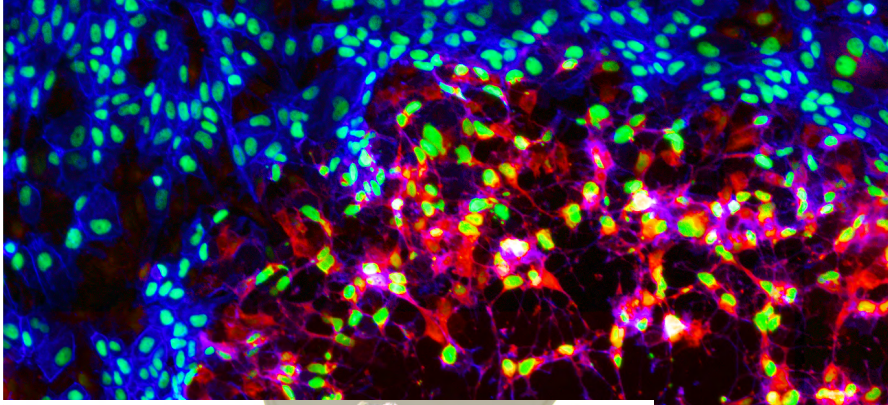


FACULTY OF
SCIENCE

THE UNIVERSITY OF
SYDNEY

SCHOOL OF MOLECULAR BIOSCIENCE
HONOURS GUIDE 2015

CONTENTS

HONOURS INFORMATION SESSIONS

Honours in Biochemistry and Microbiology
School of Molecular Bioscience

Molecular Bioscience Building,G08
Common Room, Level 4, Rm 431
Thursday 18th September, 2014

1.00 pm AND 5.00 pm

Food and drinks provided

Your chance to meet potential supervisors and current research students!

WELCOME

Welcome to the School of Molecular Bioscience Information Program for Honours 2015!

For starters, I hope that you will be able to join us at one of the information sessions on Thursday 18th September, 2014. At these sessions you will find opportunities to meet informally with potential supervisors and current research students, consider a smorgasbord of possible projects, learn more about our exciting research environment, and, of course, fuel up with food and drink.

An 'Honours' year is the capstone of your undergraduate degree and an important first step towards a career in research. A degree with Honours is highly regarded by potential employers and is a necessary prerequisite for postgraduate research, including enrolment in a PhD program.

The School of Molecular Bioscience is an excellent place to do your Honours year. First, our staff are recognised internationally for their outstanding research and mentorship. Second, you will find a broad range of research to meet your interests spanning nutrition & metabolism, structural biology, microbiology, proteomics and molecular biology & genetics. Third, our Honours Committee, will ensure you have the highest quality support and learning experience. Fourth, the School is very active socially and runs various events that include movie nights, dinners, barbecues, a ball, and a very popular trivia night.

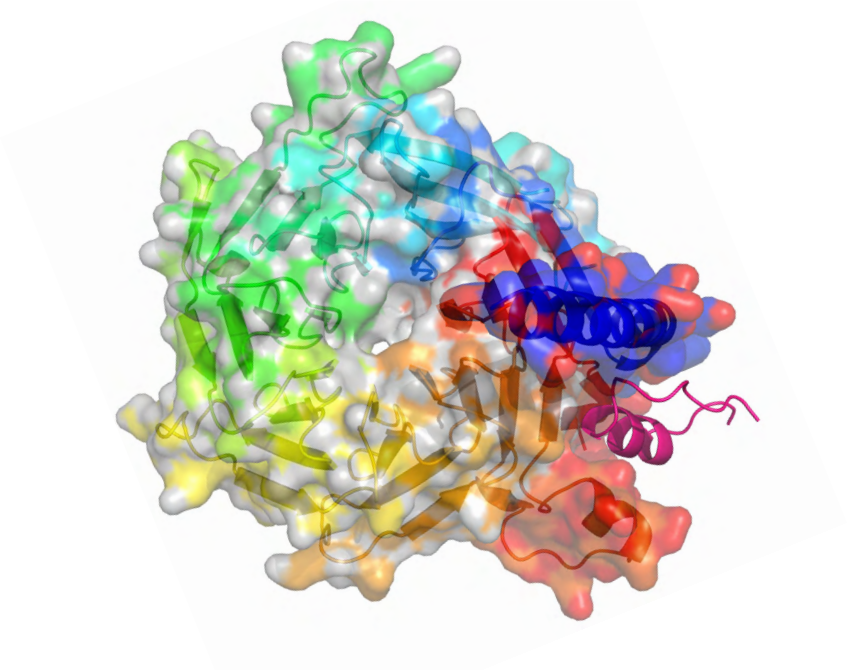
I encourage you to review this information brochure and talk to as many potential supervisors as you can – and I'll look forward to seeing you in 2015!

PROFESSOR IAIN CAMPBELL
HEAD, SCHOOL OF MOLECULAR BIOSCIENCE

If you are looking to improve your career prospects, open the door to further academic study, or simply indulge a passion, then Honours is your next step.

For many students, Honours is an introduction to further academic research with many using it as a pathway to undertake a PhD. For others, it is a stepping stone to an interesting career in Science and an opportunity to extend one's knowledge on a topic of major interest.

Even if you have plans to move into a different area in the future, an Honours degree in one of the disciplines within the School of Molecular Bioscience is an important qualification that will have a significant impact on how your academic achievements at university are judged in future years. In many instances, an Honours degree is seen as a minimum qualification for appointment to an employment position, particularly one with a research focus.



4 HONOURS ELIGIBILITY

To be eligible for Honours in Biochemistry or Microbiology, you must have qualified for the award of a pass degree and be considered by the School of Molecular Bioscience and the Faculty of Science to have the requisite knowledge and aptitude to undertake an Honours course. Specific academic requirements are:

- a completed pass degree from a relevant area in science;
- a minimum of 24 completed credit points of Senior Units of Study relating to the intended Honours area;
- either a Credit average in 48 credit points of relevant Intermediate and Senior Units of Study or a SCIWAM of at least 65; and,
- additional criteria as required by the discipline in which students intend to undertake Honours.

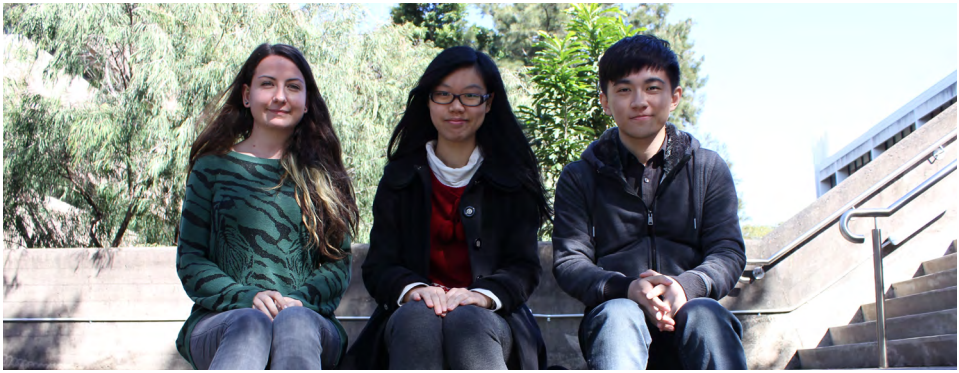
The SCIWAM is the weighted average mark calculated by the Faculty of Science from the results for all Intermediate and Senior Units of Study with a weighting of 2 for Intermediate units and 3 for Senior units.

GRADUATES FROM OTHER AUSTRALIAN UNIVERSITIES

The minimum requirement for acceptance into the Honours program is a SCIWAM of 65. The Faculty of Science will calculate your SCIWAM after you have applied for enrolment. Otherwise, the requirements for application are the same as for graduates from the University of Sydney.

INTERNATIONAL STUDENTS

If you are an International Student, you must apply through the International Office (see **sydney.edu.au/future-students/international/undergraduate/**). The International Office will assess your academic record and advise whether it is equivalent to a pass degree, at the level required for entry into Honours, from the University of Sydney. International student fees are applicable.



FINDING A SUPERVISOR

TALKING TO POTENTIAL SUPERVISORS

This is the most important part of your decision-making process. We recommend that you speak to several potential supervisors before submitting your application. It may also be helpful to speak to students currently working with a prospective supervisor. Remember, Honours is a full-time commitment – you need to know whether the environment will be one you will enjoy. Also remember that a potential supervisor will be determining whether you are suitable for their laboratory! When contacting a potential supervisor it is courtesy to first make contact via phone or email.

Please use the general research descriptions in this book as a guide. Most supervisors will be offering specific projects, and may offer projects outside those general descriptors that cannot be listed due to space. Read the guide carefully and discuss your plans with as many potential supervisors as possible.

EXTERNAL SUPERVISION

We value collaborative projects where students spend periods with other researchers based outside the School. Students who carry out such projects should note that they are required to complete all internal aspects of the final assessment, including attendance at the Coursework tutorials and School Seminar Program. The School does not offer placements in the Honours program unless a primary supervisor is located within the School.

NOMINATING SUPERVISORS

When you complete the School of Molecular Bioscience online Honours application form you will have the opportunity to nominate up to 10 potential supervisors. You are required to speak with each supervisor before nominating them on this form. The School will make every effort to accommodate your first choice of supervisor. Please note, however, that many areas are very popular and spaces within individual laboratories are limited. Please, therefore, nominate at least 5 potential supervisors.

6 APPLYING FOR HONOURS IN BIOCHEMISTRY & MICROBIOLOGY

DOMESTIC STUDENTS

Citizens or permanent residents of Australia and citizens of New Zealand must complete two forms:

1. the online School of Molecular Bioscience Honours application form; and
2. the Faculty of Science Honours online application form.

Currently enrolled students should select the Honours option for their enrolled degree. Students who are new to the University for their Honours year should select the 'Bachelor of Science (Honours)' option when applying.

For domestic students applying for entry into Honours in Semester 1, 2015, both forms must be submitted by Sunday 30 November 2014.

INTERNATIONAL STUDENTS

Both new international students external to the University of Sydney and international students who are currently enrolled in the Faculty of Science must complete two forms:

1. the online School of Molecular Bioscience Honours application form; and
2. the Faculty of Science Honours online application form.

Currently enrolled students should select the Honours option for their enrolled degree. Students who are new to the University for their Honours year should select the 'Bachelor of Science (Honours)' option when applying.

For international students applying for entry into Honours in Semester 1, 2015, both forms must be submitted by Sunday 30 November 2014.

ACCEPTANCE INTO HONOURS

Acceptance into the Honours program in Biochemistry or Microbiology is dependent on satisfying the Faculty of Science requirements for entry AND is subject to the availability of placement with an appropriate supervisor and upon resources within the School. Each year the School accepts up to 40 Honours students.

The first round of offers will be made in mid-December. Additional offers will subsequently be made to students on the reserve list if places become available.

FIND APPLICATION FORMS ONLINE

SMB Honours online application form:

sydney.edu.au/science/molecular_bioscience/honours/honours_form.php

Faculty of Science Honours online application form:

sydney.edu.au/courses/study_area/science-and-technology

MID-YEAR ENTRY

The School will be offering a limited number of places for students wishing to commence Honours in Semester 2, 2015. Please note that acceptance into the Honours program is dependent on satisfying the requirements of the Faculty of Science and the School. Please also note that mid-year entry is not possible with all supervisors.

It is important that you contact potential supervisors to determine whether they will accept mid-year entrants in 2015. Admission and enrolment in the mid-year Honours program will require submission of application forms as described previously, with a submission date of Thursday 3 April 2015 for international students and Tuesday 30 June 2015 for domestic students.

COURSE CODES FOR HONOURS ENROLMENT

Biochemistry Honours:
BCHM4011
BCHM4012
BCHM4013
BCHM4014
(Semesters 1 and 2, 2015)

Microbiology Honours:
MICR4011
MICR4012
MICR4013
MICR4014
(Semesters 1 and 2, 2015)

SCHOLARSHIPS

A limited number of Honours Scholarships are available through the Scholarships Office, see:

sydney.edu.au/scholarships/current/honours_scholarships.shtml

HONOURS COMMITTEE

- A/Prof Andrew Holmes, Chair (Microbiology)
- Dr Kim Bell-Anderson (Nutrition & Metabolism)
- Dr Dale Hancock (Molecular Biology & Genetics)
- Mrs Jill Johnston (Molecular Biology & Genetics)
- Prof Jacqui Matthews (Structural Biology)
- Dr Tim Newsome (Microbiology)
- Dr Melanie White (Biochemistry & Cell Biology)

COURSE OUTLINE

Honours students in Biochemistry and Microbiology are inducted into a joint Honours Program run by the School of Molecular Bioscience.

Students are required to:

- undertake a major research project under the supervision of an academic member of staff;
- write a thesis based on this research;
- present an Introductory and Final Seminar describing their work;
- undertake research skills training involving 6 tutorials and an examination; and
- attend the weekly School Seminar.

HONOURS COURSE DETAILS

ASSESSMENT

Thesis – 60%
The research thesis is expected to be approximately 50 pages in length (<12,000 words). Students will also undertake a short (20-30 minute) oral examination to defend their research.

Final Seminar – 15%
Students present a seminar of approximately 20 minutes describing the aims of their project, the results they obtained, and the significance of the results in the context of the published literature.

Research Skills Training – 25%
The research skills training task consists of ~ 6 x 2 hour tutorials run by the Honours Committee in small groups of 6-10 students. In these tutorials, each student will be assigned a scientific paper and will run a discussion amongst the group on that manuscript. Students will be assessed on their presentation as well as their participation in the group discussions. In the final examination, students receive a scientific paper and are required to write an appraisal of that paper, highlighting their opinions of the research described.

HONOURS YEAR CALENDAR

Early February
Honours commences and Orientation Day

Mid-February
Submission of Written Project Proposal

Late-February
Project Proposal Oral Presentation

Late-April until Early-June
Coursework Tutorials and Examination

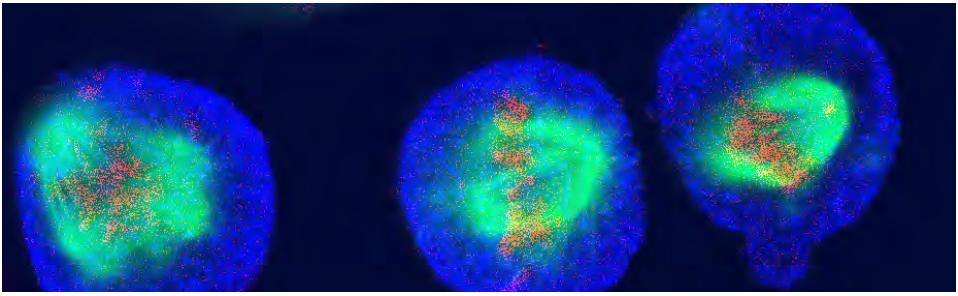
Late-July
Progress Presentation

Mid-October
Submission of Thesis

Late-October
Final Oral Presentation and Oral Examination

ALL DATES WILL BE CONFIRMED IN EARLY 2015

The Honours Orientation Day is compulsory for all students. The day will include information on laboratory safety, computer usage and safety within the School.



"The opportunity to do an honours project at SMB this year has given me an appreciation of the broad scope of scientific research and in particular, an appreciation for its role in medicine. Albeit a challenging year, it is always varied, and the freedom and independence to carry out my own research project in a lab has been a rewarding experience."

SUSANNAH HALLAL
CURRENT HONOURS STUDENT 2014

ADDITIONAL INFORMATION

WORK HEALTH AND SAFETY

The University of Sydney requires that all activities conform to relevant state and federal legislation regarding Work Health and Safety (WHS). The University WHS policy can be found on the Work Health & Safety website (**sydney.edu.au/whs/**). Information regarding your responsibilities towards WHS will be provided at the Orientation Day. Honours students are also required to complete "Working with chemicals" and "Biosafety" training courses.

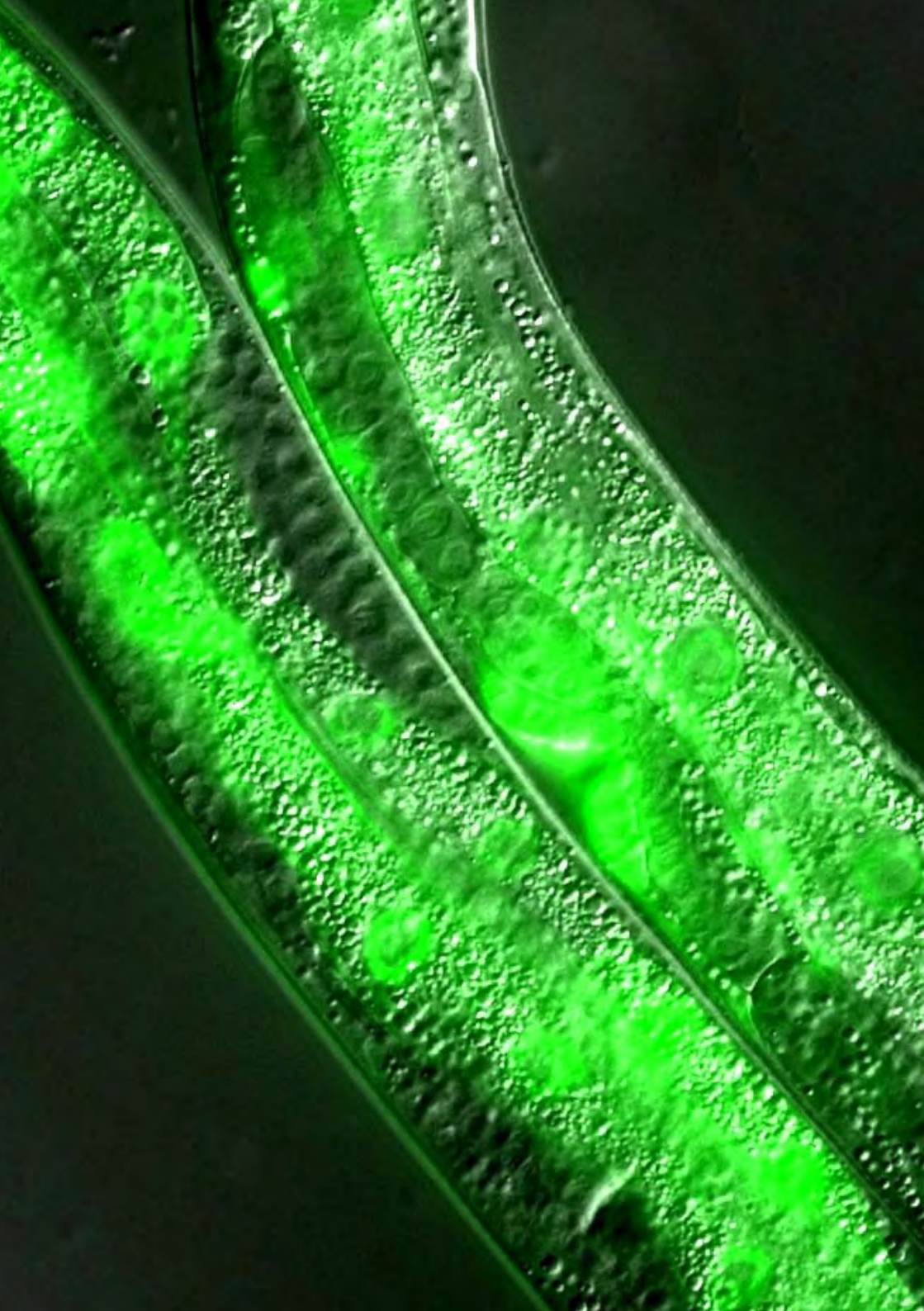
SOCIAL ACTIVITIES

The School maintains an active student social society called AMOEBA. AMOEBA organises several events for Honours students, including an introductory barbeque, a post-coursework exam barbeque and an end-of-year barbeque. Events throughout the year also include Friday Cake Days, movie and dinner nights, the SMB Trivia Night and the end of year School formal function. Honours students are encouraged to participate in events organised by AMOEBA.

EDWIN BRACKENREG, MALLORY WOOD, MELANIE DUNCAN, ANJALI GOWRIPALAN
AMOEBA EXECUTIVE 2014

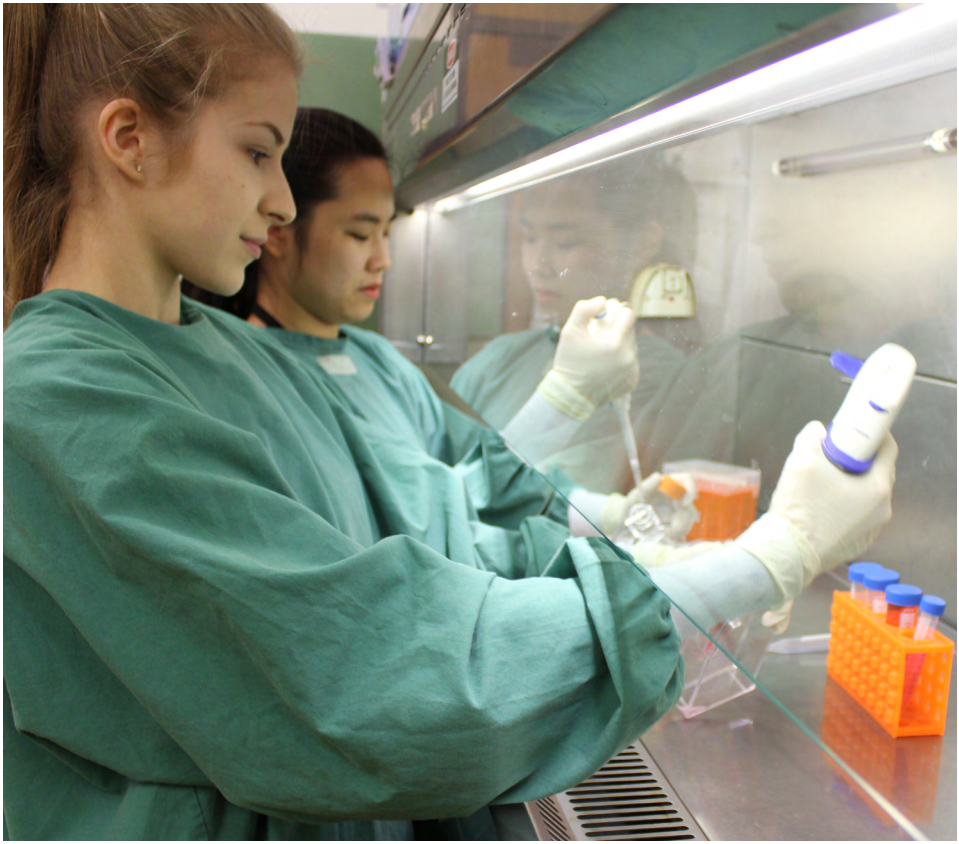
"Doing Honours exposed me to the reality of working in science and confirmed that this is what I want to do. I loved the community at SMB and the care they have for you and your development and so I continued onto my PhD here. The skills I am learning now as a PhD student will be invaluable regardless of where my career may take me."

TAYLOR SYME
CURRENT PHD STUDENT
2014



STAFF RESEARCH PAGES

The following pages provide a directory of supervisors and an outline of research programs available within the School. Please remember, there are many specific projects and projects in other research areas that cannot be listed due to space. You are encouraged to discuss your plans with as many potential supervisors as possible.



DIRECTORY OF POTENTIAL SUPERVISORS

	NAME		ROOM	EMAIL (@SYDNEY.EDU.AU)	PHONE (+61 2)	BROAD RESEARCH AREA
16	**Dr Alyson Ashe**	G08	772	alyson.ashe	9114 1310	Molecular Biology & Genetics
17	**Dr Sandro Ataide**	G08	672	sandro.ataide	9351 7817	Structural Biology
18	**Dr Kim Bell-Anderson**	CPC	Lvl 3W	kim.bellanderson	9351 6267	Nutrition & Metabolism
19	**Prof Jennie Brand-Miller**	CPC	Lvl 6W	jennie.brandmiller	9351 3759	Nutrition & Metabolism
20	**Prof Iain Campbell**	G08	710	iain.campbell	9351 4676	Molecular Biology & Genetics
21	**A/Prof Dee Carter**	G08	501	dee.carter	9351 5383	Microbiology
22	**Prof Richard Christopherson**	G08	779	richard.christopherson	9351 6031	Biochemistry & Cell Biology
23	**Dr Nick Coleman**	G08	564	nicholas.coleman	9351 6047	Microbiology
24	**A/Prof Charles Collyer**	G08	671	charles.collyer	9351 2794	Structural Biology
25	**Prof Arthur Conigrave**	CPC	Lvl 3W	arthur.conigrave	9351 3883	Nutrition & Metabolism
26	**A/Prof Stuart Cordwell**	CPC	Lvl 4E	stuart.cordwell	9351 6050	Biochemistry & Cell Biology
29	**A/Prof Gareth Denyer**	G08	774	gareth.denyer	9351 3466	Molecular Biology & Genetics
30	**Dr Tom Ferenci**	G08	510	tom.ferenci	9351 4277	Microbiology
31	**Prof Ruth Hall**	G08	732	ruth.hall	9351 3465	Microbiology

*G08 = Molecular Bioscience Building, CPC = Charles Perkins Centre

	NAME		ROOM	EMAIL (@SYDNEY.EDU.AU)	PHONE (+61 2)	BROAD RESEARCH AREA
32	**Dr Dale Hancock**	G08	773A	dale.hancock	9351 1910	Molecular Biology & Genetics
33	**Dr Markus Hofer**	G08	705	markus.hofer	9351 2233	Molecular Biology & Genetics
34	**A/Prof Andrew Holmes**	CPC	Lvl 4E	andrew.holmes	9351 2530	Microbiology
36	**Prof David James**	CPC	Lvl 5W	david.james	8627 1621	Nutrition & Metabolism
37	**Dr Ann Kwan**	G08	280	ann.kwan	9351 4120	Structural Biology
38	**Prof Joel Mackay**	G08	674	joel.mackay	9351 3906	Structural Biology
39	**Prof Jacqui Matthews**	G08	673	jacqui.matthews	9351 6025	Structural Biology
41	**Dr Tim Newsome**	G08	562	tim.newsome	9351 2907	Microbiology
42	**Dr Hannah Nicholas**	G08	772	hannah.nicholas	9351 2549	Molecular Biology & Genetics
43	**Prof Peter Reeves**	CPC	Lvl 4E	peter.reeves	9351 2536	Microbiology
45	**Dr Nicholas Shepherd**	G08	601	nicholas.shepherd	9351 3911	Structural Biology
46	**Prof Tony Weiss**	CPC	Lvl 4E	tony.weiss	9351 3464	Proteomics & Biotechnology
47	**Dr Melanie White**	CPC	Lvl 4E	melanie.white	9036 7918	Proteomics & Biotechnology

UNDERSTANDING THE MECHANISMS OF EPIGENETIC INHERITANCE IN *C. ELEGANS*

For decades it was thought that the only information that could be transmitted from one cell to another was that encoded in the DNA sequence. However, over the last 10-15 years it has become increasingly clear that this is not the case. Studies in animal models have shown that other signals, termed epigenetic marks ("on top of" DNA), can also be inherited across cell divisions and even across generations. Understanding the way in which epigenetic marks are inherited both within an organism and between generations is vitally important as it underpins the entire development of a multicellular organism. Transgenerational effects, despite their clear fundamental importance, have proven challenging to characterize: in particular they are extremely difficult to study in mammalian systems.

My research aims to circumvent these problems by addressing the transgenerational inheritance of epigenetic marks using the model organism *Caenorhabditis elegans*. I have established a robust experimental setup with which to study transgenerational inheritance of epigenetic silencing in *C. elegans*. I have demonstrated that both chromatin-binding proteins and genes associated with small RNAs are required for effective transgenerational epigenetic inheritance (TEI) in this system. Yet the majority of the genes involved in the process of TEI, the actual inherited epigenetic mark, and the mechanistic underpinnings of the phenomenon still remain to be identified. I am also interested in understanding the biological relevance of TEI, and have started investigating this area using a naturally occurring virus of *C. elegans*.

DR ALYSON ASHE
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E alyson.ashe@sydney.edu.au

http://sydney.edu.au/science/people/alyson.ashe.php

Potential honours projects include but are not limited to:

- Generation and characterisation of a fluorescently tagged, novel chromatin protein in order to determine its role in TEI
- A genetic screen (the generation of potentially hundreds of genetic mutants) for factors involved in the transmission of epigenetic viral resistance
- Epigenetic inheritance in honey bees (in collaboration with Prof Ben Oldroyd in SOBS)

STRUCTURE & FUNCTION OF NON-CODING RNA -PROTEIN

The majority of the human genome (> 75%) is dynamically transcribed into RNA of which equates to an enormous amount of non-protein coding transcripts since only 2% of it encodes proteins. Aberrant or lost transcription underlies the pathology of the majority of human diseases. The cause of lost gene expression is often the result of epigenetic modes of gene silencing. Long non-coding RNAs are at the forefront of an emerging paradigm shift in molecular biology, as new data continually suggest they are underexplored as a key component of the gene regulatory system.

Our research aims to provide crucial information about how non-coding RNAs mediate epigenetic regulation in both health and disease. In addition to providing fundamental biomedical information, understanding this process at the molecular level has the potential to provide novel methods to treat epigenetics-related diseases.

As an example, DNA methyltransferase 3a protein (DNMT3a) is operative in lncRNA directed DNA methylation, a fundamental epigenetic gene-regulatory system. Crucially, DNMT3a is the only known de novo methyltransferase in humans and is responsible for most of the observed methylation based gene silencing observed in cancer and other human diseases.

DR SANDRO ATAIDE
Room 672, Molecular Bioscience Bldg

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Potential Honours projects include:

- Explore the structural basis of how DNMT3a interacts with lncRNAs.
- Solve the atomic structure of discrete RNA domains bound to epigenetic complexes (TrxG and PRC2).

  Both projects will involve cloning, expression and purification of proteins and in vitro transcription and purification of RNA, complex assembly, X-ray crystallography and biophysical analysis of it.
- Investigation of the role of SRP 68 and SRP 72 in triggering GTPase activity of the SRP:SR.
- Investigation and characterization of cellular partners of SRP 68 and SRP 72 outside the SRP components by deep sequencing and mass spectrometry.

MOLECULAR MECHANISMS LINKING OBESITY & INSULIN RESISTANCE

Obesity is fast becoming one of the most important public health problems. With now 1 billion people affected worldwide, this has increased the prevalence of the Metabolic Syndrome, risk of cardiovascular disease (CVD) and Type 2 diabetes Treating obesity is a real challenge in an environment with increased consumption of unhealthy, calorific foods and reduced need for physical activity. However, unraveling the molecular mechanisms underlying the accumulation of adipose tissue will aid in the identification of targets to reduce fat mass.

It is now becoming apparent that adipose tissue, once thought to be a passive storehouse for fat, is a metabolically active organ capable of regulating whole body energy balance. This may be in part mediated by its obvious role in lipid metabolism and insulin sensitivity, but also by numerous secreted adipose tissue factors, adipokines, which have recently been revealed as key players in metabolic function.

My research aims to gain greater understanding of the link between adiposity and metabolic disease, utilizing various techniques including in vivo metabolic testing of small laboratory animals, clinical biochemistry, and protein/gene expression analysis.

DR KIM BELL-ANDERSON
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sydney.edu.au/science/people/kim.bell-anderson.php

Potential Honours projects include:

- Acute nutrient regulation of insulin sensitivity
- Fat-fed insulin resistant rats can be made insulin sensitive by changing their diet. This occurs within 12 hours and suggests that nutrients can acutely modulate insulin action. The mechanism responsible is not known. We are investigating the role of the gastrointestinal tract, restricted feeding and diet composition on the reversal of this fat-induced insulin resistance in the rat.

Future studies will investigate the effect of protein quality on whole body insulin sensitivity in rodents.

CARBOHYDRATES & HEALTH

Australia, like many other countries around the world, is facing an epidemic of obesity and Type 2 diabetes. Our group's research on food carbohydrates has provided evidence that foods with a high glycemic index (GI) increase the risk of chronic diseases, thereby challenging conventional views on healthy diets. This has raised the current profile and reach of nutrition science, and its potential future impact.

PROF JENNIE BRAND-MILLER
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Potential Honours projects include:

- There's something about AMY1
  In humans, starch digestion begins in the mouth through the action of salivary amylase. AMY1, the gene that encodes salivary amylase, shows unusual and unexplained copy number variation. We found that AMY1 copy number was significantly higher in Asian vs Caucasian individuals with higher amylase activity per mL of saliva. Caucasians with high vs low copy number displayed similar glucose tolerance but higher plasma glucose and insulin concentrations after consumption of white bread and faster rates of starch digestion in vitro ($p = 0.xxxx$). The glycemic index of carbohydrate foods is therefore higher in people with more copies, implying greater β–cell insulin 'demand' and greater lifetime predisposition to insulin resistance and Type 2 diabetes. But does low copy number mean that greater amounts of starch reach the large bowel and get fermented? You might like to help to answer that question.
- The PREVIEW Study Sydney
  The University of Sydney is participating in PREVIEW Study (PREVention of diabetes through lifestyle Intervention and population studies in Europe and around the World). While it is recognised that losing excess weight can help to prevent disease development in younger adults, there is controversy as to whether weight loss programs are indicated for the management of overweight or obesity in older adults. This Honours project, a sub-study of the PREVIEW trial, aims to measure bone mass, bone turnover markers and muscle strength in younger and older adults before and after a 2-month weight loss program, as well as after 4 months on weight maintenance programs differing in protein content, glycemic index and exercise intensity. The student will be co-supervised by Professor Brand-Miller and Associate Supervisor A/Prof Amanda Salis. For more information, email: **amanda.salis@sydney.edu.au**.

MOLECULAR BIOLOGY OF CYTOKINE ACTIONS IN THE CENTRAL NERVOUS

Cytokines are hormone-like molecules that are master regulators of many cellular processes. Cytokines are implicated as major causes of tissue injury and inflammation that underlie a variety of significant neurological diseases such as multiple sclerosis, stroke and viral and bacterial encephalitis. We use molecular genetic and functional genomic approaches to determine how cytokines communicate with cells in the central nervous system (CNS) to alter cellular function and contribute to disease processes.

In our laboratory, students have the opportunity to study transgenic and/or infectious and autoimmune mouse models of neurologic disease as well as in vitro tissue culture brain cell models. Depending on the project, there is the opportunity to learn many different experimental techniques including: in vitro culture of primary and immortalized cells, DNA and RNA extraction, cloning and manipulation of plasmid DNA, viral- and liposome-mediated gene transfer, RT-PCR, RNase protection assay and in situ hybridization histochemistry, gene chip microarray analysis, immunohistochemistry, western blotting and ELISA.

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Potential Honours projects include:

- Genomic signature of the cytokine response by astrocytes and microglia. Based on DNA microarray profiling data the aim of this project is to understand that the function of genes that are differentially expressed by astrocytes and microglia in response to the cytokines IL-6 or IFN-α.
- Mechanisms of interleukin-6-activated gp130 signal transduction and actions in astrocytes and microglia. Interleukin-6 (IL-6) is a proinflammatory cytokine implicated in the pathogenesis of a variety of neurological diseases. The aim of this project is to learn how IL-6 alters the function of astrocytes and microglia, key cells involved in inflammation in the brain.
- Comparative analysis of IL-6/gp130 cytokine signalling and actions in astrocytes and microglia. The IL-6/gp130 family of cytokines includes in addition to IL-6, oncostatin M, leukemia inhibitory factor and interleukin-11. In this project we are determining the molecular mechanisms that govern the glial cell-specific actions of these cytokines and the role they play in neuroinflammation.
- Cellular and molecular functions of interferon regulatory factor (IRF) 8 the CNS. IRF8 is a myeloid transcription factor that we have identified as a key intrinsic regulator of microglial cells (the resident macrophages of the CNS). The objective of this project is to determine how IRF8 regulates microglial function in the healthy and diseased CNS.

FUNGAL PATHOGENS & ANTIFUNGAL DRUGS

There are millions of different species on fungi on earth, but relatively few are able to infect humans and animals. This is fortunate, since fungal infections are notoriously difficult to treat, and some treatments are almost as bad for the host as they are for the fungus.

In our lab we are interested in two aspects of medically important fungi: First, what makes them pathogens and how do they establish and maintain infection? And second, how we can control and treat fungal infections once they have started? We use the system-wide methods of proteomics and transcriptomics to address these questions, along with general molecular and microbiological methods to manipulate our fungal pathogens and their genomes. We focus on the yeast pathogens *Cryptococcus* and *Candida*.

A/PROF DEE CARTER
Room 501, Molecular Bioscience Bldg

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E dee.carter@sydney.edu.au

sydney.edu.au/science/people/dee.carter.php

Potential Honours projects include:

- Antifungal drug targets and the development of new therapies
  It is difficult and expensive to develop new drugs. Instead, a promising approach is to develop synergents to make existing drugs more effective. There are two projects in this area:
  - Proteomic analysis found some proteins up-regulated in the presence of the antifungal drug fluconazole that could be good targets for synergistic therapies. We will knock out the genes that encode these proteins and assess how the knockout mutants change in fluconazole resistance.
  - We will look for new synergents that can be used with antifungals. Three potential synergents of interest to our lab are alendronate (used to treat bone disorders), lactoferrin (defence protein found in milk and tears) and some types of medically active honey that are synergistic with some antibacterials.
- What makes some fungal strains more pathogenic than others?
  Strains of the yeast pathogen *Cryptococcus neoformans* can be genetically similar yet show substantial differences in virulence. We have access to a large number of *C. neoformans* strains that have been fully sequenced, allowing us to perform genome-wide association studies with virulence phenotypes. In this project we will use microbiological and immunological methods to examine factors that are known to determine differences in pathogenicity, including capsule formation, melanin production, temperature and UV sensitivity and the ability to invade and kill macrophages. We will also look for the possible role of epigenetic modulation of virulence, focusing on DNA methylation.

CANCER PROTEOMICS

The proliferation of cancer cells is driven by multiple mutations (~90) that lead to deregulation of the cycle of cell division, apoptosis and other cellular processes. These mutations change the levels of some proteins in the cancer cell. The Cancer Proteomics Laboratory uses iTRAQ, SRM and DIGE analyses to identify proteins whose cellular levels change in cancer, the functions of these proteins are then correlated with the phenotype of the cancer. The mechanisms of action of drugs such as fludarabine that induces DNA strand breaks, and LY294002 that inhibits PI3 kinase are under investigation.

We also use of patterns of proteins as 'signatures' for diagnosis of cancers, and for predicting drug sensitivity and clinical outcome (prognosis). We have developed a microarray (DotScan) consisting of 82 antibodies against surface molecules (CD antigens) found on leukocytes, and other human cells. The extensive surface profiles alone enable classification of leukaemias. A clinical trial has been completed involving 796 leukaemia patients in collaboration with the MD Anderson Cancer Center (Houston), Department of Haematology (University of Cambridge) and a number of hospitals in Australia. The results show that an extensive profile of surface molecules is sufficient for diagnosis. The DotScan microarray has been extended to obtain 'disease signatures' for stable and progressive CLL that should enable triaging of patients, with vigorous treatment for those at risk.

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DotScan has also been used to determine expression profiles of surface molecules on colorectal cancers (CRC), melanomas and exosomes secreted by cancer cells (see **www.medsaic.com** for several movies and many papers). The CRC cells are in the minority within the cell suspension from the tumour, the surface profile for just the cancer cells is obtained by labeling the captured cells with a fluorescent antibody against epithelial cell adhesion molecule (EpCAM), and a dot pattern is obtained with a fluorescence scanner. Using a fluorescent antibody against CD3, a second dot pattern can be obtained just for Tumour-infiltrating Lymphocytes (TILs) that kill the cancer. The detection of TILs may be very important for cancer prognosis and therapy that involves growing TILs *in vitro* and infusing them back into the patient for immunotherapy.

ENVIRONMENTAL MICROBIOLOGY

The mission of the Coleman lab is to use the power of microbes to develop new technologies that benefit human society and the natural environment. We take our inspiration from the quote "Microbes can do anything: microbes are smarter, wiser and more energetic than microbiologists, chemists, engineers and others" (D.Perlmon, 1980).

Techniques that our lab uses include:

- Traditional microbiology – eg. enrichment, isolation, physiology, metabolism
- Molecular microbiology – eg. genomics, proteomics, gene knockouts, gene cloning
- Culture-independent methods – eg. environmental PCR, metagenomics
- Analytical chemistry and biochemistry – eg. gas chromatography, enzyme assays

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Potential Honours projects include:

- Development of new cloning and expression systems for biocatalysis
  Monooxygenase (MO) enzymes are important in the global cycling of carbon and nitrogen, and are of interest for biocatalysis and bioremediation. Unfortunately, many of the most interesting MOs such as the sMMO and pMMO cannot be expressed in E.coli. This project will test new cloning and expression systems for MO genes using non-standard cloning vectors (e.g. chromosomal integrons) and non-standard hosts (e.g. Pseudomonas).
- Bioremediation of DDT and its persistent metabolites DDE and DDD
  DDT is an organochlorine insecticide which is a very persistent pollutant. In 2013, an Honours student in the Coleman lab isolated several bacteria which could biodegrade DDT and its persistent metabolites DDE and DDD (collectively DDx). The current Hons project aims to test whether these bacteria can degrade DDx residues in soil, and to clone dioxygenase genes and perform error prone PCR to develop a high-activity DDx-degrading variant.

PROTEIN ENGINEERING AND EVOLUTION IN A TEST TUBE

Proteins have evolved to fulfill a variety of tasks within cells. They also have potential applications in industry, bioremediation and medicine. However, a protein evolved for a specific function in a cell may not have suitable properties for other applications. It may be stable enough for carry out its role in the cell, but it may not be sufficiently stable to be useful in industry. It may catalyze a reaction in the cell, but it may have poor activity on a similar compound that may be harmful pollutant. We need to be able to modify or engineer proteins so that we can make better use of them in practical applications.

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Directed evolution is perhaps the most effective way of engineering proteins. It mimics natural evolution – a mutant library is generated and the target protein expressed and screened for the desired property. This sounds simple, but some consideration must be given to generating an appropriate library and more importantly a method to screen large libraries must be devised. The projects described below have progressed to the point where techniques to evolve the target proteins have been developed and they are now at the stage where they are suitable for honors projects.

Esterases can be evolved for improved thermal stability. Similar methods can be used to evolve lipases to have enhanced activity as well as thermal and solvent stability. Mutant enzymes would be useful reagents for the production of biodiesel and for the modification of food oils.

Glucose-6-phosphate is an enzyme that is frequently used in the production NADH or NADPH for a variety of purposes. A high throughput screen to detect mutants with enhanced activity has been devised and can now be applied to identify mutants with enhanced activity and stability. Such mutants would be of some commercial value and could be studied to obtain functional information and to identify factors important for stability.

A bacterial hemoglobin has been evolved to promote growth of *Escherichia coli* under conditions of limited oxygen. Under the conditions of our experiments *E. coli* grows to give an OD600 of about 1 while our mutant proteins allow it to grow to better that OD600 of over 5. We would like to experiment with evolution under different conditions and to look at the ability of our mutant hemoglobins to promote expression in *E. coli* of proteins that are normally difficult to fold – for example, proteins that contain cysteine residues that could be oxidized to give incorrectly formed disulfide bonds.

The project is based on an ongoing collaboration with Prof David Ollis at the ANU, the research conducted in the Collyer Lab will focus on both the evolution of novel enzymatic activities and the structural characterization of these “improved” bio-catalysts.

MOLECULAR CELL BIOLOGY OF NUTRIENT SENSING

Much of our major research interests are derived from the medical research fields of endocrinology and metabolism. Our research focuses on the molecular and cellular mechanisms that underlie nutrient sensing with a particular interest in nutrient-sensing G-protein coupled receptors (GPCRs) that coordinate responses to nutrients. Amino acids are the building blocks of proteins and, as proteins turnover, our bodies need a regular supply of amino acids to replace proteins that are "worn out". For this reason, cells are equipped with molecular sensing mechanisms that detectvariations in amino acid levels. The work of the group using state of the art techniques in molecular cell biology, demonstrates that class C GPCRs include a number of closely related, broad-spectrum L-amino acid sensors. These receptors include the so-called calcium-sensing receptor (CaSR), basic amino acid–sensing GPRC6A and heterodimeric amino acid taste receptors. Together they contribute to gut taste and digestive responses as well as the regulation of whole body metabolism.

We are currently focusing on how these receptors distinguish between different ligands and thus activate distinct ligand directed signaling pathways, how the receptors couple via their intracellular loops and carboxy-termini to G-Proteins and early signaling events, how the cells work that express them, and in identifying the roles of these receptors in whole body nutrient metabolism using transgenic mouse models.

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PROTEOMICS OF MICROBIAL PATHOGENS

The tools of proteomics are essential in the study of health and disease in the post-genome era. Our group is primarily interested in understanding disease processes with the aim of discovering new protein- and peptide-based targets for the diagnosis of disease, as well as novel vaccines and better therapies.

The work in my laboratory aims to:

- Discover membrane-associated and secreted proteins involved in the virulence of a cystic fibrosis (CF)-associated strain of *Pseudomonas aeruginosa*. *P. aeruginosa* is the major cause of death in people suffering from CF. We are working with a *P. aeruginosa* (AES-1) that is highly transmissible between patients attending CF clinics and our work is helping to characterise the molecular basis for increased infectivity caused by this 'epidemic' strain.
- Determine the function of the *N*-linked glycosylation system of *Campylobacter jejuni*. *C. jejuni* is the major cause of bacterial gastroenteritis in the developed world. We have developed strategies for identifying *C. jejuni* proteins that are post-translationally modified by the addition of a carbohydrate (glycosylation). Addition or subtraction of sugars to surface proteins from this organism may mediate host colonization. We are also examining growth conditions and proteome profiles associated with 'disease-like' environments.

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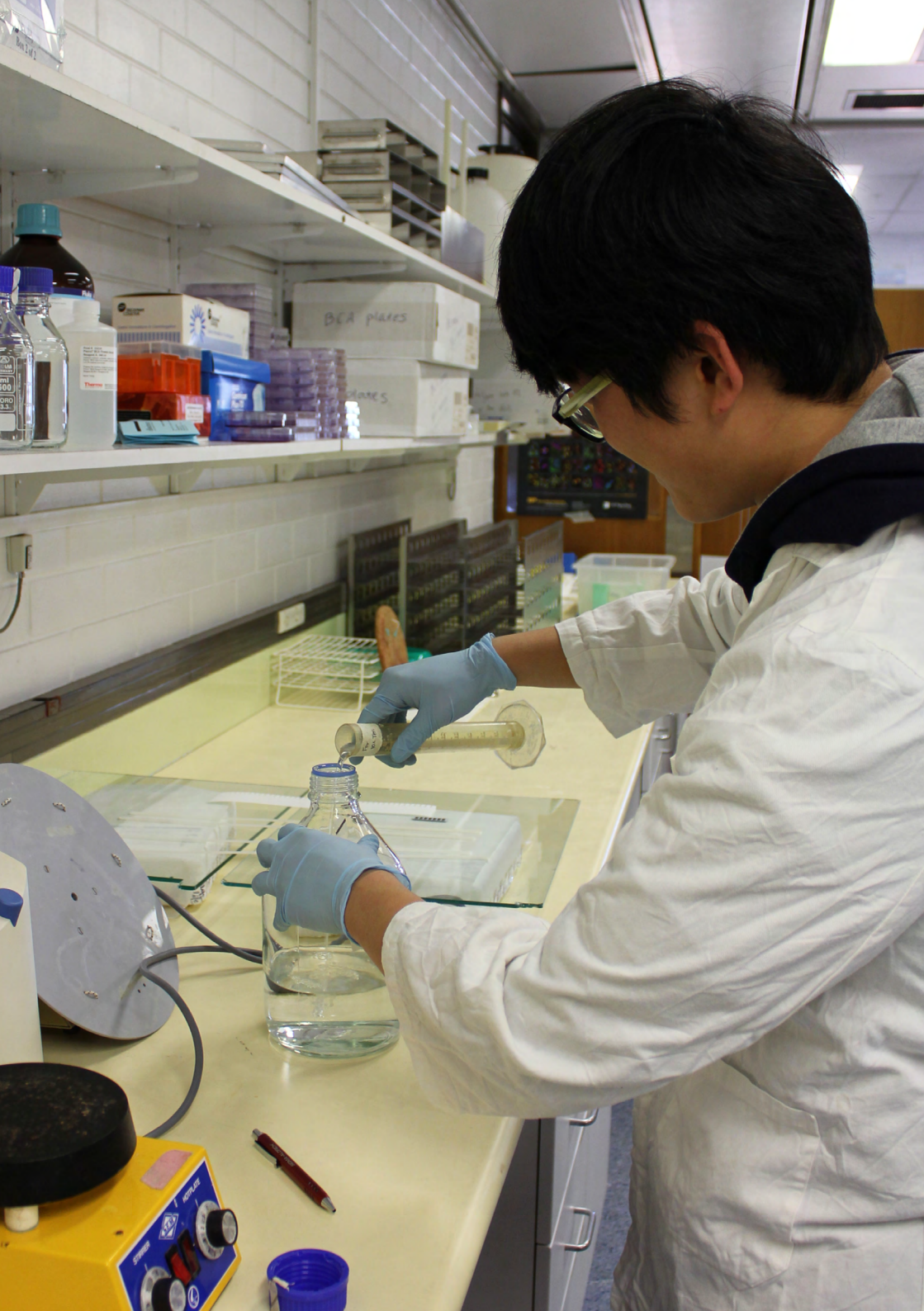
We also aim to develop new methods in proteomics and have opportunities in:

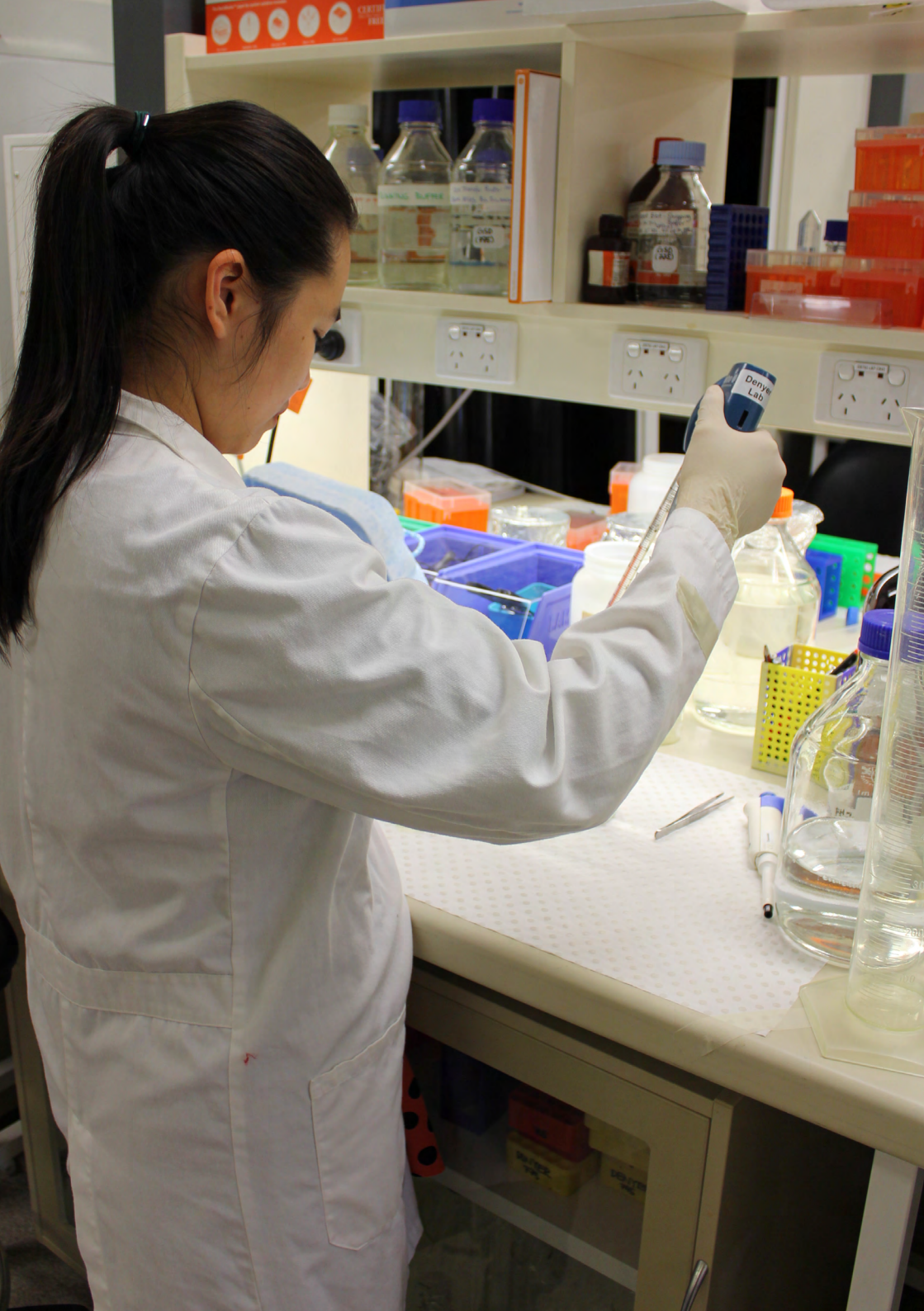
– Large-scale identification of protein post-translational modifications using mass spectrometry;
– Redox biology and disulfide proteomics using mass spectrometry;
– Development of approaches for cell-surface peptide shaving and vaccine design.

POST-TRANSLATIONAL MODIFICATION OF PROTEINS IN CARDIOVASCULAR DISEASE

In association with the Discipline of Pathology, School of Medical Sciences, our cardiovascular group is interested in understanding the molecular basis for contractile dysfunction in ischemia/reperfusion (I/R) injury. These projects examine how proteins are post-translationally modified in response to injury. Opportunities include:

- Signal (phosphorylation) pathways in pre- and post-conditioning of myocardium;
- Response of the myocardium to novel intervention strategies;
- The role of reactive oxygen species and calcium overload.

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TRANSCRIPTIONAL MEMORY IN ADIPOCYTE-MACACROPHAGE INTERACTIONS

The fat pads of obese individuals secrete a potent cocktail of inflammatory hormones into the bloodstream, and this ultimately causes Type 2 Diabetes and heart disease. These hormones come from both fat cells (adipocytes) and from the macrophages that infiltrate adipose tissue as obesity develops. Indeed, there is a positive feedback loop between the two cell types, with adipocytes and macrophages stimulating each other to produce ever increasing amounts of inflammatory agents.

We recently discovered that the response of expression of inflammatory genes in adipocytes to macrophage stimulation is more dramatic if the fat cells have previously been exposed to macrophage secretions. Not only does this have enormous physiological ramifications, it is also a rare demonstration of transcriptional memory outside the immune system.

Our aim is to understand more about this transcriptional memory phenomenon and define the underlying molecular mechanisms which, we hypothesise, are epigenetic in origin. Our strategy is to see if exposure to macrophage secretions leads to epigenetic changes in the adipocytes, especially with respect to chromatin structure, DNA methylation and miRNA expression. By doing the project, students will become skilled in cell culture and a range of fundamental molecular biology techniques.

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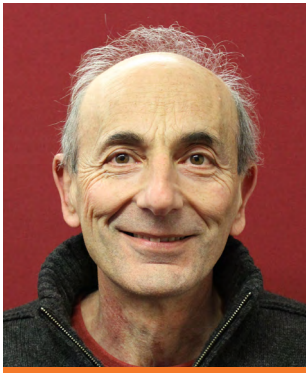
BACTERIAL ADAPTATION

Project background:
Many fundamental aspects of adaptation can be readily studied in bacterial populations. In collaboration with overseas laboratories in France, China, Brazil and U.K., we are following the molecular changes in evolving bacteria (metabolomics, genomics). An exciting major challenge is to explain diversification in bacterial evolution. Another is to identify signatures of adaptive change upon changes in environment. We aim to define the multiple mechanisms (evolutionary changes and alternative fitness solutions) which lead to bacterial adaptation. Honours projects are available to test how manipulated environments influence mutation rates, selection and how genomes change.



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Honours projects are available in several directions and using different methods and approaches:

- In a continuous culture (chemostat) model system operating over hundreds of generations we control evolution under physiological influences. The aim is to study the dynamics of change in evolving populations. Phenotypic and genotypic tests on stored day-by-day samples will be used to define the spread of mutations and the control of mutation rates during adaptation in evolved populations.
- Co-evolutionary dynamics between organisms and their environment can be discovered by following the environmental modification in nutrient-limited chemostat populations. Metabolomics studies have identified changes in metabolites excreted and exchanged between bacteria and the aim is to identify producer and user bacteria evolving towards cross-feeding interactions and the molecular changes involved.
- Bacteria can be “domesticated” and acquire metabolic/physiological changes upon lab culture. We wish to identify the changes occurring in freshly isolated natural isolates of *E. coli* under laboratory conditions. We will use phenotypic, genomic and proteomic analyses to identify the unknown mutational changes that lead to bacterial adaptation in a new environment.

ANTIBIOTIC RESISTANCE IN BACTERIA

Resistance to all or most of the antibiotics used to treat bacterial infections is a huge problem that limits therapeutic options and sometimes leaves none. As very few new antibiotics have been found in recent years, this means that the need to understand how resistance arises and is spread is more urgent than ever.

We investigate the way that multiple antibiotic resistance arises in bacteria and is spread. We study the mechanisms of mobile elements that allow resistance genes to move about, e.g. transposons, integrons and gene cassettes. We also study the epidemiology of resistant bacteria.

The work in my laboratory uses isolates from Australian hospitals and aims to:

- Study how multiple antibiotic resistance arises by determining the structure of multiple antibiotic resistance regions and using bioinformatic analysis to work out how they were created.
- Look at how multiple resistance spreads in important bacterial pathogens. Can they transfer into other bacteria? Or have the bacteria carrying them spread?
- Study the evolution of plasmid and bacterial genomes and its role in developing resistance.

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Potential Honours projects include:

- Multiply antibiotic resistant *Acinetobacter baumannii* acquired in hospitals belong to clones that have spread around the world. How did they become resistant to so many antibiotics? Are they still evolving? We have lots of Australian isolates and over 100 draft genome sequences to help address these questions.
- Healthy humans can carry antibiotic resistant *E. coli* in their commensal gut flora. Do we all carry different *E. coli* strains or do we share strains? Do we keep the same strains for a long time or do we change them regularly? What resistance genes do they carry and how is resistance here impacting treatment of infections?
- How do the mobile elements that help resistance genes to spread (integrons, gene cassettes, transposons, insertion sequences) work? We are looking at some new mobile elements that have not been studied before in order to understand this better.

ROLE OF MICRORNAS IN OBESITY & INFLAMMATION

We are interested in microRNAs and their role in gene expression, particularly in the context of obesity. It has long been known that gene expression is regulated both by transcriptional mechanisms and at the level of stability and there is now increasing experimental evidence suggesting microRNAs play a major role in the control of mRNA stability and translatability.

Changes in gene expression have strong influences on the development of the negative secondary consequences of obesity; Type 2 diabetes and cardiovascular disease. The infiltration of macrophages into obese adipose tissue and the cytokines they secrete sets up a chronic low-grade inflammatory condition which is a significant driver of changes in gene expression in obese adipocytes. The model we use is the 3T3-L1 cell, a cultured fibroblast cell line which can be stimulated with a cocktail of "goodies" to differentiate into a fat-laden adipocyte. The inflammatory stimulus comes from the secretions (conditioned medium) of another cell line, the RAW cell, which is activated with the powerful inflammatory agent LPS.

As these types of investigations are studying gene expression, those techniques which powerfully and sensitively measure gene expression are employed. Techniques used in our studies include:

- Cell culture
- Microarrays
- Real-time PCR to measure gene expression of mRNAs and microRNAs
- DNA sequencing

Eventually we hope to be able to transfect specific microRNAs and their antisense counterparts into the 3T3 cell and observe their effects on fat cell development and function.

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IMMUNOBIOLOGY AND NEUROPATHOLOGY OF INFLAMMATION

Inflammation plays a central role in the pathogenesis of most central nervous system (CNS) disorders. While it protects the brain from infection with pathogens, it also drives autoimmune diseases such as multiple sclerosis (MS). Chronic inflammation is also a key feature in many degenerative diseases of the CNS, including Alzheimer's disease. My laboratory aims to improve our understanding of the factors that cause and modulate inflammation in the brain. Our two main areas of research are:

Impact of diet on neurodegeneration: Certain diets can lead to chronic low-level inflammation that is associated with degenerative changes within the brain. Using mouse models, we explore how specific diets induce CNS inflammation and how this leads to loss of neurons and brain function.

Modulating cerebral type I interferon (IFN-I) responses: Type I interferons are major players in the immune response. However, they behave as a 'double-edged sword' in that while they protect the host against disease, they also can cause tissue damage. One of our major aims is to dissect the roles played by pivotal signalling molecules – STAT1, STAT2 and IRF9 – in this network and to clarify how the different pathways mediate their biological effects. For this we use several *in vitro* and *in vivo* models.

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Potential Honours projects include:

- Characterization of diet-driven inflammatory responses in the brain.
- The effects of deficient IFN-I signalling on the host response against viruses.
- Analysing the effects of STAT1 activation in CNS autoimmune diseases.

GUT MICROBIAL COMMUNITIES AND HEALTH (IMMUNOLOGY/METABOLISM/ECOLOGY)

Our gut microbiota has an enormous impact on our health. It consists of around 100 trillion cells and has been described as the "forgotten organ" or our "second genome". Their impact on our health and well-being is multi-factorial through their contribution to digestion and their interaction with the enteric endocrine, lymphoid and nervous systems. A dysfunctional host-microbiome interaction is a factor in many diseases including obesity, diabetes and inflammatory bowel diseases.

We have three main areas of interest:

- Identifying the mechanisms by which microbes interact with the host system.
- Developing diagnostic tests based on microbiome analysis.
- Therapeutic manipulation of the gut microbiome.

We do interdisciplinary studies that fall into two basic experimental designs. Cross-sectional studies are performed in human clinical cohorts and aimed at identifying links between microbiome composition and disease outcomes such severity or response to treatment. The aim of these studies is to identify microbiome signatures that will guide personalized health care such as identification of optimum weight loss diet strategies. Experimental intervention studies are performed in either animal models or in clinical trials and involve diet or pharmaceutical treatments. The aim of these studies is to identify the mechanistic links between diet, microbiome composition and host outcomes. We use a variety of techniques in the lab: Metagenomic (high throughput sequencing) and molecular biological approaches are used to describe the microbiome; Histological, physiological and biochemical approaches are used to describe the host system, usually in collaboration with other groups on campus.

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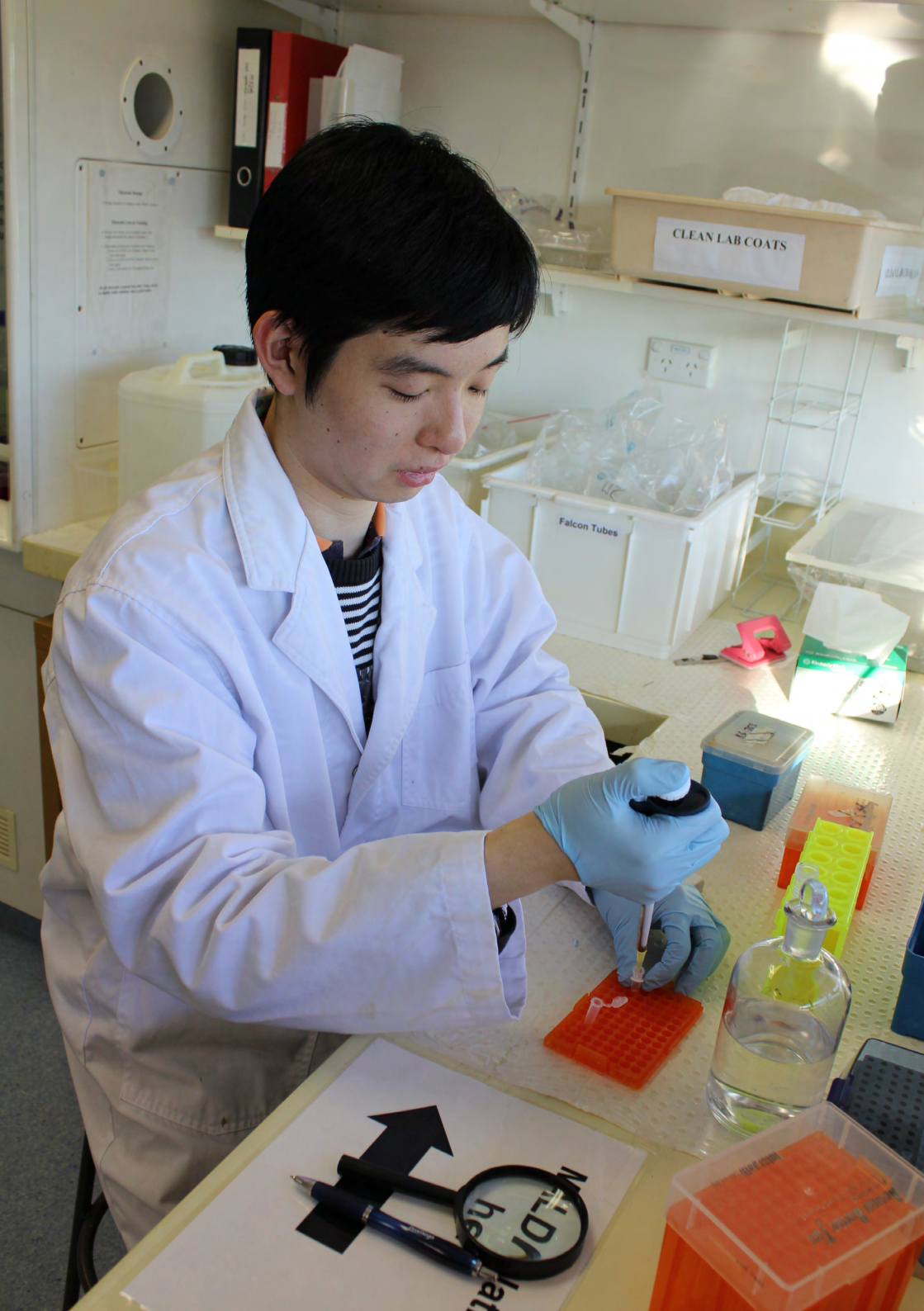
Potential Honours projects include:

- Can antibiotics be safely used as a preventative treatment in intensive care?
- Does the microbial community in diet-induced obesity impair regulation of feeding behaviour via the gut-brain axis?
- Spillback: To what extent is the human microbiome influencing the microbiome of urban wildlife?


CLEAN LAB COATS
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MOLECULAR & METABOLIC SYSTEMS BIOLOGY

Our goal is to predict the future health of individuals and to provide optimal strategies for health and longevity. Our immediate disease focus is metabolic disease like Type 2 diabetes, from which our interests in metabolism and insulin action emerges. We have discovered that metabolism and signal transduction pathways are interlinked. This has important implications for diabetes and cancer as in both cases, cells undergo major adaptations in both of these systems.

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Potential Honours projects include:

- Mapping new functions of insulin.
  We have conducted a comprehensive screen of insulin regulated protein phosphorylation in adipocytes, identifying >1,500 discrete insulin responsive phosphopeptides. This data set contains a wealth of novel targets each comprising discrete projects for functional analysis. Techniques: live cell immunofluorescence microscopy, production of recombinant mutants and expression in mammalian cells coupled with development of biological assays.
- Mechanistic analysis of the Adipocyte
  The adipocyte is one of the most important cells in metabolic disease. We have accumulated considerable information about fat cells including transcriptomic and proteomic data. In this project we aim to characterize the fat cell metabolome using steady state and flux analysis using stable isotopes. We are particularly interested in mapping the fate of different substrates including glucose and amino acids and their role in *de novo* lipogenesis.
- Dissecting the topology of the Akt signaling pathway.
  The Akt pathway plays an essential role as a signal conduit between growth factors and downstream responses like proliferation, metabolism and apoptosis. However, the connectivity between individual pathway components in individual living cells is unclear. Project involves cell biology, high-resolution live cell microscopy and analysis of protein phosphorylation.
- Insulin resistance and oxidative stress
  We have shown an intriguing relationship between oxidative stress, cholesterol metabolism and mitochondrial function that impact on insulin action in adipocytes. This project aims to identify specific molecular targets of oxidative damage that contribute to insulin resistance using mass spectometry.

STRUCTURE, FUNCTION & ENGINEERING OF FUNCTIONAL AMYLOIDS

Amyloids were once thought to be biological mistakes but organisms from bugs to humans actually can use these deposits to achieve biological functions. Our goals are to understand the structure and function of functional amyloids and to manipulate them for biotechnological applications.

Class I hydrophobins are fungal proteins that self-assemble from a soluble form into insoluble rodlet layers with amyloid properties. The layer confers water resistance to fungal structures and mediates biological processes such as host infection. The unique properties of hydrophobins make them good candidate "scaffold" proteins for making functionalised coatings. Examples include drug delivery systems, emulsion stabilisers and coatings for medical implants.

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Potential Honours projects include:

- Engineering fluorescent hydrophobins
  You will optimise the use of cell-free expression technology to produce hydrophobins. Cell-free expression allows a straightforward method to incorporate non-natural amino acids and labelled amino acids in proteins. As a proof of principle, you will experiment with incorporating fluorescent non-natural amino acids into hydrophobins. This will allow their easy visualization in subsequent applications and assist with the structural studies of hydrophobin layers.
- Interactions of hydrophobins with substrates
  Hydrophobin rodlet layers are robust, biocompatible and can reverse surface wettability of materials that they coat. You will examine the adhesion of hydrophobins and mutants to substrates and characterise the complexes. The substrates will range in hydrophobicity, surface roughness, surface charge and particle sizes. The most promising hydrophobin:substrate pairs will be subjected to more in-depth structural and application studies.

What you will learn:
Both projects involve interdisciplinary research and allow you to gain experience in a range of techniques from molecular biology, protein expression, purification and chemistry, biophysical characterisation (e.g. fluorescence and NMR spectroscopy), microscopy, surface measurements and amyloid-specific assays. The projects will be jointly supervised by A/Prof Margaret Sunde, Department of Pharmacology.

REGULATION OF GENE EXPRESSION

Work in our laboratory is currently focused on answering the broad question: What are the molecular mechanisms underlying gene expression?

The proper control of gene expression is essential for all organisms. We are trying to understand how transcription factors turn genes on and off by defining the interactions that they make with co-regulators. Currently, we have a focus on the Nucleosome Remodeling and Deacetylase (NuRD) complex, which is an essential co-regulator of the transcription factor GATA1 and is essential for embryonic development. Deregulation of the activity of this complex and its components is associated with diseases such as cancer, as well as with the symptoms of ageing.

This project has the potential to involve mammalian cell culture, DNA cloning, protein expression and purification, structural analysis by X-ray crystallography, NMR or electron microscopy and mass spectrometry/proteomics.

A second focus is on asking whether sequence-specific DNA-binding transcription factors might also (or instead) act as RNA-binding proteins. Several examples are already known in which transcription factors bind both to the promoters of target genes and also to mRNA transcripts to regulate their expression. We are carrying out both large scale and focused studies to ask whether this activity is a general property of transcription factors and represents a new layer of gene regulation.

This project would potentially involve recombinant DNA work, protein expression and purification, RNA-binding assays, structural work and cell culture.

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REGULATORY PROTEINS IN DEVELOPMENT & DISEASE

Regulatory proteins in disease and development. The main focus of my research is a family of proteins that play essential roles in mammalian development, but are also involved in human disease. This family of LIM-only (LMO) and LIM-homeodomain (LIM-HD) proteins are transcription factors or transcriptional regulators that help specify cell type and make decisions about when to differentiate or proliferate. At the molecular level, these proteins behave the same way in normal development and disease; in the latter case they are just in the wrong place or time. All of these proteins form multiprotein complexes that bind to DNA, and we are trying to tease out how these complexes assemble, what they look like and how we might disrupt or enhance complex formation to ultimately treat disease. In this area the major focus is on:

- LMO2 – blood cell development/ T-cell leukemia
- LMO4 – brain development and a problem protein in breast cancer
- LIM-homeodomain proteins – tissue specific development including neuronal, pituitary, heart and pancreatic development, and hormone production.

Methodologies – My lab uses predominantly *in vitro* techniques to characterise (or modify) protein structure and function

- Molecular biology (e.g. cloning, mutagenesis, yeast two hybrid analysis, EMSA)
- Biophysical characterisation (e.g. circular dichroism, protein-protein and protein0DNA interactions using FRET/calorimetry/MST, scattering methods)
- Structure determination (X-ray and NMR)

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HOST-PATHOGEN INTERACTIONS DURING POXVIRUS INFECTION

Viruses have co-evolved with their cellular hosts in an unceasing arm's race occurring over millennia. What viral pathogens have learnt about their host's biology is written down in their genomes, a toolbox used to prise open their hosts, subvert signalling pathways and build viral progeny. Viral infection exerts an extraordinary range of effects upon their cellular hosts, influencing survival, adhesion and propensity to divide and migrate, all of which contribute to enhancing virus replication and spread. We use large DNA viruses as probes to elucidate fundamental mechanisms of cellular processes as well as to identify molecular links that could be targeted by antiviral agents in the treatment of disease. Our favourite workhorses are poxviruses such as *vaccinia* and *ectromelia*, which are closely related to the causative agent smallpox. Recently, we have also initiated similar studies on another DNA virus, the human pathogen *herpes simplex* virus. These are subjected to a variety of cell-based, molecular and imaging approaches.

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Potential Honours projects include:

- Cell-based transport of poxviruses
  Although many viruses take advantage of the host cytoskeleton to aid their intracellular transport, usurpation of cell migration is another pathway used to aid virus spread. Orthopox viruses are able to subvert signaling through Rho GTPases enabling virus spread via cell vectors. We are currently engaged in probing this mechanism in cell-based and animal studies.
- Imaging host/pathogen interactions
  Poxviruses are highly amenable to labelling with fluorescent proteins due to their large size (300 nm), ease of genetic manipulation and relatively relaxed capsid structure. We have generated a large number of singly- and multiply-tagged fluorescent recombinant viruses that allow us to study many aspects of the virus life-cycle in real time with wide-field and confocal microscopy. We are currently using this approach to gain insights into virus entry, intracellular transport of virus particles and the impact of virus infection of cell behaviour.
- Role of actin in viral replication
  We are investigating the regulation of the host actin cytoskeleton by herpes simplex virus. The aim is to determine how a key viral envelope protein, glycoprotein E, engages and regulates the arrangement of actin to facilitate viral entry, egress and cell to cell spread. For this study we also have access to a range of multiple-tagged fluorescent recombinant viruses.

NEURONAL DEVELOPMENT AND AGING

Much of our work aims to understand how genes are regulated to control development, with a specific focus on neuronal development. We use the nematode *Caenorhabditis elegans* as a model organism for many of our investigations. With a defined and invariant cell lineage, the nematode is a particularly powerful system for developmental studies. Using fluorescent reporter genes we have discovered that a transcriptional co-repressor protein called CTBP-1 is highly expressed in C. elegans neurons and is required for the correct development of several types of neurons. Through a range of approaches, we are identifying CTBP-1 target genes, with the view to understanding how CTBP-1 directs neuronal development.

In addition to investigating neuronal development, we are also studying the process of neuronal aging. As humans (and worms) age, physical changes occur in the nervous system that are linked to a progressive impairment of cognitive function. We have discovered that a nematode protein called PTL-1 is required for maintaining the integrity of neurons during aging and is also required for normal lifespan. PTL-1 is homologous to a human protein called Tau, which is implicated in the pathogenesis of Alzheimer's disease and other neurodegenerative diseases. We are now investigating the mechanism by which PTL-1 contributes to neuronal aging and longevity.

Although most of our work is done using the nematode as a model organism, the discoveries we make in the worm will also shed light on mechanisms that are similarly important for normal human development and for the prevention of disease.

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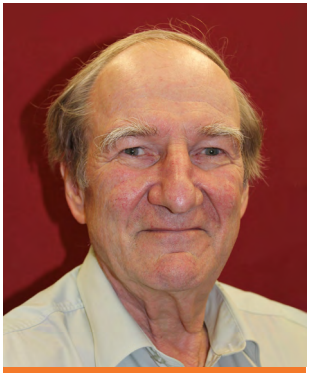
Potential Honours projects include:

- Validation of putative CTBP-1 target genes and investigation of their roles in neuronal development
- Investigation of the role of PTL-1 in neuronal aging and lifespan regulation

MOLECULAR EVOLUTION IN BACTERIA

Our group seeks to better understand how bacteria adapt and evolve. We use a variety of techniques from the fields of microbiology (e.g. bacterial culturing and isolation, phenotypic profiling), molecular biology (e.g. gene knockouts, gene replacements, gene cloning, assembly of operon constructs), and bioinformatics (e.g. DNA sequencing and analysis).

Project areas are listed below, but the list is not exhaustive. We encourage you to meet with us to discuss projects. Data from recent honours projects have been published in scientific journals.



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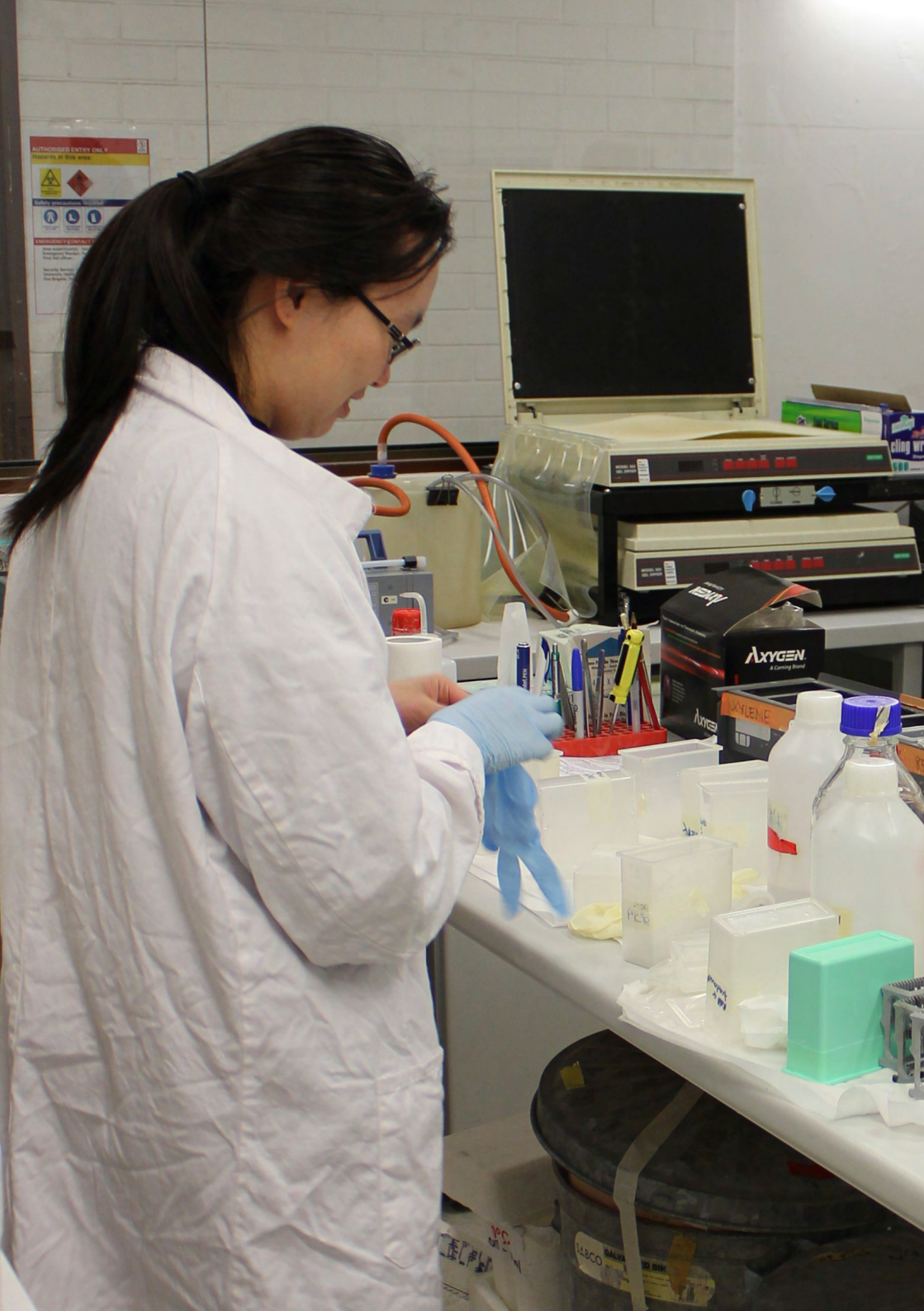
Potential Honours projects include:

- Biology of O antigen gene clusters
  Surface-associated polysaccharides, which are often the major surface components of bacteria, play an important role in cell protection and survival. The polysaccharide structures are enormously diverse: *E. coli* alone has about 200 different forms of O antigen. This structural diversity plays a critical role in evasion of host immune responses.

  The genes for synthesis of both O antigens and capsules are clustered, and sequencing gene clusters gives a good understanding of the genetic basis of polysaccharide structure diversity. Recent examples are from *E. coli, Salmonella* and *Acinetobacter*. This opens up the option to use PCR or microarrays to monitor disease pathogens, or replace serology with DNA-based techniques.

  The proteins Wzx and Wzy respectively flip polysaccharide subunits across the membrane, and then polymerise subunits to long chains. We have projects that will focus on sequencing gene clusters or elucidating the nature and extent of substrate specificity of specific Wzx or Wzy.

- Evolution of bacterial populations
  We have an ongoing collaboration with a group in China with the capacity to undertake multiple whole genome sequencing projects and the associated bioinformatic analyses. For example, we are currently analysing sets of genome sequences from *Vibrio cholerae* and *Klebsiella* to examine clonal population structures and determine how these species evolve. Honours projects could involve aspects of the analysis of these or other species based on their genome sequences.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My research is broadly focused on developing chemical tools to study biological systems. My background is in chemistry but I am interested in the way biomolecules interact at a molecular level and how this relates to their biological function. Working in collaboration with other structural biology labs our goal is to develop synthetic molecules to study, mimic and perturb transcriptional processes *in vitro* and *in vivo*.

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Potential Honours projects include:

Honours projects incorporate a mixture of chemistry and biochemistry and are centered on three main themes:

- Chemical probes to isolating and interrogating transcriptional complexes
  We are interested in developing novel chemical technologies for isolating large multi-subunit protein machines in their native form. Using synthetic molecules containing a targeting domain and a short affinity tag for purification we have been able to isolate the intact Nucleosome Remodeling and Deacetylase (NuRD) complex from mammalian cells. We are interested in developing further synthetic probes based on this strategy to isolate other large protein complexes that are involved in transcription, DNA replication and DNA repair.

- Characterisation of transcriptional complexes
  To study the structure of fragile, large multi-subunit protein complexes we are using a combination of techniques: chemical crosslinking, to determine the connectivity of adjacent subunits; quantitative mass spectrometry to determine the stoichiometry of different protein components; and multi-angle laser light scattering and electron microscopy to determine the overall size of these complexes.

- DNA/RNA labeling strategies for studying transcription factors
  My lab has been developing chemistry to label oligonucleotides with paramagnetic groups. In NMR spectroscopy these labels give rise to the Paramagnetic Relaxation Enhancement (PRE) effect, allowing determination of high resolution 3-dimensional structures of DNA/RNA binding proteins with their cognate DNA/RNA. We are also interested in developing further chemistry to incorporate other interesting labels to study the interaction of oligonucleotides with proteins.

DESIGNER PARTS TO REBUILD HUMAN TISSUE

We are building elastic tissue components in the new Charles Perkins Centre.

We welcome innovative students interested in participating in an exciting multi-disciplinary research program that blends biochemistry, medicine and 3D tissue assembly.

Professor Weiss's research is recognised by an internationally unique combination of awarded leading research funds from the USA, Australia and UK.

We use a highly durable, natural reliable elastic material. The human body relies on elastin for elasticity. Elastin is essential for tissues requiring resilience, elasticity and extraordinary persistence.

Elastin is remarkable because its multifaceted functions allow it to operate over an entire lifetime.

Our elastic biomaterials have been used successfully in three human clinical trials. We now wish to expand these studies.

We now seek Honours students interested in participating in building the next generation of elastic biomaterials for organ and tissue augmentation and repair.

Potential Honours projects include:

- Cell:molecule interplay in the assembly of human elastic tissue.
- Accelerated wound repair for human burn patients.
- 3D artery constructs.

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PROTEOMICS OF DIABETES & CO-MORBIDITIES

Cells need to adapt to intra- and extra-cellular changes in rapid, yet reversible ways. In our group, we are interested in how these cellular signals are translated by modifying existing proteins, rather than relying on transcription and translation of new proteins which can take hours to achieve. Post-translational modifications (PTM) have the ability to regulate protein structure, function and localization, enabling rapid transmission of signals to initiator and effector proteins, in response to pathogenesis.

The main focus of my research is to better understand how PTM play a role in developing disease, in particular Type 2 diabetes and the related diabetic cardiomyopathy. Using heart tissue generated on our *ex vivo* perfusion system, we can precisely monitor and also manipulate the overall environment. This allows us to monitor functional changes that correlate with the cellular PTM status. To determine which proteins are modified, we use large-scale enrichment techniques to pull down specific PTM, including antibody- and chemistry-based methods. Of particular interest are phosphorylation and oxidative modifications and the signal pathways they modulate. The large numbers of proteins that can be captured, are then separated by 2-D gel electrophoresis, native gel electrophoresis or liquid chromatography. To identify the modified residues, we use mass spectrometry to identify both the specific residue modified and the protein it originated from. We use antibody-based techniques (including Western blot and immunohistochemistry) to validate our results.

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Potential Honours projects include:

- Which classes of proteins are no longer modified with the induction of diabetes? By investigating global changes to protein phosphorylation and/or oxidation in both normal and diabetic tissues we can decipher which systems are sensitive to the pathological challenge.
- How does ischemia/reperfusion injury influence mitochondria PTM cross-talk in the diabetic heart? As the powerhouse of the cardiomyocyte, the mitochondria are essential for continued function, but very little is known about how they respond under these conditions.
- Does diabetes change the way signal cascades are initiated? To achieve this we will look at cell surface receptors and their ability to be modified and initiate intracellular signal cascades.


THE CLINIC

CHECKLIST

DOMESTIC STUDENTS

- ☐ Read about the available projects and arrange to meet with potential supervisors.
- ☐ Submit your online SMB HONOURS APPLICATION FORM with your choice of up to 10 supervisors by Sunday, 30 November, 2014.
- ☐ Submit the online FACULTY OF SCIENCE HONOURS APPLICATION FORM to the Faculty of Science by Sunday, 30 November, 2014.

INTERNATIONAL STUDENTS

- ☐ Read about the available projects and arrange to meet with potential supervisors.
- ☐ Submit the online SMB HONOURS APPLICATION FORM with your choice of up to 10 supervisors by Sunday, 30 November 2014.
- ☐ Submit the online FACULTY OF SCIENCE HONOURS APPLICATION FORM to the Faculty of Science by Sunday, 30 November 2014.

FORMS

SMB Honours online application form:
sydney.edu.au/science/molecular_bioscience/honours/honours_form.php

Faculty of Science Honours online application form:
sydney.edu.au/courses/study_area/science-and-technology

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FACULTY OF SCIENCE

THE UNIVERSITY OF SYDNEY

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