excellent post-doc positions in Australia or overseas after completion.

I believe that a key part of my role as an academic is to mentor the next generation in scientific publishing, so I have an established record of converting student projects into publications. Many of my Honours students have had work from their Honours year published, and my PhD students publish at least 5 papers on average during their time with me.

Contact Andrew about research supervision opportunities:
aj.brown@unsw.edu.au

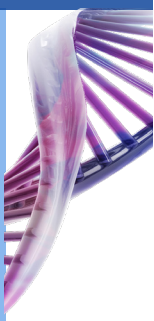


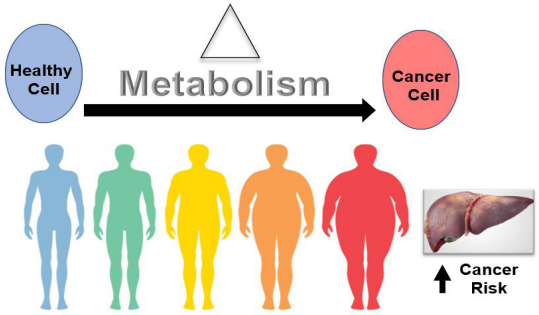
Dr Frances Byrne
SENIOR LECTURER/CANCER INSTITUTE NSW CAREER DEVELOPMENT FELLOW

Office 420B, Level 4
Biological Sciences Building D26
E frances.byrne@unsw.edu.au
babs.unsw.edu.au/frances-byrne

RESEARCH FOCUS

Identifying new drugs to target cancer cell metabolism and investigating how diet and obesity promote cancer development.





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

PROJECT 1: Investigating the anti-cancer potential of new mitochondrial uncouplers
Mitochondrial uncouplers are small molecules that make mitochondria burn (oxidise) more nutrients, such as fats, without producing ATP. Thereby they 'uncouple' nutrient oxidation from ATP synthesis. Not surprisingly, these molecules have shown great promise for the treatment of obesity. However, mitochondrial uncouplers may also be effective anti-cancer agents because they disrupt the metabolism of cancer cells. This project will investigate the anti-cancer potential of new mitochondrial uncouplers developed in our laboratory. Specifically, the anti-cancer effects of these molecules will be tested alone and in combination with drugs currently used in the clinic for the treatment of cancer. These experiments will help us determine whether these new uncouplers may be used for cancer treatment in the future.

PROJECT 2: Unravelling the links between diet, obesity, and liver cancer
Liver cancer is strongly linked to poor diet and obesity. Previous research suggests that high fructose diets may promote obesity and liver cancer development. This project will use mouse models to determine how diets high in fructose promote the growth of liver tumours. It is hoped these experiments will identify therapeutic targets or strategies to prevent the tumorigenic properties of high fructose consumption.

PUBLICATIONS OF INTEREST

Kaakoush, N. O., Olzomer, E. M., Kosasih, M., Martin, A. R., Fargah, F., Lambie, N., Susic, D., Hoehn, K. L., Farrell, R., and **Byrne, F. L.** (2022) Differences in the Active Endometrial Microbiota across Body Weight and Cancer in Humans and Mice, *Cancers (Basel).* 2022;14(9):2141. Published 2022 Apr 25. doi:10.3390/cancers14092141

Shrestha, R., Johnson, E., **Byrne, F.L.** (2021). Exploring the therapeutic potential of mitochondrial uncouplers in cancer. *Mol Metab.* 2021;51:101222. doi:10.1016/j.molmet.2021.101222

Caruana B.T. and **Byrne F.L.** (2020) The NF-κB signalling pathway regulates GLUT6 expression in endometrial cancer, *Cell Signal.* 2020;73:109688. doi:10.1016/j.cellsig.2020.109688

Byrne, F. L., et al. (2020) The Role of Hyperglycemia in Endometrial Cancer Pathogenesis, *Cancers (Basel).* 2020;12(5):1191. Published 2020 May 8. doi:10.3390/cancers12051191

Byrne, F. L., et al. (2020) Phenotypic screen for oxygen consumption rate identifies an anti-cancer naphthoquinone that induces mitochondrial oxidative stress, *Redox Biol.* 2020;28:101374. doi:10.1016/j.redox.2019.101374

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Byrne, F. L., et al. (2014) RNAi-mediated stathmin suppression reduces lung metastasis in an orthotopic neuroblastoma mouse model, *Oncogene.* 2014;33(7):882-890. doi:10.1038/onc.2013.11

Byrne, F. L., et al. (2014) Metabolic vulnerabilities in endometrial cancer, *Cancer Res.* 2014;74(20):5832-5845. doi:10.1158/0008-5472.CAN-14-0254

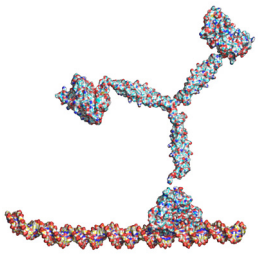
Professor Paul Curmi
Room 320E, Level 3 West
Bioscience North Building D26
E p.curmi@unsw.edu.au
research.unsw.edu.au/people/professor-paul-marie-gerard-curmi

RESEARCH FOCUS

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

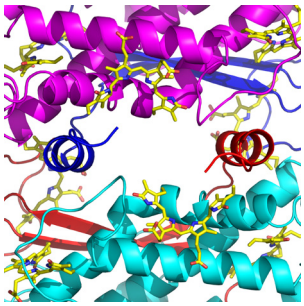
Our research focuses on understanding how proteins work at the atomic level. Proteins are nature's choice for making cellular machines. Each protein machine is composed of well-ordered structural domains that are linked together to create a dynamic, functioning system. By mapping the structures of a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

PROJECT 1
How do protein motors work? Nature has evolved spectacular protein motors such as myosin and kinesin that can "walk" down protein tracks (actin filaments and microtubules, respectively). Although these motor proteins have been studied for decades, producing a plethora of atomic structures and detailed mutagenic studies, we still have no idea how these proteins harness chemical energy (ATPase) to produce motion. A novel way to explore this question is to use a synthetic biology approach: take existing protein modules of known function and link them together to create artificial protein motors. Our lab is part of an international team that is striving to achieve this goal. We have developed a successful strategy to link functional modules together to make an artificial motor protein that will "walk" along a DNA nanotube track. This project will explore a new motor design using the same components as our current motor.



PROJECT 2 (jointly supervised with Dr Kate Michie)
How does a eukaryotic cell control the shape of the plasma membrane and associated vesicles? Underlying the eukaryotic plasma membrane is a layer of actin filaments called the cell cortex or cortical cytoskeleton. The protein ezrin (and its paralogues, the ERMs) couple membranes to cortical actin filaments. Ezrin is responsible for the maintenance of surface structures (such as microvilli) and the invagination of the plasma membrane during processes such as phagocytosis. Our key question is how does ezrin do this? We have determined crystal structures of ezrin in two states, however, we still lack a structure of the active, membrane bound form of ezrin. Preliminary cryo electron microscopy studies show that ezrin alone can deform membrane vesicles and cluster them together. The aim of this project is to determine how ezrin achieves this, with the ultimate aim of obtaining the structure of ezrin bound to a membrane, and, finally, to actin filaments.

PROJECT 3
How do light harvesting proteins capture sunlight and transmit the energy so as to power photosynthesis? Aquatic organisms have evolved elaborate light harvesting antenna systems where proteins control the capture and transfer of energy between chromophore molecules. During evolution, at least five distinct light harvesting antenna systems have been discovered. Our research focuses on the light harvesting antennae of two classes of algae: the cryptophytes and red algae, where the former evolved from the latter via secondary endosymbiosis. The aim of this project is to explore the dramatic changes that have occurred in the antenna complexes during evolution using synthetic biology approaches. By creating protein chimeras, we will explore how changes in sequence result in dramatic structural changes in protein complexes.



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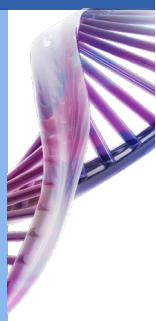
Dr Dominic Glover
SENIOR LECTURER
Room 301E, Level 3 East
Bioscience North Building D26
E d.glover@unsw.edu.au
babs.unsw.edu.au/dr-dominic-glover

RESEARCH FOCUS

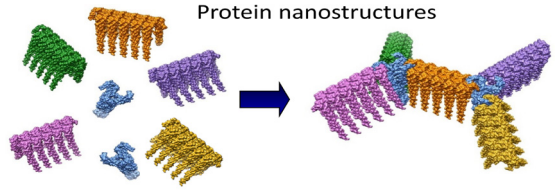
Synthetic biology and bioengineering of protein biomaterials.



RESEARCH PROGRAM

The intricate and ordered complexes that proteins adopt in nature is central to many biological processes, ranging from cellular scaffolding provided by cytoskeletal proteins to the encapsulation of nucleic acids in viral capsids. Exploiting this remarkable fidelity and precision in self-assembly is highly attractive for the fabrication of structurally defined materials with nanometer dimensions. Advances in the computational prediction of protein folding have enabled the design of proteins that self-assemble into complex yet predictable shapes.

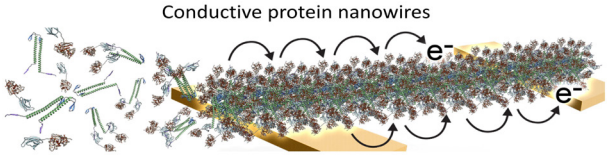
The research program in my group applies synthetic biology for the engineering of proteins into structured and functional biomaterials. Central to this approach is the creation of standardised protein building blocks that can be assembled into geometrically-defined structures of controllable size and shape. This ability to design protein nanostructures with atomic-level accuracy opens new possibilities in biomaterials. Applications of these protein-based biomaterials include the creation of electrically conductive protein nanowires for biosensors and enzyme catalysis, the engineering of metabolic pathways, and the fabrication of tissue scaffolds for regenerative medicine.



SPECIFIC PROJECTS

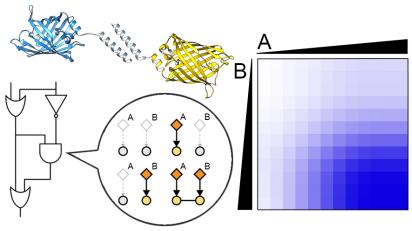
Project 1: Conductive protein nanowires for bioelectronics and biosensors

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



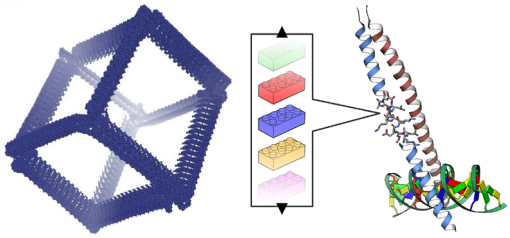
Project 2: Design of synthetic transcriptional factors

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



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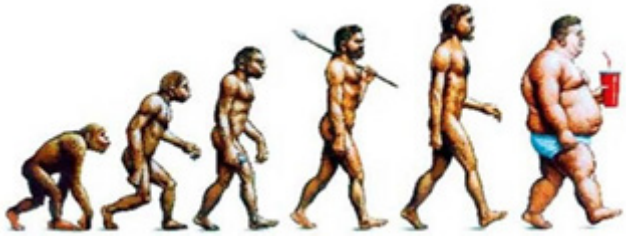
Professor Kyle Hoehn
Room 420A, Level 4 West
Bioscience South Building D26
E k.hoehn@unsw.edu.au
babs.unsw.edu.au/kyle-hoehn

RESEARCH FOCUS

Mechanisms linking altered nutrient metabolism to ageing, obesity, and diabetes.
Suitable for students who have majored in Molecular Biology.

OBESITY: THE OTHER PANDEMIC



According to the World Health Organization more than 1.9 billion adults worldwide are overweight. Australia is more overweight than the world average, with 67% of the adult population being defined as overweight by a body mass index > 25. Being overweight is associated with shortened lifespan and is a major risk factor for metabolic diseases including cardiovascular diseases, fatty liver disease, and many types of cancer. Identification of drugs that safely reverse obesity could increase healthspan, decrease disease burden, and improve quality of life. My lab is focused on developing new drugs that reverse obesity, ageing, and related metabolic disorders.

Our molecules are anti-oxidant and boost metabolism to help burn off excess fat without affecting food intake. We are seeking HDR students to join projects that will test our molecules in mice for safety and efficacy to reverse obesity, fatty liver disease, and slow age-related metabolic decline.

RESEARCH PROJECTS

- To identify new molecules that improve healthy ageing
- To identify new molecules that reverse obesity and metabolic disease

RELEVANT PUBLICATIONS

- Chen SY, Beretta M, Alexopoulos SJ, Shah DP, Olzomer EM, Hargett SR, Childress ES, Salamoun JM, Aleksovska I, Roseblade A, Cranfield C, Rawling T, Quinlan KGR, Morris MJ, Tucker SP, Santos WL and Hoehn KL. Mitochondrial uncoupler SHC517 reverses obesity in mice without affecting food intake. *Metabolism*. 2021 Apr;117:154724. doi: 10.1016/j.metabol.2021.154724.

- Alexopoulos, A.J.; Chen, S-Y.; Brandon, A.E.; Salamoun, J.; Garcia, C.J.; Beretta, M.; Olzomer, E.; Byrne, F.B.; Shah, D.; Lawrence, R.; Carrive, P.; Tucker, S.P.; Cooney, G.J.; Santos, WL, Hoehn KL. Mitochondrial uncoupler BAM15 reverses diet-induced obesity and insulin resistance in mice. *Nature Communications*. 2020 May 14;11(1):2397. doi: 10.1038/s41467-020-16298-2

- Salamoun J, Garcia C, Hargett S, Murray J, Chen SY, Beretta M, Alexopoulos S, Shah D, Olzomer E, Tucker S, Hoehn KL*, and Santos WL*.6-Amino-[1,2,5]oxadiazolo[3,4-b]pyrazin5-ol Derivatives as Efficacious Mitochondrial Uncouplers in STAM Mouse Model of Non-alcoholic Steatohepatitis. *Journal of Medicinal Chemistry.* Jun 11;63(11):6203-6224. doi: 10.1021/acs.jmedchem.0c00542. *co-corresponding.

Associate Professor Christopher Marquis

Room 320A, Level 3 West
Biological Sciences North Building D26
E c.marquis@unsw.edu.au
babs.unsw.edu.au/christopher-marquis

RESEARCH FOCUS

Protein biotechnology.

RESEARCH PROGRAM

A/Prof Marquis trained as a biochemical engineer and has current interdisciplinary research projects across protein biotechnology and in the bio-nanotechnology interface. Current projects include developing recombinant enzymes for organohalide bioremediation, searching for and developing improved versions of the enzyme gamma glutamyltransferase for dipeptide bioproduction, integrating new microfluidic devices into mammalian cell bioprocesses and evaluation of new materials for biofilm deterrence. Newer collaborations include the development of methods to generate recombinant spider silks.

In addition A/Prof Marquis is the Director of the Recombinant Products Facility (www.proteins.unsw.edu.au), which houses research infrastructure for fermentation, cell culture, mid-stream and downstream processing for protein production, purification and characterisation. The facility also provides expertise in developing and optimising bioprocesses. The primary role of the Facility is to provide research support to the UNSW research community, however the facility provides contract services for the wider research community and also industry. The RPF has fermentation capacity to 20L and a variety of mid and downstream processing capabilities for the production and purification of proteins for research. In addition to running contract projects we have a number of internal initiatives to investigate and optimise bioprocesses.

Available projects can be viewed here.

Dr Kate Michie
SENIOR RESEARCH ASSOCIATE & LECTURER
Room 320D, Level 3 West
Bioscience North Building D26
E k.michie@unsw.edu.au
analytical.unsw.edu.au/facilities/sbf

RESEARCH FOCUS

Structural biology of protein machineries.

Structural Biology Facility

RESEARCH AREAS

We want to understand how biology uses proteins to control the shape of membranes. In particular we focus on the proteins essential to the processes of cell division and building cell surface structures such as villi and vesicles. The proteins involved in these processes interact with themselves and with the membrane to bend and shape it, and to tether other proteins to it. The types of proteins involved arise in all the domains of life— archaea, bacteria and eukaryotes, and, maybe not surprisingly, are often carried out by related proteins.

We focus on understanding structurally the proteins that carry out these tasks. We use X-ray crystallography, cryo-electron microscopy and a range of protein and biophysical experiments to probe our targets.

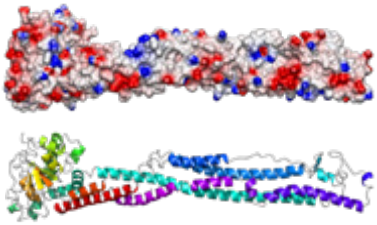


Figure 1: Electrostatic potential and crystal structure of LeoA- a bacterial dynamin-like protein.

CURRENT RESEARCH ACTIVITIES

- Dynamin-like Proteins in Bacteria
- Tubulin-like proteins in Bacteria and Archaea
- Ezrin/Moesin and Merlin and the membrane in humans (Jointly supervised with Prof Curmi)

Dr Michie also collaborates other researchers. If you are interested in structural biology, introduce yourself to explore potential paths forward.

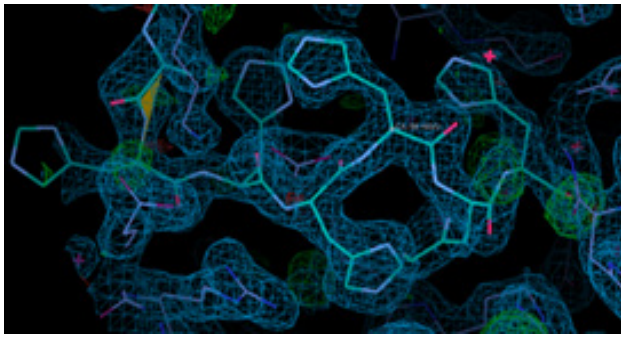


Figure 3: Electron density and protein model showing a his-tag on a recombinant protein structure

BIOGRAPHY

Dr Kate Michie is an Adjunct Lecturer (BABS) and Senior Research Associate in the Mark Wainwright Analytical Centre. Dr Michie completed her PhD at Sydney University (2004). She was an International L'Oreal UNESCO Fellow (2005) and Marie Curie Fellow (2006-2007) at the Medical Research Council Laboratory of Molecular Biology (LMB) in Cambridge UK with Dr Jan Löwe, and a Research Associate at St John's College. She was made an Investigator Scientist at the LMB in 2008 working on the structural biology of bacterial cytoskeletal proteins. Returning to Australia in 2010, Dr Michie worked on heart proteins with Professors Guss and Trewhella (Syd Uni). She moved to UNSW in 2016 to work with Professor Paul Curmi on Ezrin (a membrane shaping cytoskeletal protein) and light-harvesting complexes. In 2019 she was employed to set up and run the Structural Biology Facility within the Mark Wainwright Analytical Centre.

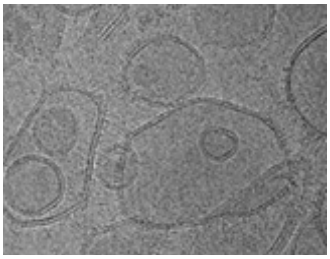


Figure 2: Cryo EM image of Ezrin binding on the surface in regular arrays to lipid vesicles.

SELECT PUBLICATIONS

- Scaffolding proteins guide the evolution of algal light harvesting antennas. HW Rathbone, KA Michie, MJ Landsberg, BR Green, PMG Curmi. *Nature communications* 12 (1), 1-9. 2021
- Two sides of the coin: ezrin/radixin/moesin and merlin control membrane structure and contact inhibition. KA Michie, A Bermeister, NO Robertson, SC Goodchild, PMG Curmi. *International journal of molecular sciences* 20 (8), 1996. 2019
- CetZ tubulin-like proteins control archaeal cell shape. IG Duggin et al. *Nature* 519 (7543), 362-365. 2015
- LeoA, B and C from enterotoxigenic Escherichia coli (ETEC) are bacterial dynamins. KA Michie, A Boysen, HH Low, J Møller-Jensen, J Löwe. *PloS one* 9 (9), e107211. 2014

Scientia Associate Professor Kate Quinlan

Room 3102, Level 3 West
Bioscience South Building E26
E kate.quinlan@unsw.edu.au
babs.unsw.edu.au/kate-quinlan

RESEARCH FOCUS

Regulation of energy expenditure in adipose tissue.

We study mammalian metabolism and gene regulation, with the aim of identifying biological pathways to target for anti-obesity therapies. White adipose tissue can be converted to 'beige' adipose tissue, which burns energy to produce heat rather than storing energy. We aim to better understand beige adipose tissue so that this knowledge can be harnessed to reverse obesity.

Currently, our collaborative research group includes a lab manager, 7 PhD students and 2 Honours students. We are seeking new HDR students for 2023.

TECHNIQUES

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

BIOGRAPHY

Kate is a Scientia Associate Professor in the School of Biotechnology and Biomolecular Sciences (BABS). She runs a research group interested in gene regulation, with a particular focus on understanding the communication between immune cells and fat cells within adipose tissue to uncover new therapeutic targets for obesity. Kate completed her Bsc (Hons) (Advanced) at the University of Sydney. She went to overseas to work as a Research Assistant at the University of Cambridge for a year before returning to the University of Sydney to complete her PhD in transcription factor biology. Kate moved to the Children's Hospital at Westmead as a post-doc, where she studied the effects of the human *ACTN3* gene polymorphism on skeletal muscle performance and metabolism. She continued her post-doctoral training at the University of Cambridge (2008-2010), researching pluripotency of embryonic stem cells and targeted differentiation of these cells towards skeletal muscle satellite cells. She then returned to the University of Sydney to lead a program of research into the human *ACTN3* gene polymorphism, with the aims of uncovering mechanisms behind changes to muscle function and metabolism in individuals homozygous for this polymorphism, and translating findings from model organisms to humans. In 2014 Kate joined UNSW, to study the transcriptional regulation of haematopoiesis and transcription factor mechanisms in addition to continuing an independent research program focussed on skeletal muscle metabolism. She became an independent group leader in 2018. Kate mentors a number of PhD and Honours students.

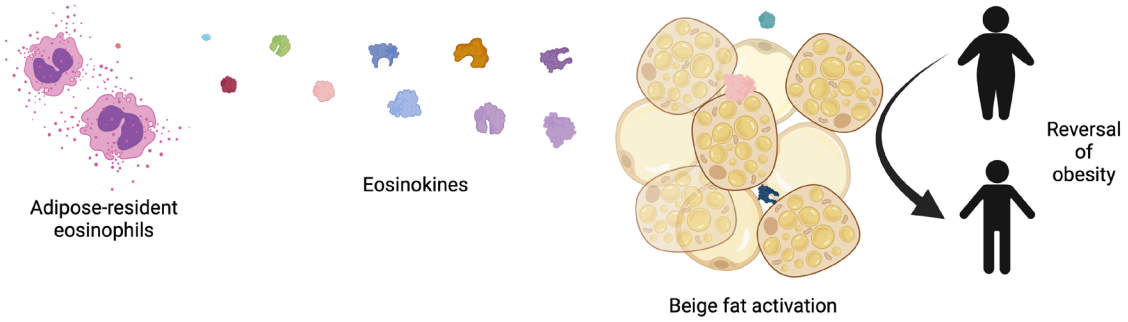
RECENT PUBLICATIONS

'Shades of white: new insights into tissue-resident leukocyte heterogeneity' *FEBS J.*, 2022, 289(2):308-318.

'Eosinophil Function in Adipose Tissue Is Regulated by Krüppel-like Factor 3 (KLF3)' *Nature Communications*, 2020, 11(1):2922.

'Krüppel-like Factor 3 (KLF3) Suppresses NF-κB-driven Inflammation in Mice.' *J Biol Chem.*, 2020, 295(18):6080-6091.

'EoTHINophils: Eosinophils as Key Players in Adipose Tissue Homeostasis' *Clin Exp Pharmacol Physiol,* 2020, 47(8):1495-1505.



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

Associate Professor Vladimir Sytnyk
Room 3101, Level 3 West
Bioscience South Building E26
E v.sytnyk@unsw.edu.au
babs.unsw.edu.au/vladimir-sytnyk

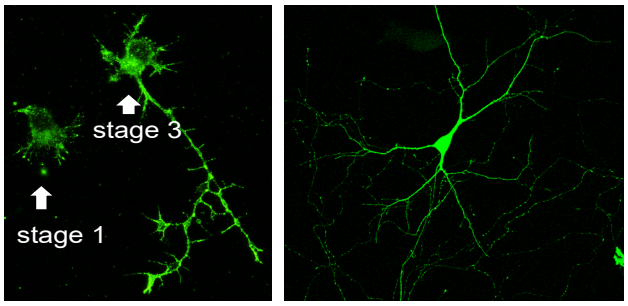
RESEARCH FOCUS

Neurobiology, neuroscience, recognition and cell adhesion in neurons.

RESEARCH INTERESTS AND CONTRIBUTIONS

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.

The formation and maintenance of the neuronal networks and synapses is regulated by neural cell adhesion molecules expressed at the cell surface of neurons (see our review Sytnyk et al., Trends in Neurosciences, 2017). Our laboratory is interested in understanding the molecular and cellular mechanisms of this regulation and effects of its loss in disease. We also develop new technologies aimed at improving brain performance, enhancing learning and maintaining memory by modulating neural cell adhesion molecules.



My early work showed that neural cell adhesion molecules are the first proteins accumulating at nascent synaptic contacts between developing neurons and that these proteins stabilize the contacts and induce their transformation into mature synapses by capturing synaptic precursor organelles (Sytnyk et al., Journal of Cell Biology, 2002, featured on the cover page). We then found that neural cell adhesion molecules regulate the key processes involved in neuronal growth and synapse formation including intracellular signalling (Leshchyns'ka et al., Journal of Cell Biology, 2003; Bodrikov et al., Journal of Cell Biology, 2005, 2008; Sheng et al., Journal of Neuroscience, 2015), the assembly of the cytoskeleton (Puchkov et al., Cerebral Cortex, 2011; Li et al., Journal of Neuroscience, 2013) and polarised intracellular transport (Chernyshova et al., Journal of Neuroscience, 2011). We demonstrated that neural cell adhesion molecules modulate the assembly and maturation of the neurotransmitter-releasing machinery in axons (Leshchyns'ka et al., Neuron, 2006; Shetty et al., Journal of Neuroscience, 2013) and neurotransmitter-detecting machinery in dendrites of neurons (Sytnyk et al., Journal of Cell Biology, 2006; Sheng et al., Cerebral Cortex, 2019).

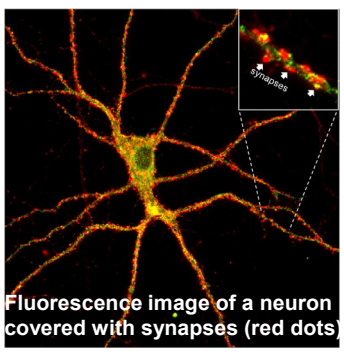
By using a novel technique for analysis of synapses in brains of individuals affected by neurodegenerative disorders, we demonstrated that the loss of synapses in Alzheimer's disease is linked to the degradation of synaptic neural adhesion molecules (Leshchyns'ka et al., 2015; featured at the Medical News website and others, the front page of the UNSW website and in the Newsletter (Summer 2015/16) of the Australia and New Zealand Society for Cell and Developmental Biology). Currently, we analyse mechanisms of this loss and develop strategies that can be used to prevent it. We also investigate changes in neural cell adhesion in other neurodegenerative disorders such as Parkinson's disease and motor neuron disease and use new transgenic mice to model abnormal function of neural cell adhesion molecules in these disorders and study its effects on the brain.

REFERENCES

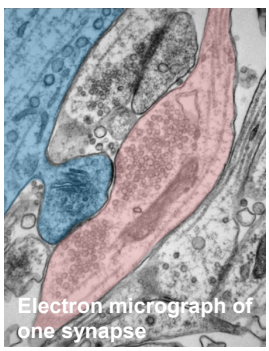
» Leshchyns'ka I et al. 2015, 'Aβ-dependent reduction of NCAM2- mediated synaptic adhesion contributes to synapse loss in Alzheimer's disease', *Nature Communications,* 6:8836.

» 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.



Fluorescence image of a neuron covered with synapses (red dots)


Electron micrograph of one synapse

Professor H. Robert Yang
Room 3104, Level 3 West
Bioscience South Building E26
E h.rob.yang@unsw.edu.au
babs.unsw.edu.au/h-robert-yang

RESEARCH FOCUS

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

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

PROJECT 1: Oxysterol binding proteins, intracellular lipid trafficking and cancer
Aberrant distribution of lipids causes heart disease and cancer. We have identified novel proteins that regulate lipid transport in cells. We now aim to identify additional regulators of cellular cholesterol distribution, and to understand how these proteins may regulate cancer. The students will learn key techniques in cell biology such as cell culture, fluorescence microscopy etc.

SELECTED REFERENCES

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

PROJECT 2: Seipin, lipid droplets, adipose tissue development and human obesity
Human obesity is, in essence, the accumulation of lipid droplets, which are storage granules of fat. We have uncovered a role for a human disease gene – SEIPIN – in lipid droplet formation. Our recent data suggest that Seipin may regulate the metabolism of fatty acids and phospholipids.

Our current aim is to determine the molecular function of SEIPIN, and how it regulates lipid droplet morphology and adipocyte development. We are also studying other proteins that regulate lipid storage. Students will learn techniques in molecular biology such as CRISPR and lipid analyses.

SELECTED REFERENCES

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

APPROVED EXTERNAL SUPERVISORS

HDR may also be undertaken with approved external supervisors located in institutions affiliated with the School of BABS. Students can contact external supervisors directly for information on available projects. Please note that it is BABS policy that a BABS academic must be assigned as joint supervisor.

FREQUENTLY ASKED QUESTIONS

1. I'm interested in postgraduate study in BABS - where do I begin?

First and most importantly, it is essential that you identify an appropriate academic supervisor in BABS and obtain their agreement prior to submitting an application for postgraduate study.

It is recommended that you peruse the School's current research clusters to obtain an understanding of the areas of study available within BABS. You should try and align your topic of interest with the research area of one of the affiliated academics. Contact details for individuals can be found in the BABS Academic and Research Leaders Directory. This handbook has also been designed to capture this information within the Research Supervisors sections. We also produce a BABS Honours Information Booklet which lists supervisors and honours projects (particularly relevant for prospective Graduate Diploma & MPhil students).

In your email, it is recommended that you:

a. Identify which research area you are interested in, and why
b. Indicate which term you intend on commencing (Term 1, 2 or 3)
c. Advise your availability times for an interview
d. Attach a copy of your CV and academic transcript
e. Confirm you have available funding to cover both living expenses and the tuition fees
f. Indicate clearly that you have appropriate visa status (or will apply for same)

NB: If you submit an application for postgraduate study without a nominated supervisor, it is likely to be declined.

Identifying and negotiating with prospective supervisors is up to you. Your ideal supervisor will be knowledgeable in your topic of interest, have good research skills and experience, and be someone you feel you can work well with. Choosing the right supervisor is very important. It is recommended that you meet and/or correspond with those academics in BABS that you feel have expertise in your area of interest to identify the best person to ask to be your supervisor. Note, however, that as most of our academic staff receive between 50 and 200 requests from prospective postgraduate students each year, please understand they may not always be able to assist you.

2. What are the visa requirements?

Overseas postgraduate students must obtain an appropriate visa that allows them to study in Australia. Please refer to the Australian Dept of Home Affairs and UNSW visa information to ensure you are aware of the specific requirements in regard to obtaining the correct visa. This process can be very time-consuming, so please make sure you know what is required.

FREQUENTLY ASKED QUESTIONS

3. What are the academic entry requirements?

All entry requirements for the particular degree must be met (for instance, an Honours undergraduate degree is generally a pre-requisite for entry into a PhD program). Admission criteria are an academic matter and you will need to provide evidence that you have attained the appropriate pre-requisites for the degree you are applying for. Requirements for each degree is provided in this handbook and can also be found online.

4. What scholarships are available?

Please note that the School does not provide scholarships to support either living expenses or tuition fees for postgraduate students. The cost of living in Sydney can be high, and part-time employment may not be readily available or permitted under some visa conditions. Accordingly, it is your responsibility to ensure you have adequate funding to cover both of these necessities. The University of NSW does provide some postgraduate scholarship opportunities, which are detailed in this handbook and can be found on the UNSW Graduate Research Scholarships website and the UNSW Scholarships website.

BABS has some scholarship opportunities available for students once they are enrolled.

5. What are the English language requirements?

Full information on the English language requirements of this University is available here.

6. How do I apply?

Once you have found a supervisor, please see the Graduate Research Submit an Application webpage if you are applying for PhD, MSc or MPhil. Students can apply for the UNSW scholarships during their admission application. HDR admission and scholarship FAQs are available here. Please note that the Graduate Research School administers postgraduate research study only. Postgraduate coursework (Graduate Diploma) and undergraduate programs are administered by The UNSW Nucleus Student Hub.

All applications for entry to UNSW for postgraduate study (Graduate Diploma) must be submitted via UNSW Apply Online. You will then be advised of details of all the necessary documentation that you need to provide, including proof of contact with your proposed supervisor. Graduate Diploma application FAQs are available here.

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