



THE UNIVERSITY OF  
**SYDNEY**

School of Molecular  
Bioscience

# HONOURS GUIDE 2016



#### IMPORTANT NOTE:

As of 1 January 2016, the School of Molecular Bioscience will be joining other life science focussed Schools to form the new School of Life and Environmental Sciences (SOLES). While this merger will not change the requirements, course codes or assessment for Honours, there may be a change in the web addresses used throughout this booklet. Please use the contacts at the back of this guide if you have any queries or concerns.

## HONOURS INFORMATION SESSIONS

Honours in Biochemistry and Microbiology  
School of Molecular Bioscience

Your chance to meet potential supervisors and  
current research students

Thursday, 17 September 2015  
Molecular Bioscience Building G08  
Common Room, Level 4, Room 431  
1:00pm and 5:00pm  
Food and drinks provided



School of Molecular Bioscience

# Honours Guide 2016

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# WELCOME

## Welcome to the School of Molecular Bioscience Information Program for Honours 2016!



I hope that you will be able to join us at the special information sessions on Thursday, 17 September, 2015 and meet with members of our staff to discuss your interests and needs.

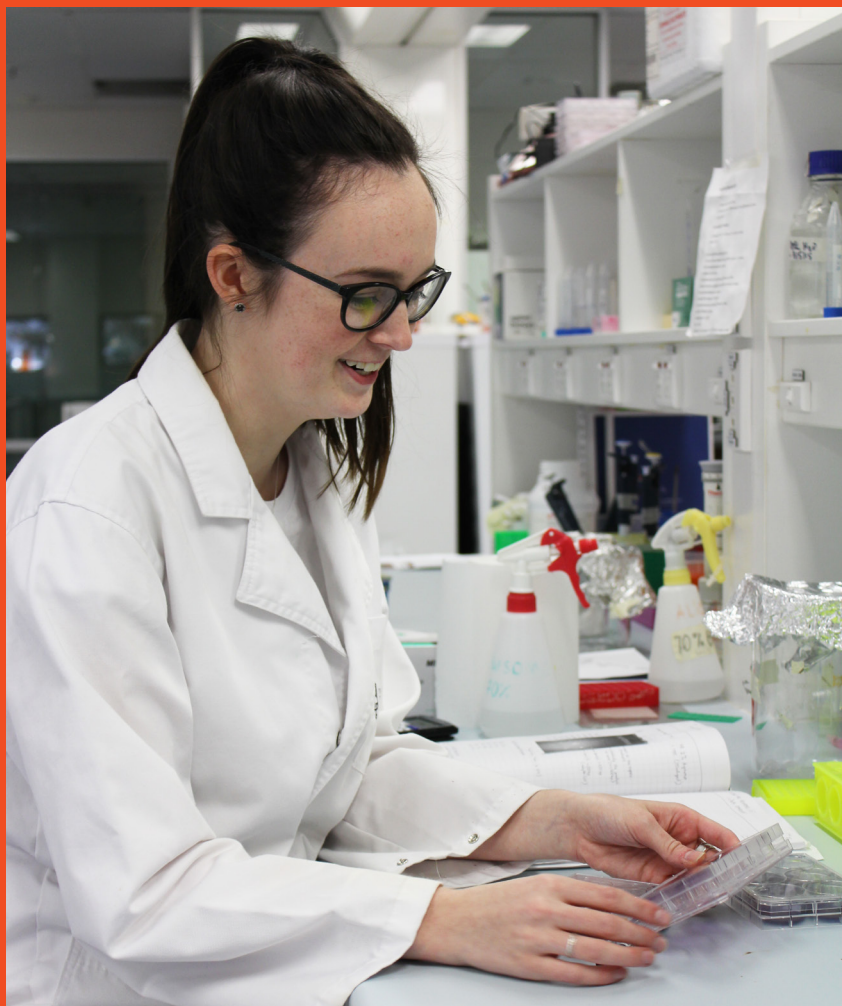
At the information sessions you will find opportunities to meet informally with supervisors and current research students, mull over a variety of potential projects, learn more about our exciting research environment and, of course, avail yourself of food and drink that will be provided.

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 (SMB) is an excellent place to do your Honours year. Our staff are made up of world class researchers and experienced and effective mentors. You will find a broad range of research projects available to meet your specific interests spanning biochemistry, structural biology, microbiology and molecular and cellular biology. As part of a major restructuring of the life sciences at the University of Sydney in 2016, SMB will cease to exist and will be amalgamated into the new School of Life and Environmental Sciences (SoLES). However, for your Honours year you will still have the same choice of academic staff and research projects to choose from and the same opportunities currently on offer from SMB and depending on who your supervisor will be, you will be located either in the Molecular Bioscience Building (G08) or the Charles Perkins Centre (D17). School-life will be supported by two research clusters in biochemistry, molecular and cellular biology and microbiology. An Honours Committee, will oversee the overall organisation of the year, and will be composed of representatives from each cluster. Finally, numerous activities will be held locally to provide an active and engaging social agenda.

I encourage you to review this information brochure and talk to as many potential supervisors as you can – and I look forward to seeing you in 2016!

Professor Iain Campbell  
Head, School of Molecular Bioscience



"An honours project at SMB is so much more than an academic experience. The most important and unique aspect of it is the family you gain the minute you walk into the building. They will push you to excel, catch you when you fail, and encourage greatness in all your endeavours. This is what sets SMB apart."

Caitlin Abbott

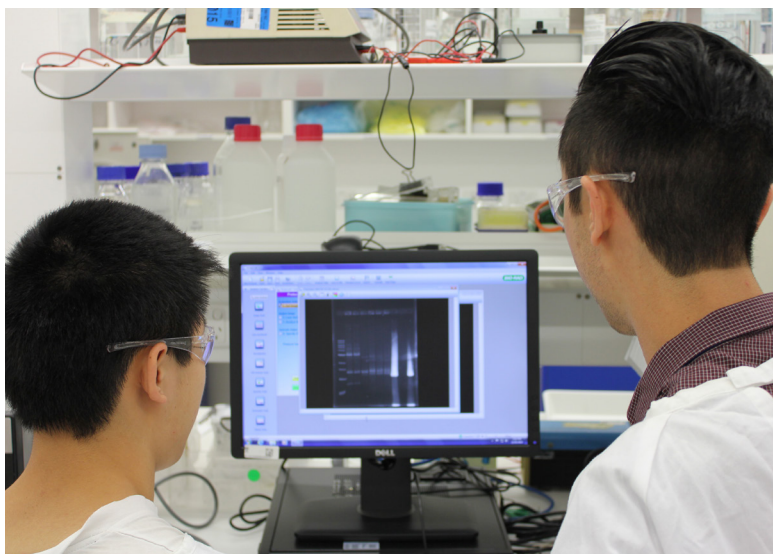
Honours Student 2015  
Newsome Laboratory

# WHY DO HONOURS?

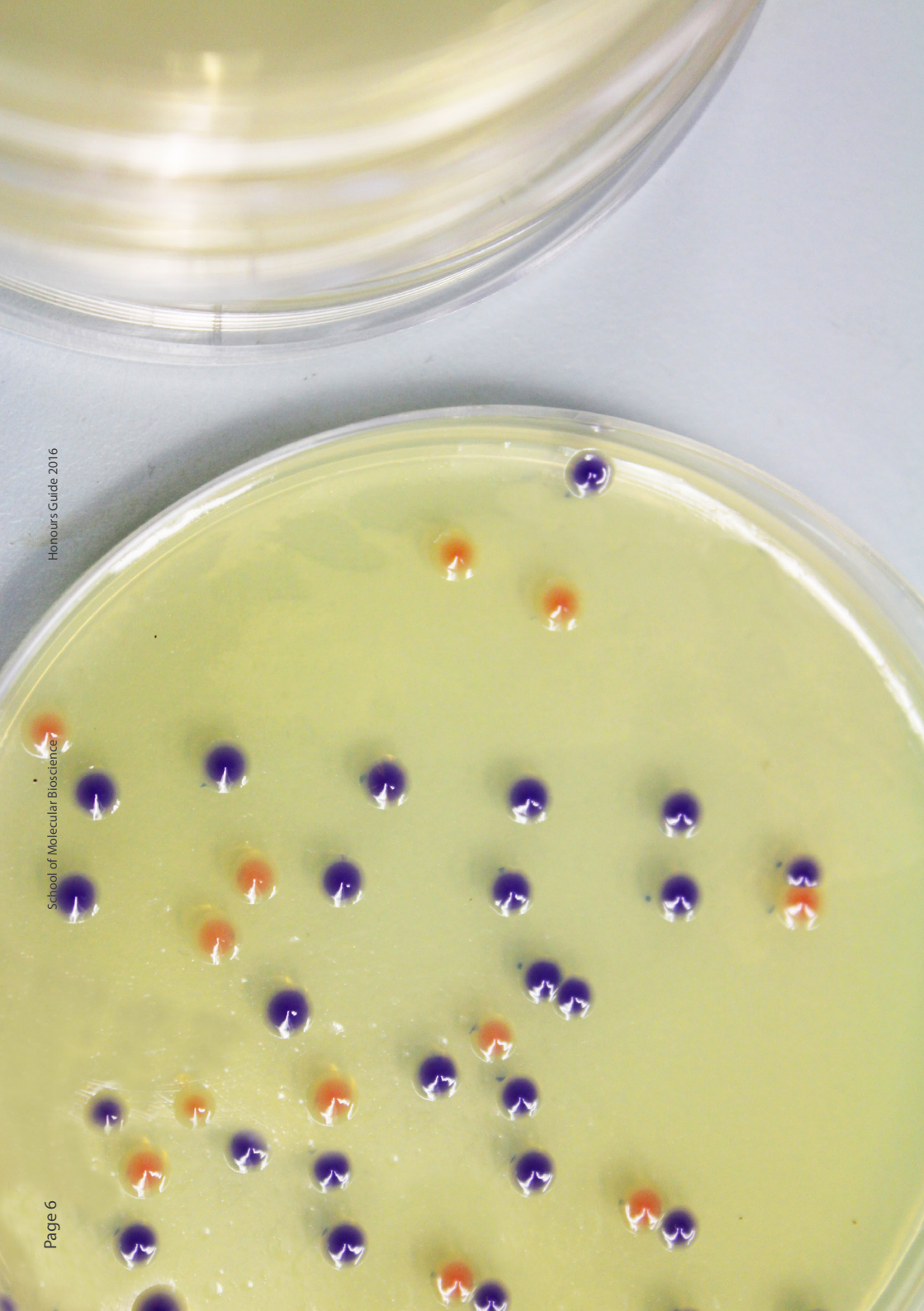
If you are looking to improve your career prospects, open the door to further academic study, or simply indulge a passion, then Honours is your next step.

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 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 research focus.







# HOW DO I QUALIFY FOR HONOURS?

To be eligible for either 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 Faculty of Science to have the required 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 in Biochemistry or Microbiology;
- either a Credit average in 48 credit points of relevant Intermediate and Senior Units of Study or a SCIWAM of at least 65; and,
- you must have a provisional acceptance of project supervision by at least one academic (School enrolment form)

## Graduates from other Australian Universities

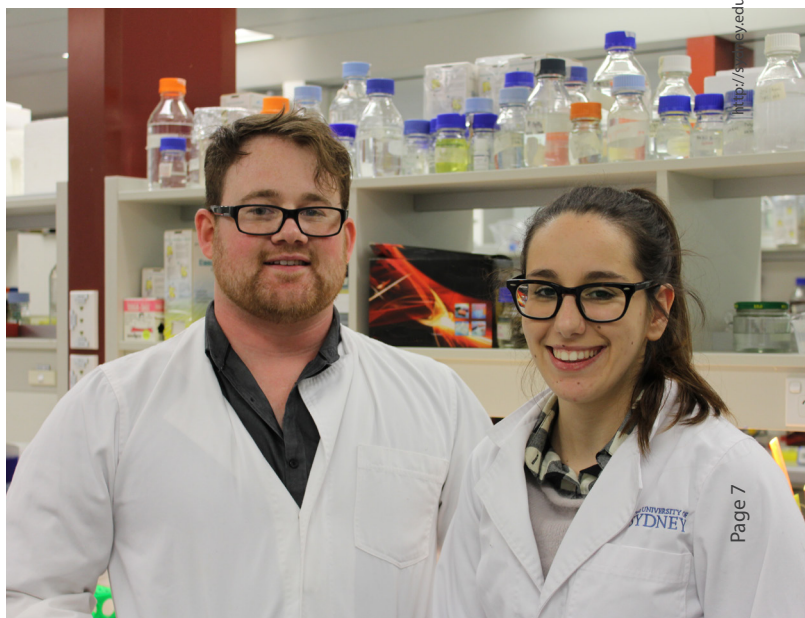
The minimum requirement for acceptance into the Honours program is SCIWAM of 65. The Faculty of Science will calculate your SCIWAM after you have applied. Otherwise, the requirements for application are the same as for graduates from the University of Sydney.

## International students

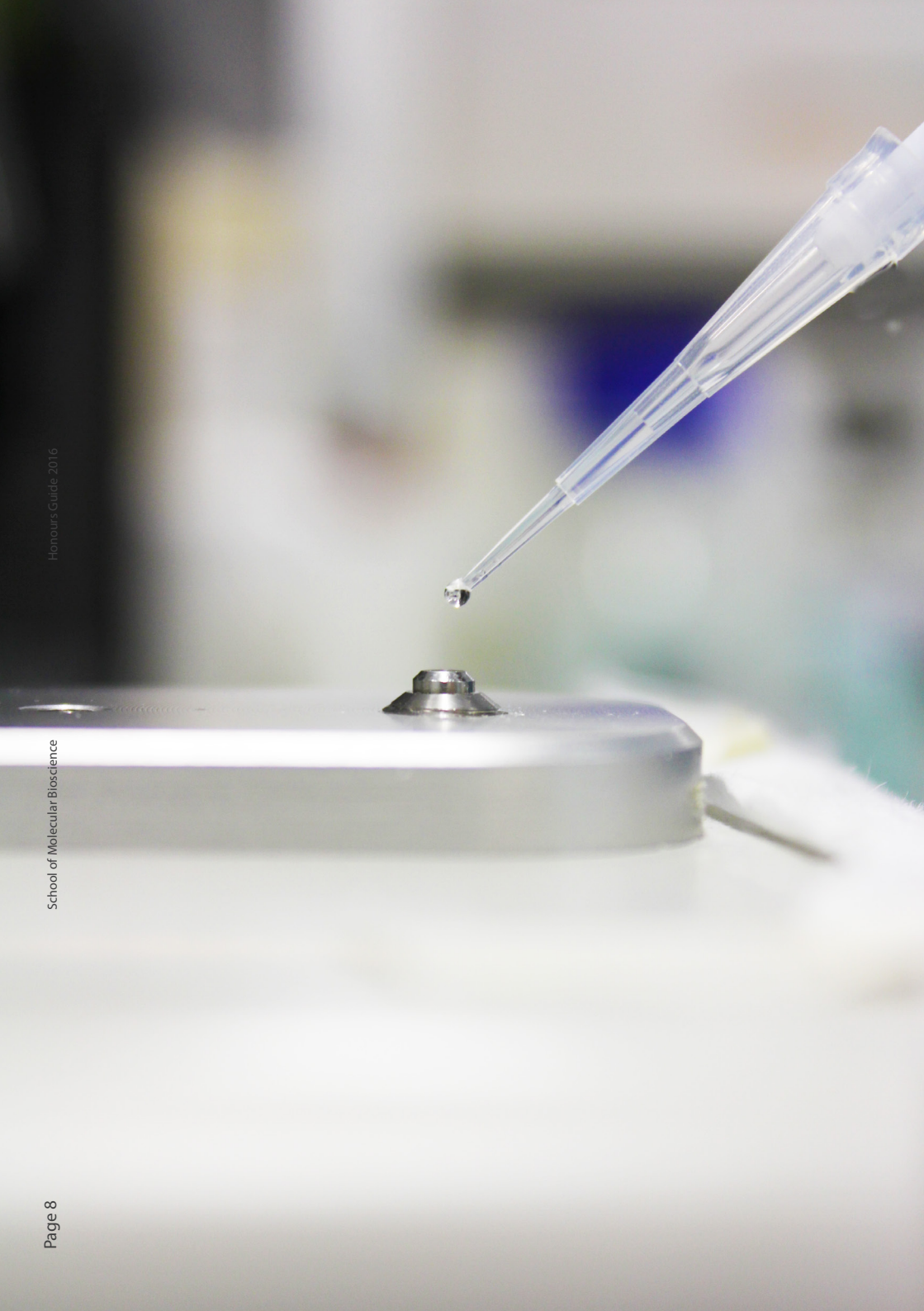
International Services will assess your academic record and advise whether it is equivalent to a pass degree, at the level required for entry into Honours, from the University of Sydney.

[sydney.edu.au/internationaloffice/index.shtml](http://sydney.edu.au/internationaloffice/index.shtml)

[http://sydney.edu.au/science/molecular\\_bioscience/honours/index.php](http://sydney.edu.au/science/molecular_bioscience/honours/index.php)







# HOW DO I APPLY?

## SEMESTER 1, 2016

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### Application Deadline

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Sunday, 29 November 2015

ALSO submit an International Undergraduate Student Application Form to the International Student Office for visa processing. Part-time enrolment is not available for international students.

### Step 1

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Find a project and supervisor.

Please refer to "How do I find a supervisor?" on Page 18.

#### External international students

Contact SMB Honours Coordinator (details at the back of this guide) before applying through the International Student Office. You will need to provide evidence in your application form that you have secured an academic contact/supervisor.

### Step 2

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Submit the SMB Honours application form:  
[sydney.edu.au/science/molecular\\_bioscience/honours/honours\\_form.php](http://sydney.edu.au/science/molecular_bioscience/honours/honours_form.php)

You must complete an "International Undergraduate Student Application Form" and lodge this form at the International Student Office. Part-time enrolment is not available for international students.

### Step 3

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#### Domestic students - internal (currently enrolled) and external

Submit the Faculty of Science Honours application form:  
[sydney.edu.au/science/fstudent/undergrad/course/honours/apply.shtml](http://sydney.edu.au/science/fstudent/undergrad/course/honours/apply.shtml)

#### Internal (currently enrolled) international students

Submit the Faculty of Science Honours application:  
[sydney.edu.au/science/fstudent/undergrad/course/honours/apply.shtml](http://sydney.edu.au/science/fstudent/undergrad/course/honours/apply.shtml)

### Acceptance into Honours

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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.



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## SEMESTER 2, 2016

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### Application Deadline

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Please refer to [sydney.edu.au/science/dates.shtml#application\\_deadlines](http://sydney.edu.au/science/dates.shtml#application_deadlines)

The School will be offering a limited number of places for students wishing to commence Honours in Semester 2, 2016. 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.

### Step 1

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It is important that you contact potential supervisors to determine whether they will accept mid-year entrants in 2016.

### Step 2 and Step 3

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Please follow the same format as Semester 1, 2016.

## COURSE CODES FOR HONOURS ENROLMENT

(Semester 1 and 2, 2016)

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### Biochemistry Honours

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BCHM4011  
BCHM4012  
BCHM4013  
BCHM4014

### Microbiology Honours

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MICR4011  
MICR4012  
MICR4013  
MICR4014

# HONOURS COURSE DETAILS

## 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 six tutorials and an examination; and
- attend the weekly School Seminar

## 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 approximately 6 x 2 hour tutorials run by the Honours Committee in small groups of 6 to 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 (dates to be confirmed early 2016)

### Early-February

Honours commences and Orientation Day. Please note: Orientation Day is compulsory for all students. The day will include information on laboratory safety, computer usage and safety within the school.

### 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

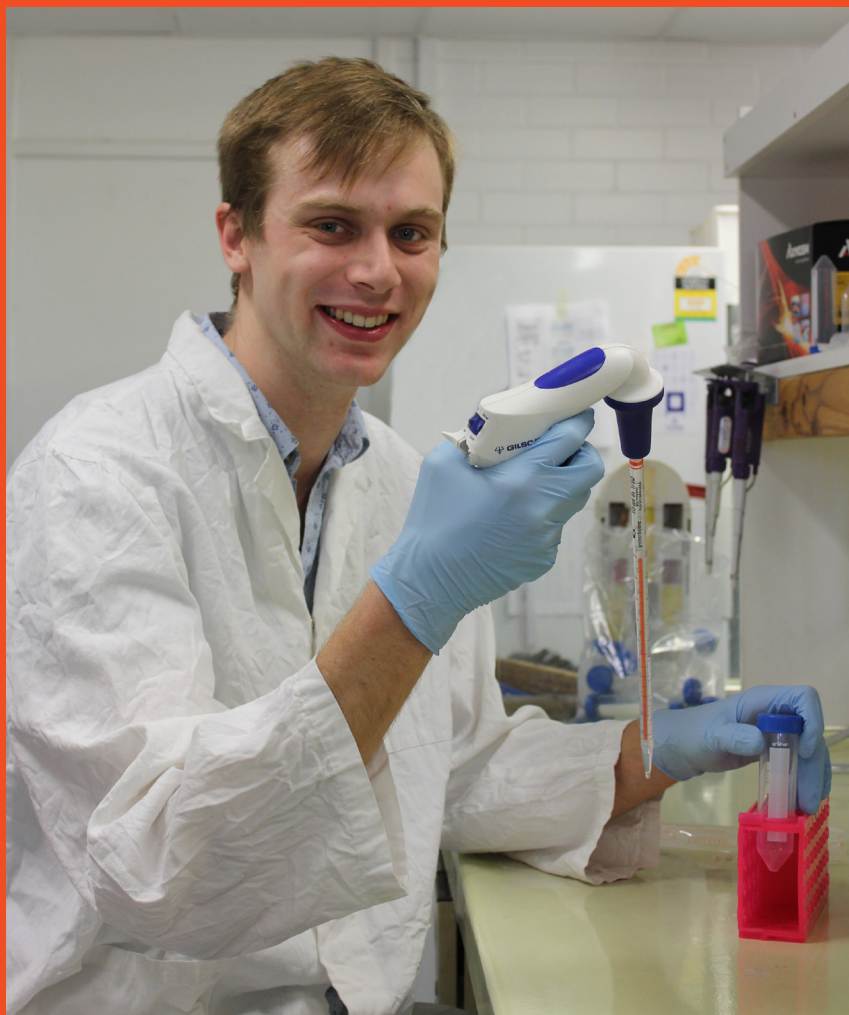
### Mid-October

Submission of Thesis

### Late-October

Final oral presentation and oral examination





[http://sydney.edu.au/science/molecular\\_bioscience/honours/index.php](http://sydney.edu.au/science/molecular_bioscience/honours/index.php)

"Doing Honours was my first real experience of independent scientific research and the skills and experiences I had were both invaluable and unforgettable. The teaching and the community at SMB is outstanding. I loved the experience of doing Honours at SMB so much that I came back to do my PhD here!"

Phillip West  
PhD Candidate  
Campbell Laboratory

# 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 is available on the Safety Health & Wellbeing website [sydney.edu.au/whs/](http://sydney.edu.au/whs/)

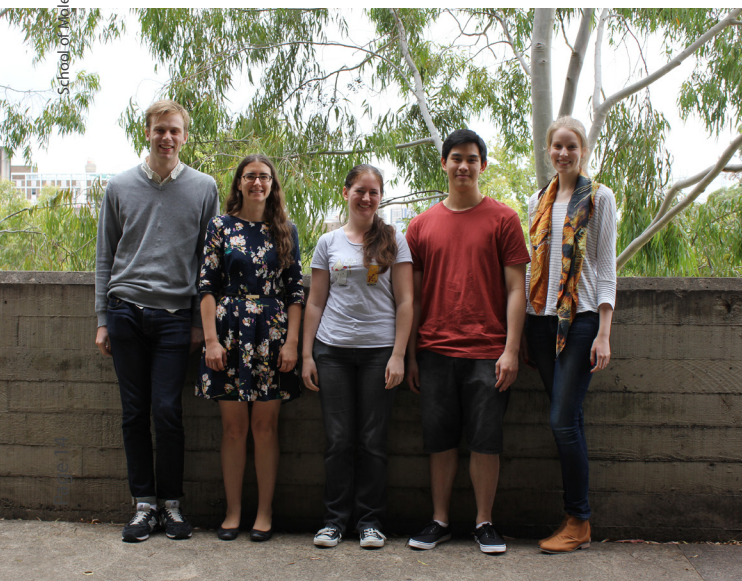
Information regarding your responsibility towards WHS will be provided at the Orientation Day. Honours students are also required to complete "Working with chemicals" and "Biosafety" training courses. In addition, projects involving animals, will require the completion of "Working with animals" training course.

## Scholarships

A limited number of Honours Scholarships are available through the Scholarships and Financial Support Service website [sydney.edu.au/scholarships/current/honours\\_scholarships](http://sydney.edu.au/scholarships/current/honours_scholarships)

## Social Activities

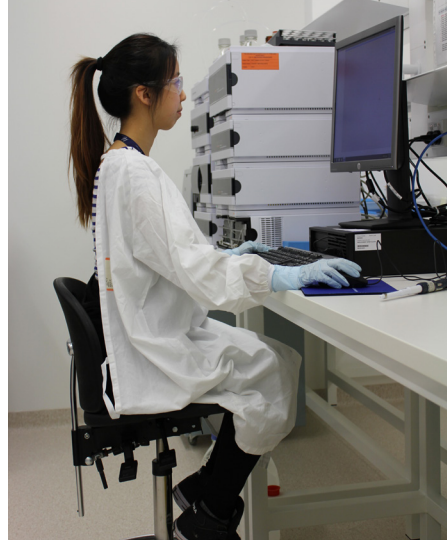
The School maintains an active student social society called AMOEBA. This group organises several events for Honours students, including an introduction barbeque, a post-coursework exam barbeque and an end-of-year barbeque. Events throughout the year also include Friday Cake Days, movie and dinner nights,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



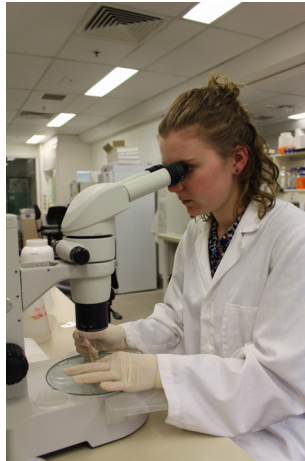
Amoeba Committee (left to right):  
Phillip West, Amanda Grech,  
Ngaio Smith, Barney Viengkhou  
and Tamara Suprunenko

"After completing my honours year, I saw a lot of potential in my project to pursue further research by commencing a PhD. The challenges and obstacles I faced in my Honours year helped me build upon my critical thinking and problem solving skills. My advice for students is to do Honours, because you don't understand what being a Scientist is like until you get into the lab and do hands on research. "

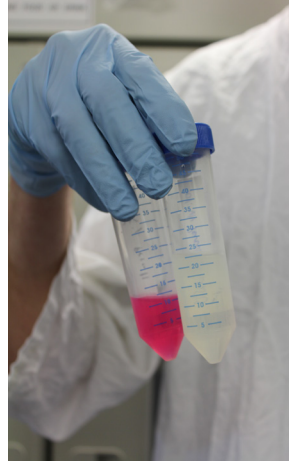
Pearl Lee  
PhD Candidate  
Weiss Laboratory



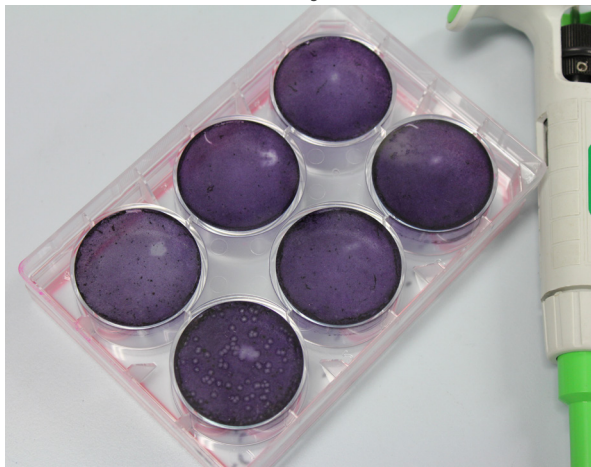
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3



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- 1 Pearl Lee  
PhD Candidate Weiss Laboratory
- 2 Tessa Sherry  
Honours Student Nicholas Lab
- 3 Buffers
- 4 Viral Plaque Assays



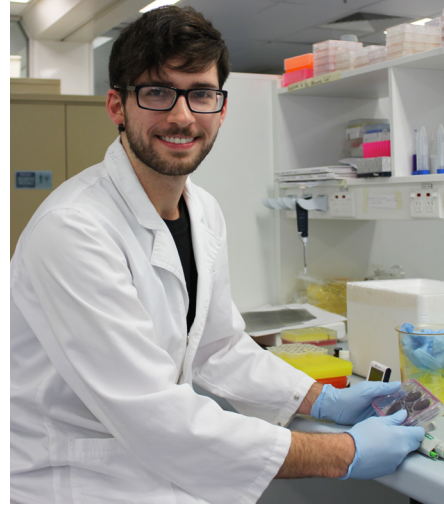
"The Honours year is an exciting time, a chance to finally put your undergraduate years into practice and immerse yourself in the science! You will join a friendly and very social community of like-minded individuals in SMB who can provide you with all the support and advice you will need. No two days have been the same for me, providing a challenging, yet thoroughly stimulating and rewarding experience. I would definitely recommend Honours to anyone who is thinking of pursuing a career in science, or indeed anyone who simply wants to develop valuable generic skills such as time management, critical thinking and communication skills; an attractive skill set for any employer!"

Tara Bartolec  
Honours Student 2015

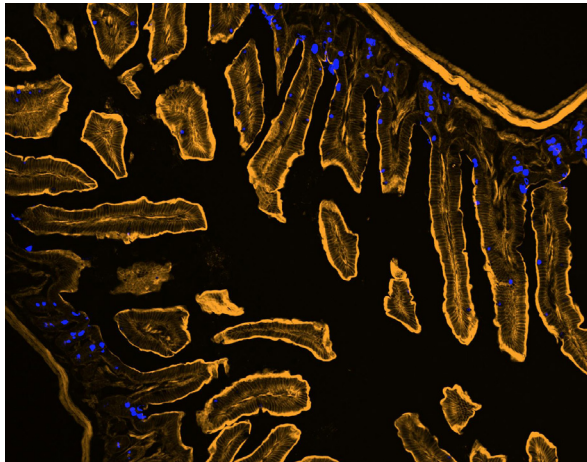


“SMB offer such a wide variety of projects that it’s hard not to feel overwhelmed. But it’s an opportunity to choose the first step of your future”

Christopher Denes  
Honours Student 2015  
Newsome Laboratory



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- 1 Christopher Denes  
Honours Student Newsome Laboratory
- 2 Microscopy work undertaken by  
Tara Bartolec
- 3 Centrifuge rotors
- 4 Green light microscopy with Matthew Hoe  
PhD Candidate, Nicholas Laboratory
- 5 Pipetting in action



3



4



5



# HOW DO I FIND A SUPERVISOR?

Talk to them!

Firstly, read through the following pages to find supervisors whose research interests you. Then email or phone to set up a meeting.

Next, come prepared with some questions about their research programs, and be prepared to answer questions about your interests and future plans.

Finally, speak to more than one potential supervisor.



1



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- 1 School of Molecular Bioscience (SMB) Building Code G08
- 2 Charles Perkins Centre (CPC) Building Code D17

# DIRECTORY OF POTENTIAL SUPERVISORS

Page	Name	Research Area	Building*	Email (@sydney.edu.au)
20	Dr Alyson Ashe	Molecular Biology & Genetics	G08	alyson.ashe
21	Dr Sandro Ataide	Structural Biology	G08	sandro.ataide
22	Dr Kim Bell-Anderson	Nutrition & Metabolism	D17 (CPC)	kim.bellanderson
23	Prof Jennie Brand-Miller	Nutrition & Metabolism	D17 (CPC)	jennie.brandmiller
24	Prof Iain Campbell	Molecular Biology & Genetics	G08	iaian.campbell
25	A/Prof Dee Carter	Microbiology	G08	dee.carter
26	Em/Prof Richard Christopherson	Biochemistry & Cell Biology	G08	richard.christopherson
27	Dr Nick Coleman	Microbiology	G08	nicholas.coleman
28	A/Prof Charles Collyer	Structural Biology	G08	charles.collyer
29	Prof Arthur Conigrave	Nutrition & Metabolism	D17 (CPC)	arthur.conigrave
30	A/Prof Stuart Cordwell	Biochemistry & Cell Biology	D17 (CPC)	stuart.cordwell
31	A/Prof Gareth Denyer	Molecular Biology & Genetics	G08	gareth.denyer
32	Dr Tom Ferenci	Microbiology	G08	tom.ferenci
33	Prof Ruth Hall	Microbiology	G08	ruth.hall
34	Dr Dale Hancock	Molecular Biology & Genetics	G08	dale.hancock
35	Dr Markus Hofer	Molecular Biology & Genetics	G08	markus.hofer
36	A/Prof Andrew Holmes	Microbiology	D17 (CPC)	andrew.holmes
37	Prof David James	Nutrition & Metabolism	D17 (CPC)	david.james
38	Dr Melkam Kebede	Nutrition & Metabolism	D17 (CPC)	melkam.kebede
39	Dr Ann Kwan	Structural Biology	G08	ann.kwan
40	Prof Joel Mackay	Structural Biology	G08	joel.mackay
41	Prof Jacqui Matthews	Structural Biology	G08	jacqueline.matthews
42	A/Prof Greg Neely	Nutrition & Metabolism	D17 (CPC)	greg.neely
43	Dr Tim Newsome	Microbiology	G08	tim.newsome
44	Dr Hannah Nicholas	Molecular Biology & Genetics	G08	hannah.nicholas
45	Prof Peter Reeves	Microbiology	D17 (CPC)	peter.reeves
46	Prof Tony Weiss	Proteomics & Biotechnology	D17 (CPC)	tony.weiss
47	Dr Melanie White	Proteomics & Biotechnology	D17 (CPC)	melanie.white

\* G08 = Molecular Bioscience Building, D17 (CPC) = Charles Perkins Centre



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

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DR ALYSON ASHE

Room 772, Molecular Bioscience Bldg

T +61 2 9114 1310

E [alyson.ashe@sydney.edu.au](mailto:alyson.ashe@sydney.edu.au)

[sydney.edu.au/science/people/alyson.ashe](http://sydney.edu.au/science/people/alyson.ashe)

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*.

### Honours Projects

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- 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

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DR SANDRO ATAIDE  
Room 672, Molecular Bioscience Bldg  
T +61 2 9351 7817  
E [sandro.ataide@sydney.edu.au](mailto:sandro.ataide@sydney.edu.au)

[sydney.edu.au/science/people/sandro.ataide](http://sydney.edu.au/science/people/sandro.ataide)



The majority of the human genome (> 75%) is dynamically transcribed into RNA, 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.

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.

## Honours Projects

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- 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).



## MOLECULAR MECHANISMS LINKING OBESITY & INSULIN RESISTANCE

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DR KIM BELL-ANDERSON

Level 3 West, Charles Perkins Centre Bldg

T +61 2 9351 6267

E [kim.bellanderson@sydney.edu.au](mailto:kim.bellanderson@sydney.edu.au)

[sydney.edu.au/science/people/kim.bellanderson](http://sydney.edu.au/science/people/kim.bellanderson)

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.

### Honours Projects

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**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

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PROF JENNIE BRAND-MILLER  
Level 6 West, Charles Perkins Centre Bldg  
T +61 2 9351 3759  
E [jennie.brandmiller@sydney.edu.au](mailto:jennie.brandmiller@sydney.edu.au)

[sydney.edu.au/science/people/jennie.brandmiller](http://sydney.edu.au/science/people/jennie.brandmiller)



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.

## Honours Projects

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### 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*. The glycemic index of carbohydrate foods is therefore higher in people with more copies, implying greater b-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](mailto:amanda.salis@sydney.edu.au)



## MOLECULAR BIOLOGY OF CYTOKINE ACTIONS IN THE CENTRAL NERVOUS SYSTEM

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PROF IAIN CAMPBELL

Room 710, Molecular Bioscience Bldg

T +61 2 9351 4676

E [iain.campbell@sydney.edu.au](mailto:iain.campbell@sydney.edu.au)

[sydney.edu.au/science/people/iain.campbell](http://sydney.edu.au/science/people/iain.campbell)

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.

### Honours Projects

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#### 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- $\alpha$ .

#### 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

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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 fungal infections once they have started? We use the system-wide proteomics and transcriptomics and general molecular and microbiological methods to manipulate our fungal pathogens and their genomes. We focus on the yeast pathogens *Cryptococcus* and *Candida*.

## Honours Projects

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### Antifungal drug targets and the development of new therapies

As it is difficult and expensive to develop new drugs we aim to develop synergents to make existing drugs more effective. There are two projects in this area:

- *Cryptococcus* is highly sensitive to medically active honey, while *Candida* is relatively resistant. We will expand on this by i) testing more strains of *Cryptococcus*; ii) testing more honey types, including native Australian honeys and New Zealand manuka honey; iii) fractionating honey to find antifungal fractions; and iv) testing honey in combination with antifungal drugs to see if it acts synergistically.
- Lactoferrin, a natural iron chelator and antimicrobial protein found in milk and tears, is synergistic with the antifungal drug amphotericin. To date all our studies have been *in vitro*. We will perform *in vivo* analysis in a wax moth larva model, which is a good proxy for mammalian infection, and test *Candida albicans* and non-*albicans Candida* species that are important emerging pathogens.

### What makes some fungal strains more pathogenic than others?

*Cryptococcus neoformans* strains can be genetically similar yet show substantial differences in virulence. We have access to a large number of clinical 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 at epigenetic modulation of virulence via chromatin modification.



## CANCER PROTEOMICS

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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, DIGE and antibody microarray analyses to identify proteins whose cellular levels change in cancer; their functions are then correlated with the phenotype of the cancer. The mechanisms of action of drugs such as fludarabine that induces DNA strand breaks, and the therapeutic antibody, rituximab, 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 involving 796 leukaemia patients has been completed 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. A modified DotScan microarray has been used to obtain 'disease signatures' for stable and progressive CLL in a clinical trial involving 96 patients that should enable triaging of patients, with vigorous treatment for those at risk. A further clinical trial with 400 CLL patients is planned prior to release of this rapid diagnostic test for progressive CLL.

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](http://www.medsaic.com) for several movies and many papers). Identification of unusual pairs of CD antigens on cancers provides a dual target for therapeutic antibodies called demibodies, that only combine at the surface of cells that express both antigens. The higher level of selectivity for cell killing by demibodies has provided a basis for granted US and European patents. In collaboration with Prof Jacqui Matthews, we are designing synthetic genes for demibodies, expressing them in *Escherichia coli*, purifying them, and testing their selectivity using human cancer cell lines. Subsequent work will involve development of demibodies that kill cultured CLL cells from patients.



# ENVIRONMENTAL MICROBIOLOGY

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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

## Honours Projects

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### Bioremediation of organochlorines – DCA and DDT

Organochlorine compounds are widely used as pesticides and solvents, which has led to environmental pollution. We are interested in developing biological methods for the cleanup of the solvent 1,2-dichloroethane (DCA), and the insecticide DDT. Previous students in the lab have isolated bacteria that can biodegrade DCA and DDT. New Honours projects would investigate the genetic basis of these biodegradation processes, and attempt to reconstruct the biodegradation process in *E. coli* via synthetic biology methods.

### Ethylene-oxidising bacteria for controlling produce freshness

Ethylene is a gaseous plant hormone, which controls ripening, among other processes. Previous work in the lab has shown that bacteria that grow on ethylene can influence the ripening of fruit, by reducing the atmospheric concentration of this gas. This is a promising new biotechnology, which could replace mechanical and chemical methods of ripening control. The Honours student would aim to isolate new and better ethylene-oxidising bacteria for this purpose, and develop engineering approaches to integrate the bacteria with an appropriate support matrix.



## DNA TRANSLOCASES AND PROTEIN ENGINEERING OF ENZYMES

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### Honours Projects

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#### DNA translocases and the remodelling of chromatin

As part of a collaborative program of research directed at understanding the mechanisms of human gene regulation, we are probing the structure and biochemical function of proteins that control gene expression at the level of transcription. Honours projects in this area will involve recombinant DNA work, protein biochemistry and structural analysis. The focus will be on proteins such as CHD4, which are ATP-dependent DNA translocases that are involved in the remodelling of chromatin.

The project is based on collaboration with Prof Joel Mackay, the research conducted in the Collyer Lab will focus on both the characterisation of enzymatic activities and the structural analysis of these proteins.

#### Protein engineering and evolution in a test tube

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. 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. New 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.

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 AND CELL BIOLOGY OF NUTRIENT SENSING

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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) including amino acid/calcium-sensing receptors and amino acid/glucose/fructose-sensing receptors that coordinate responses to nutrients.

We are currently focusing on how these receptors distinguish between different ligands and thus biased signaling pathways, how the receptors couple via their intracellular loops and carboxy-termini to G-Proteins and early signaling events, how the receptors switch between signaling pathways via their interactions with scaffolding proteins such as Homer-1, how splice variants of Homer-1 (a, b and c) modulate signaling, and how signaling pathways downstream of nutrient receptors engage in cross-talk with signaling pathways downstream of local factors or hormones. Ultimately, we are working to understand how cells respond to nutrients, and the impacts of nutrient-sensing receptors on whole body nutrient metabolism.

Our work involves cell culture, molecular engineering, transfection and transduction of vectors and plasmids, protein detection and purification, analysis of protein interactions, biochemical pathway analyses and phenotypic characterisation of transgenic mouse models.

## PROTEOMICS OF MICROBIAL PATHOGENS

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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.

### 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.



## TRANSCRIPTIONAL MEMORY IN ADIPOCYTE- MACROPHAGE INTERACTIONS

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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.



## BACTERIAL ADAPTATION

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Many fundamental aspects of adaptation can be readily studied in bacterial populations. Everything from the basics of genetic variation to the complex diversification in bacterial evolution can be analyzed in the laboratory. We aim to define the multiple mechanisms (the rates and spectrum of mutations, 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.

### Honours Projects

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- 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.
- We have exciting new data that the environment has a major say in what kind of genetic variation occurs in bacteria. For example, *E. coli* contains different point mutations, indels and transpositions depending on whether, for example, it grows aerobically or anaerobically. The mechanisms and consequences of having different starting points for evolution can be investigated.
- 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 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

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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 the evolution of plasmid and bacterial genomes and their role in developing resistance to antibiotics.
- Study how multiple antibiotic resistance arises using bioinformatic analysis to work out how multiple antibiotic resistance regions they were created.
- Look at how multiple resistance spreads in important bacterial pathogens. Are they on plasmids or genomic islands? Can they transfer into other bacteria? How do plasmids and integrating elements interact?

### Honours Projects

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- Multiply resistant *A. baumannii* acquired in hospitals belong to clones that have spread around the world. We have lots of Australian, multiply antibiotic resistant *Acinetobacter baumannii* isolates and over 200 draft genome sequences to help address questions such as where did they come from? How did they become resistant to so many antibiotics? Are they still evolving?
- Healthy humans can carry antibiotic resistant *E. coli* in their commensal gut flora. We have draft genomes from many of these and can now examine where the resistance genes they carry are and if they can transfer to new hosts.
- How do the mobile elements that help resistance genes to spread (transposons, insertion sequences, integrons, gene cassettes) work? We are looking at a mobile element that has not been studied before, IS26 and transposons flanked by it.



## ROLE OF MICRORNAS IN OBESITY & INFLAMMATION

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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.



# IMMUNOBIOLOGY AND NEUROPATHOLOGY OF INFLAMMATION

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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.

## Honours Projects

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- 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 MICROBIOME AND HEALTH (IMMUNOLOGY/METABOLISM/MICROBIAL ECOLOGY)

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Our gut microbiota has an enormous impact on our health. It consists of around a 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 as 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.

## Honours Projects

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- Quantifying the microbiome impact on nutrition – what happens when they are knocked down?
- Does the microbial community in diet-induced obesity impair regulation of feeding behaviour via the gut-brain axis?

# MOLECULAR AND METABOLIC SYSTEMS BIOLOGY

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Our overarching 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.

## Honours Projects

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### Mapping new functions of insulin and exercise

We have conducted a comprehensive screen of insulin and exercise regulated protein phosphorylation in adipocytes and human muscle respectively, identifying 1,000s of discrete phosphorylation sites that are regulated by these agonists. These data sets contain 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 and AMPK signaling pathways

The Akt pathway plays an essential role as a signal conduit between growth factors and downstream responses like proliferation, metabolism and apoptosis. The AMPK pathway is activated by exercise and plays a key role in the adaptations to exercise in muscle. 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 spectrometry.



## BETA-CELL FUNCTION AND DYSFUNCTION IN TYPE 2 DIABETES

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The obesity epidemic is bringing a parallel epidemic in metabolic diseases including type 2 diabetes (T2D), hypertension, cardiovascular disease and kidney disease. Genetic factors contribute to these diseases and obesity acts as a stressor that provokes phenotypes that might otherwise be silent. It is well established that obesity causes insulin resistance; an inability of insulin to elicit its normal physiological response. In the early stages of insulin resistance, the pancreatic  $\beta$ -cells produce and secrete more insulin in order to compensate for the insulin resistance. Type 2 diabetes occurs when the  $\beta$ -cells are not able to produce enough insulin to meet the increased demand for insulin brought about by insulin resistance.

Using mouse genetics, it was identified that a single mutation in the *Sorcs1* gene is associated with low circulating insulin levels and susceptibility to T2D. Subsequent studies show that *Sorcs1* is also involved in human T2D and diabetes complications.

When we deleted the *Sorcs1* gene in a mouse, the mouse develops severe diabetes due to a severe depletion of insulin granules from its pancreatic  $\beta$ -cells. We are currently investigating the direct role of *Sorcs1* on insulin granule formation and  $\beta$ -cell function.

### Honours Projects

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**Investigating how deletion of *Sorcs1* leads to a severe depletion of insulin from pancreatic  $\beta$ -cells**

In this project we will employ techniques such as tissue culture, *in vitro* hormone secretion assays, western blotting and fluorescence microscopy.

**Understanding the functional consequence of the mutation on the *Sorcs1* gene**

We obtained a clue to the functional consequence of the mutation when we overexpressed the two variants in  $\beta$ -cells. It appears that the mutation resulted in a processing defect of the *Sorcs1* proteins. We will investigate the mechanism behind this differential processing as well as the functional consequence(s) of this defect on insulin production and  $\beta$ -cell function. In this project we will employ techniques such as tissue culture, *in vitro* hormone secretion assays, western blotting, fluorescence microscopy, mass-spectrometry and cloning.

# FUNCTIONAL AMYLOIDS: STRUCTURE, FUNCTION AND DRUG DELIVERY APPLICATIONS

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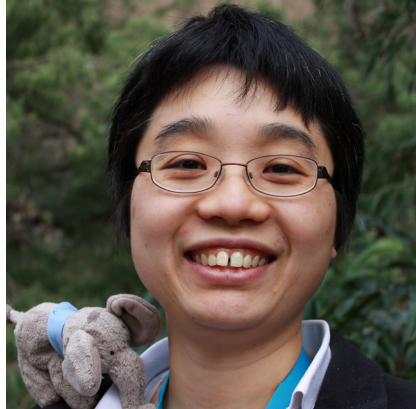
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Amyloid structures were once thought to be limited to biological mistakes but organisms from bugs to humans have now been discovered to use these structures to achieve a diverse range of biological functions. Our goals are to understand the structure and function of functional amyloids and to manipulate them for biotechnological and drug delivery applications.

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

## Honours Projects

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### Can hydrophobins be combined with nanomaterials for medical and biotechnological applications?

Assembled hydrophobin layers are robust, biocompatible and can reverse surface wettability of materials that they coat. You will examine the ability of hydrophobins to adhere to various nanomaterials including potential drug carriers (e.g. nanodiamonds) to increase their solubility or biocompatibility. You will then characterise the complexes that form using a range of biochemical and biophysical techniques.

### Engineering fluorescent hydrophobins for imaging applications and structural studies

You will optimise the use of cell-free and recombinant expression systems to produce fluorescently labelled hydrophobins. This will allow their easy visualization in imaging applications and assist with the structural studies of hydrophobin layers.

### 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, microscopy, surface measurements to amyloid assays. The projects will be jointly supervised by A/Prof Margaret Sunde, Department of Pharmacology.





## REGULATION OF GENE EXPRESSION

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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.

## REGULATORY PROTEINS IN DEVELOPMENT & DISEASE

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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 and their binding partners 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, how they trigger gene activation, 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 (LIM-HD) proteins – tissue specific development including neuronal, pituitary, heart and pancreatic development, and hormone production
- Ldb1 – a chromatin looping factor required for the biological activity of LMO and LIM-HD proteins

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 protein-DNA interactions using FRET/calorimetry/MST, scattering methods)
- Structure determination (X-ray and NMR)



## FUNCTIONAL GENOMICS

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The human genome project was a major advance that provides us molecular access to the genetic causes of complex human diseases. The real question now is, "what do these genes do, and how do they participate in human disease?" Despite massive genome-wide efforts to identify the genetic contribution of various human traits or diseases, to date the identified heritability of even simple traits like height is only ~10% of the known genetic contribution.

In our lab we use functional genomics approaches to identify some of the other ~90% of the genetic component for complex diseases. Genomic dissection of organ function in model organisms has been greatly expanded by new tools to perform large scale, tissue-specific gene silencing. For example, various libraries comprised of ~40 000 transgenic fly lines have been generated that allow for tissue-specific functional annotation of all genes in the *Drosophila* genome. We have considerable expertise using these tools to identify conserved genes involved in heart function, pain perception, neurodegeneration, lifespan and metabolic disorders, kidney function, and cancer.

## Honours Projects

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### Characterization of novel conserved pathways that extend lifespan

Evaluation of lifespan, molecular characterization of novel longevity genes using molecular biology, behavioural genetics, and electrophysiology

### Genomic investigation of chronic neuropathic pain

Evaluation of central sensitization in response to nerve injury using behavioural assays, microscopy, and electrophysiology.

### Genomic investigation of the relationship between diet and chronic pain

Will involve behavioural genomics and tissue-specific gene targeting.

### Investigation into new motor neurone disease genes

Characterization of new motor neurone disease genes using behavioural genetics, molecular biology, microscopy, and electrophysiology.

# HOST-PATHOGEN INTERACTIONS DURING POXVIRUS INFECTION

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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.

## Honours Projects

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### 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

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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.

## Honours Projects

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- 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



## BACTERIAL ADAPTATION AND EVOLUTION

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Our group seeks to better understand how bacteria adapt and evolve. We have expertise in a variety of fundamental techniques used widely microbiology (e.g. bacterial culturing and isolation, phenotypic profiling), molecular biology (e.g. gene knockouts, replacement and cloning, assembly of operon constructs), and bioinformatics (e.g. DNA sequencing and analysis), and have access to state-of-the-art equipment and services within the Charles Perkins Centre.

Two potential project areas are listed below, but this list is not exhaustive. We encourage you to meet with us to discuss projects. Many of our recent Honours students have had their work published in scientific journals.

### Honours Projects

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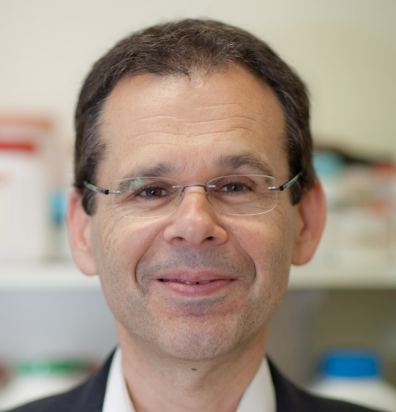
#### Biology of O antigen gene clusters

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. Each O antigen has its own set of genes predominately located within a gene cluster. These gene clusters consist of genes for sugar synthesis, sugar transfer genes to assemble a small oligosaccharide for attachment to the outer membrane, a *wzx* gene encoding a flippase to transport the oligosaccharide across the membrane, and a *wzy* gene for oligosaccharide polymerisation.

Much like the O antigens themselves, Wzx and Wzy are highly variable. However we are only now learning about their reactions and specificity. Projects could involve making gene knockouts or cloning of selected *wzx* and *wzy* genes that can provide new information on substrate specificity, protein-protein interactions or protein function.

#### Bacterial population structures and evolution

We collaborate with a Chinese group with outstanding genome sequencing capacity, and are currently working on population genetics, and evolutionary and functional analysis using genome sets from *Vibrio cholerae*, *Klebsiella*, and other species. Projects could involve aspects of the analysis of these or other species based on their genome sequences.



## DESIGNER PARTS TO REBUILD HUMAN TISSUE

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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.

Our 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.

### Honours Projects

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

## PROTEOMICS OF DIABETES & CO-MORBIDITIES

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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.

### Honours Projects

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**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.



# CHECKLIST

Read about the available projects and  
arrange to meet with potential supervisors



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