School of Biomedical Sciences and Pharmacy
College of Health, Medicine and Wellbeing

Bachelor of Biomedical Science (Honours)
Projects for Commencing Semester 1 2024

ARE YOU CONSIDERING HONOURS?

THE IMPORTANCE OF AN HONOURS YEAR

The Honours year is your opportunity to make creative use of the information you have acquired during your first 3 years of study. It should be an exciting, fulfilling experience and for those with imagination, drive and an aptitude for problem solving the Honours year will provide a logical point of entry into a research career. For many students the Honours year will lead to a higher degree. Hons 1 or 2(1) will allow access to a PhD program directly while Hons 2(2) or 3 will permit entry into a Masters program. A Masters enrolment can then be upgraded to a PhD if a sufficient level of performance is achieved.

Even if you ultimately discover that a career in research is not for you, an Honours degree will provide you with fundamental skills that are valued in the workplace and enhance your chances of finding a job; the unemployment rate amongst our Honours graduates is essentially zero.

HOW DO I FIND OUT ABOUT HONOURS AND ENTRANCE REQUIREMENTS?

Asking questions of current and past Honours students and academic staff is probably the best place to start.

There are some academic restrictions, i.e. a Credit average (GPA 5.0 overall OR for 60 units of **appropriate** 3000 level subjects) is the traditional qualification, but otherwise it is mainly a matter of finding a project and supervisor. To assist you, the Honours committee has:

- Produced these guidelines so you have a clear idea of what you are getting into and
- Posts on the Honour's website https://www.newcastle.edu.au/degrees/bachelor-of-biomedical-science-honours

WHEN SHOULD I START LOOKING FOR A SUPERVISOR AND A PROJECT?

Although you may not know whether you have qualified for Honours until the end of the semester, before you begin Honours it is important to begin to make enquiries and contact with possible supervisors as soon as possible.

SUPERVISORS AND PROJECTS

The School of Biomedical Sciences and Pharmacy offers a wide range of Honours training in the laboratory ranging from the integrated human and animal, to bench and molecular projects. It is vitally important that you are interested in the project you undertake so choose carefully. It is

also important that you make an informed decision, and this may take some time. It is often useful to actually spend some time working as a volunteer with possible supervisors. A project that sounds great on paper or in discussion may turn out not to be your thing at all. While your supervisors and co-workers will provide a lot of support, it ultimately is your project, driven by your energy and your commitment.

A student will be co-supervised by two individuals. As a guide, a supervisor is any person whose contribution to the research project is such that they would, in normal practice be recognized as authors on any publications arising from the student's project. A member of the School of Biomedical Sciences and Pharmacy will be a primary supervisor to ensure good liaison between the external co-supervisor and the School.

INTRODUCTION TO THE HONOURS PROGRAM

Welcome to the Bachelor of Biomedical Science Honours program. I am sure that you will find it an interesting and stimulating program and one which will provide a very different experience from that which you have had so far in your studies.

PURPOSE
The Bachelor of Biomedical Science Honours Program is a research training degree. The primary purpose of the Honours year is for the student to develop a new testable hypothesis after reviewing the literature, design appropriate experiments, collect, and critically evaluate the generated data, and communicate the data to others. Students should note that it is an essential component of the Honours year that they critically analyse and present their **own data that was obtained throughout their honours year**.

AIMS
An Honours year in Biomedical Science will provide you with a number of generic educational skills that will be of life long value regardless of your ultimate career path. At the most basic level you should develop attitudes and fundamental skills relevant to problem solving, self-learning and team work that will be highly valued in the workplace and the broader community. In more specific terms you should learn:
1. How to retrieve information of various kinds using electronic media.

2. How to critically evaluate the information received to develop an understanding of the background and the current status of a particular field.

3. How to use this information and your own insights to create hypotheses that can be tested experimentally.

4. How to design statistically valid experiments to test a given hypothesis.

5. The wide and exciting range of technologies that are currently available to address medical problems.

6. How to assimilate data and draw conclusions

7. How to present your results in written and oral form.

The development of these skills will be assessed by a number of indicators including a review in which you critically examine the literature that is relevant to your thesis work and a thesis summarizing the work you have done through the year. Your ability to present and discuss your work with others will be assessed through a presentation outlining your Honours proposal, a thesis review and an end of year seminar outlining your results and the conclusions that you drew from those results.

ADMINISTRATION OF THE COURSE

The Honours course is primarily administered by the Program Convenor with reference to the Head of the School of Biomedical Sciences and Pharmacy and the Bachelor of Biomedical Science Honours Committee (consisting of Program Convenor, Head of School, and Director of Research and Innovation School of Biomedical Sciences and Pharmacy).

Program Convenor:
Assoc Prof Nikki Verrills
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ASSESSMENT SYSTEM

Students are advised that the grade of Honours obtained is dependent on the standard of performance in all aspects of a student's work, not only on a mark achieved in a particular section.

Literature Review (20%), Presentation on Honours proposal (10%), Thesis plus Thesis Defence (60%), and Final Seminar (10%).

Your final result will be an Honours grade, not a specific mark. The following is an outline of the Honours grades along with a general description of what would be expected to achieve a particular grade in a specific task.

Honours 1: 85% or higher
Work of exceptional quality and independence, showing a very high level of understanding of subject matter and appreciation of issues; well formulated; arguments sustained; figures and diagrams relevant; appropriate literature referenced; strong evidence of creative ability and originality; high level of intellectual work.

Honours 2(1): 75.0 - 84.9%
Work of high quality and substantial independence, showing a strong level of understanding of subject matter and appreciation of dominant issues but not necessarily of the finer points; arguments clearly developed; figures and diagrams relevant; relevant literature referenced; evidence of creative ability and solid intellectual work.

Honours 2(2): 65.0 - 74.9%
Work of solid quality showing competent understanding of subject matter and appreciation of main issues but with some lapses or inadequacies; clearly identifiable deficiencies in logic or originality; some evidence of creative ability; reasonably well prepared and presented.

Honours 3: 50.0 - 64.9%
Adequate report, reasonable quality but showing a minimal understanding of the research area with major deficiencies in content or experimental rigor; little evidence of creative ability or

Fail: 49.0% or less

APPROVED PROJECTS

A list of approved available Honours projects are provided below, followed by a detailed description of each project, including contact details of supervisors.

	Title	Primary supervisor	Secondary Supervisors
1	Effect of bushfire and bushfire smoke on cardio and cerebrovascular diseases: evidence from 20 years of hospitalized patient data from Hunter New England Local Health District.	Neil Spratt	Dr Md Golam Hasnain
2	Central role of a master regulator of cellular signalling in development, function and disease of the epidermis	Severine Roselli	Nikki Verrills, Heather Murray
3	Targeting a novel mechanism of therapy resistance in ER+ breast cancer.	Nikki Verrills	Severine Roselli, Heather Murray
4	How does fatigue accumulate over a work shift, and how does this influence performance?	Dr Mitch Smith	Dr Mitch Naughton; Prof Rohan Walker
5	Interplay between sex hormones and metabolism in the pathogenesis and severity of asthma	Jay Horvat	Hayley Scott; Lisa Wood
6	Alcohol use disorder: Understanding the role of the serotonin system in mice.	Dr Erin Campbell	Dr Lizzie Manning
7	Improving fertility education in Australian adolescents.	Jessie Sutherland	Emmalee Ford; Kirsty Pringle; Catherine Chojenta
8	Mechanisms of sex-based differences in cachexia and heart muscle loss during colorectal cancer	Doan Ngo	Aaron Sverdlov
9	Investigating the role of female sex hormones in women with asthma	Hayley Scott	Evan Williams, Lisa Wood, Jay Horvat
10	Investigating the impact of air pollution on cardiovascular health	Doan Ngo	Tatt Jhong Haw, Aaron Sverdlov

11	Investigation of shear-activated nanoparticles in intracerebral hemorrhage.	Daniel Beard	Neil Spratt
12	The discovery of cardioprotective drugs in Carfilzomib-induced cardiotoxicity	Doan Ngo	Lohis Balachandran, Aaron Sverdlov
13	Investigating changes in antigen presentation between types of vaccines.	Alex Spencer	Alexandra Brown
14	Elucidating the Mechanism that Initiates Premature Birth	Jonathan Hirst	Tamas Zakar
15	Improving IVF outcomes by enhancing sperm production	Mark Baker	Xu Dong Zhang
16	Development of New Therapeutics for the Treatment of Preeclampsia	Kirsty Pringle	Saije Endacott
17	Characterising placentas from women with gestational diabetes	Saije Endacott	Kirsty Pringle, Jessie Sutherland
18	Trends in Stillbirth in Hunter New England Local Health District	Jonathan Hirst	Craig Pennell
19	The association between prenatal maternal physical activity and fetal brain development	Sarah Valkenborghs	Oun Al-Iedani, Saadallah Ramadan
20	Establishing pregnancy-specific accelerometer data processing cut-points to enable accurate measurement of physical activity in pregnant women.	Sarah Valkenborghs	Mitch Duncan, Elroy Aguiar, Mitch Naughton
21	Prenatal maternal physical activity and stress – downstream effects on offspring brain development	Sarah Valkenborghs	Marina Paul, Tegan Grace
22	Prenatal maternal physical activity, stress and umbilical cord blood neurosteroid concentrations	Sarah Valkenborghs	Julia Shaw
23	Nutraceutical effects on neurometabolism in people with MS	Oun Al-iedani	Saadallah Ramadan, Jeannette Lechner-Scott
24	The role of the brainstem in asthma associated cough: does bushfire smoke exacerbate the problem?	Melissa Tadros	Phillip Jobling, Henry Gomez
25	Impact of NKI antagonist on stroke brain proteome	Kirsten Coupland	Neil Spratt
26	Brain tumour volume delineation using MRI	Paul Tooney	Saadallah Ramadan, Oun Al-iedani
27	Brain circuits involved in reproductive tract signalling.	Phil Jobling	Brett Graham
28	Preventing Preterm Birth: Characterisation of Myometrial Transformation	Marina Paul	Jonathan Paul

A) **Project Title:** Effect of bushfire and bushfire smoke on cardio and cerebrovascular diseases: evidence from 20 years of hospitalized patient data from Hunter New England Local Health District.

B) **Supervisory Details (must be completed):**

Primary Supervisor Name: Professor Neil James Spratt
Location: MSB/HMRI
Email: neil.spratt@health.nsw.gov.au
Phone: 0403 363 981

Co-Supervisor Name (must be completed):
Location: Level 3 East, HMRI Building, Lot 1 Kookaburra Cct, New Lambton Heights NSW 2305.
Email: abir.hasnain@newcastle.edu.au
Phone: 0450 394 297

** Up to 2 additional co-supervisors can be included (maximum 4 supervisors in total), please copy and paste the above information for each additional co-supervisor **

C) **Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach: *(MAX HALF-PAGE).***

In many places of the globe, bushfires are an unavoidable and growing threat. Global warming increases the amount of very hot and dry days in certain areas, making bushfires more common. Both gaseous and particle matter are present in high amounts in bushfire smoke and are of major concern due to their potential influence on health. Australia had a severe bushfire season in 2019-20. We recently did a retrospective study to assess the impact of the 2019-20 bushfire season and high smoke days on cerebrovascular disorders, and discovered a singinficantly increased rate of hospitalisation for acute ischemic stroke on high bushfire smoke days. However, the results of this small-scale research need to be validated, and with larger numbers we believe we will be able to identify the most susceptible populations during wildfire season and heavy smoke days in order to design suitable intervention and preventative strategies.

Therefore, this study aims to:

- assess the effect of bushfire period and high smoke days on daily number and monthly incidence rate of hospital admissions across different sub-groups of cardio- and cerebro-vascular diseases.
- identify clinico-demographic markers for increased incidence and hospitalizations of cardio- and cerebro-vascular diseases during bushfire and high-bushfire smoke days.

Twenty-three years of hospitalisation data has already retrieved from the Hunter New England Local Health District local electronic database for admitted patients with cardio- and cerebrovascular diseases, which includes information on discharges from

all publicly funded hospitals. All cases are also coded according to the World Health Organization's (WHO's) International Classification of Diseases, 10th Revision (ICD-10). Ethics approval has already been taken from the Hunter New England Research Ethics Committee (2020/ETH01801).

D) Laboratory Location

Level 3 East, HMRI Building, Lot 1 Kookaburra Cct, New Lambton Heights NSW 2305.

A) Project Title: Central role of a master regulator of cellular signalling in development, function and disease of the epidermis

B) Supervisory Details (must be completed): Dr Severine Roselli
Email:severine.roselli@newcastle.edu.au
Phone: 49215915

Co-Supervisor Name (must be completed):
Location: LS3-37
Primary Supervisor Name: A/Prof Nikki Verrills
Location: LS3-46
Email: nikki.verrills@newcastle.edu.au
Phone: 4921 5619

Co-Supervisor Name (must be completed): Dr Heather Murray
Location: LS3-37
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Phone:

C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach: *(MAX HALF-PAGE).*

Protein phosphatase 2A (PP2A) is a master regulator of cellular signalling, controlling over 50% of serine/threonine dephosphorylation in cells. We recently generated the first constitutive (full body) knockout mouse model of the *Ppp2r2a* gene encoding the B55α regulatory subunit of PP2A which allowed us to reveal some of its essential functions. Homozygous knockout of *Ppp2r2a* is embryonic lethal and associated with strongly impaired skin formation, as well as limb and neural defects. The skin defect is characterized by incomplete epidermal barrier acquisition, associated with poorly differentiated stratified epithelium with weak attachment to the underlying basement membrane (Panicker *et al* 2020 https://www.frontiersin.org/articles/10.3389/fcell.2020.00358/full) .

These findings led us to hypothesize that B55α is involved in the regulation of keratinocyte cell adhesion to the basement membrane, a crucial component of skin integrity and the wound healing process. To achieve this we have generated a conditional knockout mouse where *Ppp2r2a* is deleted from keratinocytes. We are also generating a conditional model where *Ppp2r2a* will be specifically deleted from fibroblasts. These two unique models will enable us to define the relative contribution of B55α in the two major cell types of the skin.

This project will contribute to testing our hypothesis through the following aims:
Aim1- Characterize keratinocyte and fibroblast specific *Ppp2r2a* knockout mouse models.
Aim2- Characterize the keratinocyte adhesion defect to the underlying basement membrane using a combination of skin tissue from the mice and human keratinocyte cell lines to allow wound healing *in vitro* studies.

Aim3- Perform proteomic and phosphoproteomic studies to decipher the network of signalling pathways controlled by B55α in the skin.

Overall, the study will delineate the role of B55α in epidermal development, adhesion and wound healing, and thus could lead to identification of new targets for a range of debilitating skin disorders. The student will be trained in cutting edge biochemistry, cell biology and animal techniques in a dynamic laboratory environment, and the findings published in a high impact international journal.

D) **Laboratory Location**

Life Sciences Building LS3-26 and LS3-17

A) Project Title: Targeting a novel mechanism of therapy resistance in ER+ breast cancer.

B) <u>Supervisory Details (must be completed)</u>: as above

Primary Supervisor Name: A/Prof Nikki Verrills
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Co-supervisor Name: Dr Severine Roselli
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Co-Supervisor Name (must be completed): Dr Heather Murray
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C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach: *(MAX HALF-PAGE).*

Breast cancer kills over 3,000 Australians every year. Estrogen receptor-positive (ER+) tumours make up >70% of all breast tumours, and at least initially respond well to endocrine therapies. However, therapy resistance is a major cause of disease relapse and mortality. We have identified a novel mechanism of resistance to endocrine therapy. Large scale genomic analyses have identified recurrent loss of the *PPP2R2A* gene in poor outcome breast cancers, most commonly in ER+ tumours. *PPP2R2A* encodes the protein phosphatase 2A regulatory subunit protein, PP2A-B55α. Until now, why low B55α predicted for poor outcome was not known. We have discovered that B55α inhibition induces resistance to endocrine therapy in ER+ breast tumour cells, via increased activity of multiple cellular survival and growth signalling pathways. Importantly, we further found that B55α-low ER+ breast tumours respond to pharmacological PP2A activators, and this sensitizes to endocrine therapy.

Hypothesis: Boosting the activity of the PP2A enzyme via PP2A pharmacological activation is an effective treatment strategy for endocrine resistant ER+ breast cancer.

We will test this hypothesis in vivo, using a combination of cell- and patient-derived xenografts to address the following AIMS:

1. Determine the in vivo efficacy of pharmacological activation of PP2A in a panel of endocrine resistant ER+ breast cancer cell derived xenografts (CDXs).

2. Test whether PP2A activation can potentiate endocrine therapies in treatment naïve and endocrine resistant patient derived xenografts (PDXs).

This innovative study has the potential to identify new approaches to treat therapy resistant breast cancer, and ultimately lead to improved survival for breast cancer patients.

The student will be part of a passionate and dynamic research team and will learn a range of techniques including animal handling, molecular techniques, state of the art mass-spectrometry based proteomics and phosphoproteomics, bioinformatics analyses, cell culture, cytotoxicity assays, western blotting, The findings from this project will be published in a high impact international journal and could identify novel therapeutic approaches for treating therapy-resistant breast cancer.

D) **Laboratory Location**
Life Sciences Building LS3-26 and LS3-17

A) Project Title: How does fatigue accumulate over a work shift, and how does this influence performance?

B) <u>Supervisory Details (must be completed)</u>:

Primary Supervisor Name: Dr Mitchell Smith
Location: Ourimbah/Callaghan
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Co-Supervisor Name (must be completed):
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Co-Supervisor Name: Prof. Rohan Walker
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Email: rohan.walker@newcastle.edu.au
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** Up to 2 additional co-supervisors can be included (maximum 4 supervisors in total), please copy and paste the above information for each additional co-supervisor **

C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach: *(MAX HALF-PAGE).*

Military personnel, even in non-deployed settings, are frequently exposed to prolonged duty and challenging operational environments. These demanding conditions, inherent to their profession, put them under substantial physical and psychological stress which may predispose them to occupational-related fatigue. This occupational-related fatigue can have mental and physiological contributory factors which influence a range of mental and physical performance outcomes.

This project will be conducted with current serving military personnel and is aimed at elucidating how typical occupational activities influence physiological fatigue-related responses (e.g., heart rate variability, salivary markers [IGA, cortisol], physical performance (e.g., force, power output), perceptual fatigue-related responses (e.g., rating of fatigue scale, NASA-TLX), and cognitive performance (e.g., speed and accuracy of decisions). Participants will be required to undertake their typical work shift (or a simulated analogue) whilst relevant fatigue-related measures are captured continuously or at regular intervals throughout their work.

Fatigue has the potential to negatively influence performance, which in military settings has significant implications. Until we understand the accumulation and influence of this occupational-related fatigue on performance outcomes, we can not develop strategies which attenuate or mitigate fatigue and its impact.

D) Laboratory Location

This project may involve work at Callaghan (MS building) and the RAAF base (Williamtown).

A) **Project Title: Interplay between sex hormones and metabolism in the pathogenesis and severity of asthma**

B) **<u>Supervisory Details (must be completed)</u>:**

Primary Supervisor Name: Jay Horvat
Location: HMRI – Level 2 East
Email: jay.horvat@newcastle.edu.au
Phone: x20220

Co-Supervisor Name (must be completed):
Location: Hayley Scott
Email: Hayley.scott@newcastle.edu.au
Phone: 02 4042 0113

Co-Supervisor Name (must be completed):
Location: Prof Lisa Wood
Email: lisa.wood@newcastle.edu.au
Phone: 02 4921 7485

** Up to 2 additional co-supervisors can be included (maximum 4 supervisors in total), please copy and paste the above information for each additional co-supervisor **

C) **Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach: *(MAX HALF-PAGE).***

In Australia, asthma affects >10% of adults and costs $28 billion per year. The highest burden occurs in women, particularly those with severe asthma. Severe, steroid-resistant disease is the biggest unmet need in asthma therapy. Patients have greatly reduced quality of life, unresolved symptoms and frequent exacerbations. There are few effective therapies for severe asthma, particularly non-type 2 (non-T2) disease, as the underlying mechanisms are largely unknown.

We show that sex hormones affect T2 and non-T2 immune responses and asthma severity, that the oral contraceptive pill may be more effective than steroids in controlling asthma and that hormones mediate these effects by modifying cellular metabolism (immunometabolism). Our idea is to extend upon our findings and identify novel therapies for both T2 and non-T2 severe asthma that target sex hormone-mediated effects on cellular metabolism.

Hypotheses: Sex hormones modify asthma pathogenesis and severity by modulating immunometabolism. Sex hormones, or their metabolic effects, may be therapeutically manipulated to improve control in severe asthma.

Aim:

1. To determine how sex hormone level and manipulation affects immunometabolism in specific immune cell populations and to test novel therapies, in mouse models and cells isolated from subjects with severe asthma

These ground-breaking studies will determine how sex hormones and immunometabolism interact in asthma, and establish whether this varies by asthma severity and by T2/non-T2 phenotype, and identify novel therapeutic strategies for severe and non-severe asthma that harness hormone-mediated effects on immunometabolism.

A) Laboratory Location

HMRI Building – Level 2 East

A) Project Title: The association between prenatal maternal physical activity and fetal brain development

B) <u>Supervisory Details (must be completed)</u>:

Primary Supervisor Name:	**Dr Sarah Valkenborghs**
Location:	**MS305c**
Email:	**sarah.valkenborghs@newcastle.edu.au**
Phone:	**40420819**
Co-Supervisor Name (must be completed):	**Dr Oun Al-Iedani**
Location:	**HMRI Imaging Centre**
Email:	**Oun.Alledani@newcastle.edu.au**
Phone:	**40420019**
Co-Supervisor Name (must be completed):	**Associate Professor Saadallah Ramadan**
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Phone:	**40420573**

** Up to 2 additional co-supervisors can be included (maximum 4 supervisors in total), please copy and paste the above information for each additional co-supervisor **

C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach: *(MAX HALF-PAGE).*

Accumulating pre-clinical evidence shows physical activity during pregnancy has direct beneficial intergenerational effects on baby brain development. That is, maternal physical activity during pregnancy enhances offspring brain health via enhancements in brain growth factor expression, neurogenesis and brain structure. Our lab's recent scoping review reveals that little is known about the direct intergenerational effects of maternal physical activity in humans. Therefore, the aim of this project will be to investigate the relationship between maternal physical activity levels during pregnancy and fetal brain development.

This world-first pilot study will be conducted within the pre-existing and ongoing NEW1000 longitudinal pregnancy cohort study at HMRI which aims to elucidate mechanisms responsible for the developmental origins of health and disease (DOHaD). Physical activity during pregnancy will be measured by an accelerometer and analysed using the GGIR pipeline in R-studio. Fetal brain development will be measured via in-utero MRI at 36-week's gestation and analysed using cutting-edge semi-automated fetal brain segmentation pipelines. This project will be well-suited to a student with knowledge of/interest in learning coding.

Elucidating the fetal brain health benefits of physical activity during pregnancy will empower and motivate more women to remain physically active during pregnancy – in the same way that pregnant women alter their diet, as well as stop smoking and consuming alcohol.

D) Laboratory Location: This project will involve being located across both Callaghan (MS building) and HMRI (clinical trials unit, and Imaging Centre) sites.

A) Project Title: Establishing pregnancy-specific accelerometer data processing cut-points to enable accurate measurement of physical activity in pregnant women.

B) <u>Supervisory Details (must be completed)</u>:

Primary Supervisor Name:	**Dr Sarah Valkenborghs**
Location:	**MS305c**
Email:	**sarah.valkenborghs@newcastle.edu.au**
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Co-Supervisor Name (must be completed):	**Professor Mitch Duncan**
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Co-Supervisor Name (must be completed):	**Dr Elroy Aguiar**
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Phone:	**n/a**
Co-Supervisor Name (must be completed):	**Dr Mitch Naughton**
Location:	**EXSS Offices, Ourimbah**
Email:	mitch.naughton@newcastle.edu.au
Phone:	**0413288621**

** Up to 2 additional co-supervisors can be included (maximum 4 supervisors in total), please copy and paste the above information for each additional co-supervisor **

C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach: *(MAX HALF-PAGE).*

Tri-axial accelerometers are the gold-standard approach to objectively measuring habitual physical activity. Accelerometer data is processed using cut-points (specific threshold values) to categorize the intensity of physical activity a person was performing – generally, the more and the faster the accelerations detected, the higher the estimate of the intensity of physical activity. However, the relative intensity of any movement varies according to a number of factors – the most common being age, fitness and health state. This requires use of different cut-points for different population groups to ensure that we are estimating the intensity of their physical activity as accurately as possible. As part of the NEW1000 pregnancy cohort study at HMRI, our lab is using accelerometers to monitor the physical activity of hundreds of pregnant women from the Newcastle-Hunter region. At present

there are no pregnancy-specific accelerometer data processing cut-points and this limits our capacity to estimate their physical activity levels.

This honours project aims to develop and validate pregnancy-specific accelerometer data processing cut-points. Two groups of n=15 pregnant women will be recruited to undertake a series of activities of daily living (e.g., overground walking, treadmill walking, stair climbing, sweeping, etc). During these activities accelerometer data will be collected using an ActiGraph GT9X-Link accelerometer while metabolic data (breath-by-breath gas exchange) will be collected using a COSMED K5 portable gas analyser. Data from the first group will be used to establish the cut-points while data from the second group will be used to validate the cut-points. This project is well-suited to a student who likes working with humans, enjoys processing physiological datasets, and ideally has an interest in physical activity.

D) **Laboratory Location:** This project will involve being located at Medical Sciences building and the HPE building. The project may also involve a small amount of data collection at the Exercise Science facilities on the Ourimbah campus, but this is TBC and can be discussed.

A) Project Title: Prenatal maternal physical activity and stress – downstream effects on offspring brain development

B) <u>Supervisory Details (must be completed)</u>:

Primary Supervisor Name:	**Dr Sarah Valkenborghs**
Location:	**MS305c**
Email:	**sarah.valkenborghs@newcastle.edu.au**
Phone:	**40420819**
Co-Supervisor Name (must be completed):	**Dr Marina Ilicic**
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Co-Supervisor Name (must be completed):	**Dr Tegan Grace**
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Phone:	**4042 0345**

** Up to 2 additional co-supervisors can be included (maximum 4 supervisors in total), please copy and paste the above information for each additional co-supervisor **

C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach: *(MAX HALF-PAGE).*

Prenatal maternal stress is associated with poor neurodevelopment in offspring. Prenatal physical activity may confer resilience to maternal psychosocial stress and nurture offspring neurodevelopment. This project will investigate the cross-sectional relationship between prenatal physical activity with maternal stress and mental health, and offspring neurodevelopment.

This pilot project will be conducted within the pre-existing and ongoing NEW1000 longitudinal cohort study which aims to elucidate mechanisms responsible for the developmental origins of health and disease (DOHaD). The NEW1000 study recruits pregnant women (currently *n*=10-15 per week) during their first trimester through the John Hunter First Trimester Screening Clinic and follows them up at HMRI throughout pregnancy, birth, and post-partum. Hair samples are collected at 20 weeks gestation, from which cortisol can be isolated and used as a biomarker of psychosocial stress during the previous two months. Participants wear an accelerometer for one-week to track their habitual physical activity levels and also complete a battery of physical fitness tests and questionnaires on physical activity and mental health. Infant neurodevelopment is assessed at 6-months post-partum.

Physical activity is associated with mental health in pregnant women but most are not physically active. Elucidating fetal health benefits may motivate women to remain physically active during pregnancy.

D) Laboratory Location: This project will involve being located across both Callaghan (MS building) and HMRI (clinical trials unit and level 3 east wet lab) sites.

A) Project Title: Prenatal maternal physical activity, stress and umbilical cord blood neurosteroid concentrations

B) <u>Supervisory Details (must be completed)</u>:

Primary Supervisor Name:	**Dr Sarah Valkenborghs**
Location:	**MS305c**
Email:	**sarah.valkenborghs@newcastle.edu.au**
Phone:	**02 40420819**
Co-Supervisor Name (must be completed):	**Dr Julia Shaw**
Location:	**HMRI Level 3 East**
Email:	Julia.C.Shaw@newcastle.edu.au
Phone:	

** Up to 2 additional co-supervisors can be included (maximum 4 supervisors in total), please copy and paste the above information for each additional co-supervisor **

C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach: *(MAX HALF-PAGE).*

Prenatal maternal stress is associated with poor neurodevelopment in offspring and may be mediated by decreased concentrations of neurosteroids. Prenatal physical activity may confer resilience to maternal psychosocial stress and nurture offspring neurodevelopment by increasing neurosteroids concentrations. This project will investigate the cross-sectional relationship between prenatal physical activity with maternal stress, umbilical cord blood neurosteroid concentrations, and offspring neurodevelopment.

This pilot project will be conducted within the pre-existing and ongoing NEW1000 longitudinal cohort study which aims to elucidate mechanisms responsible for the developmental origins of health and disease (DOHaD). The NEW1000 study recruits pregnant women (currently *n*=10-15 per week) during their first trimester through the John Hunter First Trimester Screening Clinic and follows them up at HMRI throughout pregnancy, birth, and post-partum. Participants wear an accelerometer for one-week to track their habitual physical activity levels and also complete a battery of physical fitness tests and questionnaires on physical activity, stress and mental health. Umbilical cord blood samples are collected at birth, from which concentrations of neurosteroids such as allopregnenalone can be isolated. Infant neurodevelopment is assessed at 6-months post-partum.

Physical activity is associated with mental health in pregnant women but most are not physically active. Elucidating fetal health benefits may motivate women to remain physically active during pregnancy.

D) Laboratory Location This project will involve being located across both Callaghan (MS building) and HMRI (clinical trials unit and level 3 east wet lab) sites.

A) Project Title: Nutraceutical effects on neurometabolism in people with MS

B) <u>Supervisory Details</u> :

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C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach:

Background: Therapeutic clinical trials have demonstrated the efficacy of many disease-modifying therapies (DMT) including dimethyl fumarate (DMF) and fingolimod in relapse-remitting MS (RRMS) by reducing magnetic resonance imaging (MRI)-detected disease activity.

Recent magnetic resonance spectroscopy imaging (MRSI) methodological improvements have overcome the limitations of single voxel measurement (MRS) and perform now neurometabolic mapping covering the whole brain, with high spatial resolution and short acquisition times.

Hypothesis & aims: Novel MR spectroscopic method can identify a clinically significant metabolic marker associated with a combination of nutraceutical supplements in people with MS.

Hypothesis: Nutraceutical supplements will lead to return to near normalcy of neurometabolic profile in comparison to placebo.

Aim: Evaluate the longitudinal neurometabolic changes of nutraceutical supplements chosen for the benefit on mitochondrial metabolism.

General methods: A 3 Tesla system (Magnetom Prisma, Siemens Healthineers, Erlangen, Germany) at HMRI was used for all imaging and spectroscopic measurements (MRI and MRSI). MRSI data were collected from the people with MS on intervention and compared to placebo to assess the neuro-metabolic changes at baseline and 4 months.

D) Laboratory Location

A) Project Title: The role of the brainstem in asthma associated cough: does bushfire smoke exacerbate the problem?

B) <u>Supervisory Details:</u>

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C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach:

Cough is initiated by airway irritation, whereby sensory receptors along the respiratory tree are activated and transmit this information, via the vagus nerve, into brainstem centres associated with respiration. These signals are then integrated into complex networks, resulting in activation of respiratory, airway and trunk musculature to cause forceful expulsion of air, ie a cough. Alterations at any of the nodes in this pathway can change the way an individual coughs, which can have a significant impact on quality of life. Individuals with asthma are at risk of developing chronic cough, a condition which is exacerbated by exposure to irritants such as air pollution and particulate matter.

Hypothesis: Asthmatic mice exposed to bushfire smoke will show greater neuronal and glial activation in their brainstem cough centres and alterations in their sensory receptors within the upper airways compared to non-asthmatic mice, and that this will be exacerbated in mice with severe asthma.

Aim 1: To investigate the activation of both neurons and glia within cough centres in the brainstem in control, moderate and severe asthmatic exposed to low and high doses of bushfire smoke, and correlate these levels of activation with physiological measurements of airway hyperresponsiveness.

Aim 2: To investigate the sensory nerve terminals and their receptors within the trachea of control, moderate and severe asthmatic exposed to low and high doses of bushfire smoke, and correlate these changes with physiological measurements of airway hyperresponsiveness.

Methods: The honours student will use a combination of anatomical techniques (embedding, sectioning, and immunofluorescence) to assess both neurons and glia within the brainstem, as well as sensory nerve terminals within the trachea. Automated cell counting and measurements of morphology will be applied to tissue examining glial activation. Organ baths will be utilised to measure contractility of upper airway smooth muscles.

D) **Laboratory Location:** Medical Sciences Building, labs 3.12 and 4.14

A) Project Title: Impact of NKI antagonist on stroke brain proteome

B) <u>Supervisory Details (must be completed)</u>:

Primary Supervisor Name:	Dr. Kirsten Coupland
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** Up to 2 additional co-supervisors can be included (maximum 4 supervisors in total), please copy and paste the above information for each additional co-supervisor **

C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach: *(MAX HALF-PAGE).*

Background: A serious complication of large strokes is swelling of the brain (cerebral oedema). One type of oedema occurs when the blood brain barrier breaks down which allows blood and other substances to leak into the central nervous system. This sets off a chain reaction part of which involves the release of substance P, a which has been demonstrated to play a role in the formation of cerebral oedema.

Treatment options for oedema involve highly invasive surgery, or osmotic and pharmacological interventions which are yet to be demonstrated to be capable of independently improving outcomes for stroke patients. A promising novel pharmacological intervention is neurokinin-1 (NKI) receptor antagonists. These drugs block the NK1 receptor which binds to substance P. Trials of one NK1 receptor antagonist in a large animal model of stroke demonstrated that it is as effective as surgical intervention at preventing oedema-related exacerbation of stroke. As with any drug, there is the potential that NKI receptor antagonists have off-target effects that assist in the protective effect after stroke.

Hypothesis: The NKI antagonist triggers changes to the brain proteome that are likely protective after stroke.

Aim: Characterise changes to the brain proteome after stroke that are likely due to NKI treatment.

Experimental Approach: Using brain tissue from an ovine (sheep) model of stroke (provided by our collaborators at the University of Adelaide) we will extract proteins for analysis by mass spectrometry. These sheep have had a surgically induced stroke and been allowed to recover for six or 28 days. Surgical control animal brain tissue will be the comparator. Stroke animals were treated with a NK1 receptor antagonist. Proteins will be extracted from both the stroke hemisphere (ipsilateral) and the non-stroke hemisphere (contralateral). Peptides generated from

extracted proteins will be analysed using mass spectrometry. Bioinformatic analysis will then allow us to map the identified peptides to proteins. From there we will use QIAGEN Ingenuity Pathway Analysis (IPA) software to determine which canonical pathways and disease processes are altered by NKI treatment and whether they are more or less activated after NK1 treatment.

D) Laboratory Location: LS 4.27

A) **Project Title:** Brain tumour volume delineation using MRI

B) <u>Supervisory Details</u>:

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C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach.

Background: Radiological imaging of the brain is an essential component in the treatment of brain tumours. MRI is routinely performed to visualise these tumours, which helps to plan surgical resection and radiotherapy treatment. However, the tumour is made up of multiple regions, not all of which should be targeted by each treatment. The tumour margins are usually estimated based on manual interpretation of the MRI images, but a more accurate and efficient method of delineating these margins is needed.

Hypothesis: Standard/conventional volumetric MRI images/data can be better utilised to accurately define the different regions in brain tumours.

Aims: To develop a means/method/process of differentiating/delineating/segmenting/defining different radiological tumour regions in the brain (such as the tumour core, the region of infiltration, the peritumoral oedema, and the active tumour region).

Methodological Approach: MRI scans were performed at the HMRI Imaging Centre on a 3T Siemens scanner. This data can be used to develop and test techniques of defining the tumour margins. These methods will be developed using software processing tools, specific to the analysis of MRI data.

The student will be introduced to MRI data and the processes involved in interpreting and manipulating it to provide useful information.

D) Laboratory Location

Hunter Medical Research Institute (HMRI)

A) Project Title: Brain circuits involved in reproductive tract signalling.

B) <u>Supervisory Details:</u>

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C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach:

Pain from the reproductive tract is poorly characterised compared with pain from other tissues. While the location of neurons within the spinal cord have been partly characterised, the location of neurons within the brain is less well known.

Hypothesis: Neurons activated by vaginocervical stimulation will activate regions of the central nervous system typically excited by somatic painful stimuli but also stimulate regions involved in visceral control.

Aim 1: To characterise the distribution of sensory axons in the female reproductive tract expressing markers of nociceptive neurons.

Aim 2: To map the location of neurons within the central nervous system following optogenetic stimulation of axons innervating the cervix and vagina.

Methods: You will use a combination of anatomical techniques (embedding, sectioning, and immunofluorescence) to assess the distribution of sensory axons within the female reproductive tract. For the functional experiments, following optogenetic vaginocervical stimulation, you will use immunofluorescence to look for neurons expressing markers of excitation and map these within spinal cord and brain regions involved in sensory processing.

D) Laboratory Location: Medical Sciences Building, labs 409 and 414A

A) Project Title: Preventing Preterm Birth: Characterisation of Myometrial Transformation

B) Supervisory Details (must be completed):

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** Up to 2 additional co-supervisors can be included (maximum 4 supervisors in total), please copy and paste the above information for each additional co-supervisor **

C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach: *(MAX HALF-PAGE).*

Preterm birth (birth prior to 37 completed weeks of gestation) is the leading cause of death and disease in children <5 years of age worldwide. Each year, approximately 15 million babies are born preterm. You can help improve our understanding of premature labour!

When a woman goes into labour, either at term or preterm, the myometrium (uterine smooth muscle) transforms from a relaxed to a contractile phenotype. This transformation coincides with increased expression of contraction-associated proteins (CAPs) and decreased expression of relaxation-association proteins (RAPs). Importantly, we have discovered that when myometrium biopsied from pregnant women who are not in labour is placed into culture, the 'non-labouring' tissue transforms to a 'labouring phenotype', whereby some important CAPs are upregulated and important RAPs are downregulated, the same as labour onset in vivo. Additionally, when we place strips of non-labouring myometrium in our organ bath contraction assay, the tissue transitions from being non-contractile to contractile across a period of 2 – 3 hours. You can help us understand how!

You will attend Caesarean section deliveries at John Hunter Hospital (you will see babies being born!) to collect uterine smooth muscle biopsies. You will then use fundamental scientific techniques, such as quantitative PCR and Western blotting, to compare freshly biopsied non-labouring myometrium against myometrium that you transition to a labouring, contractile phenotype. By doing this, you will characterise the important changes that occur leading to the onset of labour, which is directly relevant to understanding preterm birth.

D) Laboratory Location: HMRI, Level 3 East Wing (Mothers and Babies Research Program).

A) **Project Title:** Alcohol use disorder: Understanding the role of the serotonin system in mice.

B) **<u>Supervisory Details:</u>**

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C) **Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach:** Alcohol misuse is by far Australia's most problematic substance use disorder. Alcohol use disorder is a relapsing brain disease that persists for life. Treatments for alcohol use disorder exist, but they are ineffective at a population level and have low adherence rates. Treatments can be improved by identifying the neurochemical mechanisms driving relapse to inform targeted medication development. For several years, we have used rodent models to identify the brain mechanisms driving relapse to alcohol use. Unfortunately, these studies that aimed to 'forward translate' findings from animal models to the clinic have had limited success. Our lab uses an alternate strategy where we reverse translate successful studies in humans back into animal models. Our recent clinical data showed that lorcaserin, a serotonin$_{2C}$ receptor agonist, reduced craving for alcohol in individuals with alcohol use disorder. Unfortunately, lorcaserin was subsequently withdrawn from the market due to concerns over potential off-target effects with long-term use. Our clinical findings, along with several decades of human and animal research, provide evidence for targeting the serotonin system for the treatment of relapse to alcohol use. This project aims to use our clinical findings to reverse translate to animals to examine new medications for relapse prevention. It is hypothesized that manipulation of the serotonin$_{2C}$ receptor system and associated neural pathways will prevent relapse to alcohol use in mice. This project will focus on mouse behaviour, small animal surgery and neural manipulation techniques.

D) **Laboratory Location:** Bioresources Building

E) Project Title Improving fertility education in Australian adolescents.

F) Supervisory Details:

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G) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach:

Fertility information is a critical component of comprehensive sexuality and sexual health education, but the extent that adolescents are taught or informed about fertility is unknown in Australia. We examined knowledge of fertility using an anonymous, online survey of >2,600 adolescents aged 15-18 in Australia. Respondents were asked to report their age, and future parenting intentions. Respondents also completed thirteen knowledge-based multiple-choice items about sexual and reproductive health. Findings from the survey indicated average knowledge of fertility was significantly poorer compared to average knowledge of reproductive and sexual health content linked to the national curriculum. In addition, 30 participants were invited to participate in focus groups to further explore their sexual and reproductive health educational experiences and needs, with a focus on fertility. These findings will help inform the development of a pilot educational program to improve fertility knowledge for adolescents as well as provide recommendations for the implementation of an education program in Australian high schools.

Aims:

1. To conduct a qualitative thematic analysis of the focus group data to identify key themes related to fertility education.

2. To work with our youth advisory group to develop, test and evaluate a pilot educational session on improving fertility knowledge to our target audience.
3. To develop a series of recommendations for fertility education in Australian high schools based on evidence from the knowledge survey and focus groups.

Hypothesis: Overall fertility knowledge is low in Australian adolescents due to limited exposure to factual and engaging content during high school education. Australian adolescents have valuable insights into how reproductive and sexual health education should be offered and delivered.

In this project, the analysis of these findings will be used to provide evidence that including fertility content explicitly within Australia's national curriculum can increase adolescent understanding of fertility.

H) Laboratory Location HMRI Level 3 East

A) **Project Title: Mechanisms of sex-based differences in cachexia and heart muscle loss during colorectal cancer**

B) **<u>Supervisory Details (must be completed)</u>:**

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** Up to 2 additional co-supervisors can be included (maximum 4 supervisors in total), please copy and paste the above information for each additional co-supervisor **

C) **Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach: *(MAX HALF-PAGE).***

Severe weight loss (cachexia) occurs in ~50% of cancer patients, characterised by loss of skeletal muscle and adipose tissue mass. Cancer-associated cachexia is a whole-body condition that affects multiple organs and tissues, and notably, can result in loss of heart muscle mass and poor outcomes such as heart failure, reduced quality of life survival. Limited studies suggest that cachexia, including that of the heart, occurs disproportionately in men, however, the mechanisms behind this disadvantage and the relative protection of women are not well understood. In a murine model of cancer-induced cachexia vs healthy controls we **<u>Aim</u>**: **1)** To investigate different morphological changes in male/female murine hearts; **2)** To investigate whole-transcriptomic mechanisms in male/female murine heart tissues; **3)** To investigate molecular differences between male/females in other major organs. **Hypothesis:** Male mice will display a worse cardiac phenotype accompanied by adverse molecular changes in multiple organ tissues compared to female mice; and that females may possess protective mechanisms. **Experimental plan**: We have previously conducted a mouse model as follows: Male and female wild-type C57BL/6 mice subjected to the AOM-DSS model of colorectal cancer, in parallel with healthy controls. Histological slides and echocardiography data collected during this model will be analysed to address A**im 1**. Stored heart tissues will be used to conduct RNA-seq, bioinformatic pathway enrichment analyses, and validation via western blot/immunohistochemistry to address **Aim 2.** Stored skeletal muscle and liver tissues will be used to conduct qPCR and western blot analyses to address **Aim 3.** These preliminary experiments will help us to identify detrimental and/or protective mechanisms involved in cancer-induced cachexia, which may lead to future treatment opportunities that can improve the quality of life and survival of patients suffering from cachexia.

D) Laboratory Location

Newcastle Cardio-oncology Centre of Excellence

Hunter Medical Research Institute; Level 3 East

Project Title: Investigating the role of female sex hormones in women with asthma

B) Supervisory Details:

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C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach:

In Australia, asthma affects >10% of adults and costs $28 billion/year. Asthma is worse in women, suggesting female sex hormones may have a role. We have shown that women using the contraceptive pill have fewer asthma symptoms and less airway inflammation than women not using the contraceptive pill. This may be due to the contraceptive pill preventing cyclical sex hormone fluctuations and eliminating spikes in estrogen and/or progesterone levels, which could influence immune responses. We therefore hypothesise that the contraceptive pill reduces asthma symptoms in women with asthma, and that these effects are modulated by the immune system.
The aims of this project are:
1. To characterise the association between sex hormone levels, immune markers, and asthma symptoms, in women with asthma; and
2. To determine the modifying effect of contraceptive pill use.

Blood samples will be collected by the clinical team and delivered to the laboratory for analysis. This project will include two groups: 1) premenopausal women with asthma using the contraceptive pill, and 2) premenopausal women with asthma not using any hormonal contraception.
The student will receive training and support to complete laboratory analyses on blood samples, which will include flow cytometry, PBMC isolation and PBMC culture. Flow cytometry will be completed on whole blood to determine the proportion and activation of immune cell subsets. PBMC's will be isolated from whole blood via density centrifugation. PBMC's will then be pre-treated with testosterone alone, or combinations of estrogen and progesterone to mimic fluctuations in the menstrual cycle. PBMC's will then be stimulated with various stimuli to mimic both obesity and a viral infection. Training and support will be provided by the supervisors throughout the project,

including for statistical analysis, presentation of the study findings, and preparation of the Honours thesis.

D) Laboratory Location HMRI Building

A) Project Title: Investigating the impact of air pollution on cardiovascular health

B) Supervisory Details (must be completed):

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C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach: *(MAX HALF-PAGE).*

Exposure to particulate matters (PMs) from air pollution from natural disasters (e.g., bushfire), industry (e.g., coal mining), and urban pollution (e.g., traffic) are becoming a major public health challenge and impose substantial economic burdens in Australia. Various studies have shown that exposure to these PMs have been linked with increased hospitalisation due to cardiovascular adverse events (CVAEs) and even death. CVAEs such as cardiac arrest, coronary heart disease, cardiac arrhythmia, and heart failure is one of the major disease burdens. Current interventions/advises are limited and only involved exposure/risk reduction by staying indoor and/or wearing facial masks. However, there is no 'safe' lower exposure level and CVAEs can occur at levels below current regulatory standards. The is a lack of effective intervention is largely due to a significant gap in knowledge pertaining to the underlying molecular mechanisms of air pollution PM-induced CVAEs.

To address this clinical urgency, we now propose an exciting and important study to investigate the effects of two air pollution PMs (bushfire PM and coal dust) on cardiovascular health. The proposed study will use a combination of primary human cardiomyocyte cell cultures and cutting-edge discovery science techniques (RT^2 Profiler PCR Arrays and RNA-sequencing) to determine whether if there is a common molecular mechanism that underlie PM-induced CVAEs. We **hypothesised** that air pollution PMs, in particular bushfire PM and coal dust, elicit a common gene signature and molecular mechanism to induce cardiomyocyte dysfunction and in that lead to CVAEs. We **aim** to **1)** delineate the effects of air pollution PMs on primary human cardiac cell cultures, **2)** delineate potential overlapping molecular mechanisms with next-generation RNA sequencing, and **3)** validate these findings with immunoassays (e.g., western blots, ELISA).

These exploratory studies will help us gain crucial insights and better understanding on how air pollution PM exposures provokes CVAEs. Importantly, a common mechanism may reveal novel biomarkers and reveal novel therapeutic targets/interventions to mitigate the detrimental effects of PM exposures, reduce healthcare burden, and improve cardiovascular health of Australians.

D) Laboratory Location

Hunter Medical Research Institute, Level 3 East
Centre of Excellence Newcastle Cardio-Oncology

A) **Project Title:** Investigation of shear-activated nanoparticles in intracerebral hemorrhage.

B) **Supervisory Details:**

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C) **Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach:**

Background: Our group have developed a novel shear-stress activated vasodilating nanoparticle therapy that can selectively enhance collateral blood flow around the site of blockage to preserve brain tissue following ischaemic stroke. We believe our novel nanoparticle therapy could be administered to stroke patients in the ambulance to slow down the rate of brain cell death, "buying" the patient time to be transported to hospital for reperfusion therapy. However, prehospital administration of stroke therapies is complicated by the inability to differentiate ischaemic (blockage) from haemorrhagic (bleeding) stroke before the patient arrives at hospital. Therefore, for our novel nanoparticle therapy to be used in the ambulance we must show that it is safe to be administered in haemorrhagic stroke.

Hypothesis and aims: We hypothesise that our nanoparticle therapy will not exacerbate brain damage in haemorrhagic stroke. To test this hypothesis our aim is to determine the effect of nanoparticle administration on brain damage in a model of intracerebral haemorrhage (haemorrhagic stroke).

Experimental Approach: Twelve-week-old Wistar rats will undergo experimental intracerebral haemorrhage (ICH) induced using the collagenase model. Briefly, bacterial collagenase is injected into the striatum where it degrades collagen in the basal lamina of blood vessels leading to spontaneous haemorrhage and bleeding into the parenchyma. Animals will be randomised to receive control or nanoparticles, commencing 25 minutes after ICH, and ending 70 minutes after its onset. Haematoma volume and brain oedema (brain damage) will be scored at 24 hours post ICH.

Laboratory Location: MS504 and F-building.

A) Project Title: Interplay between sex hormones and metabolism in the pathogenesis and severity of asthma

B) <u>Supervisory Details (must be completed)</u>:

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C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach: *(MAX HALF-PAGE).*

In Australia, asthma affects >10% of adults and costs $28 billion per year. The highest burden occurs in women, particularly those with severe asthma. Severe, steroid-resistant disease is the biggest unmet need in asthma therapy. Patients have greatly reduced quality of life, unresolved symptoms and frequent exacerbations. There are few effective therapies for severe asthma, particularly non-type 2 (non-T2) disease, as the underlying mechanisms are largely unknown.

We show that sex hormones affect T2 and non-T2 immune responses and asthma severity, that the oral contraceptive pill may be more effective than steroids in controlling asthma and that hormones mediate these effects by modifying cellular metabolism (immunometabolism). Our idea is to extend upon our findings and identify novel therapies for both T2 and non-T2 severe asthma that target sex hormone-mediated effects on cellular metabolism.

Hypotheses: Sex hormones modify asthma pathogenesis and severity by modulating immunometabolism. Sex hormones, or their metabolic effects, may be therapeutically manipulated to improve control in severe asthma.

Aim:

1. To determine how sex hormone level and manipulation affects immunometabolism in specific immune cell populations and to test novel therapies, in mouse models and cells isolated from subjects with severe asthma

These ground-breaking studies will determine how sex hormones and immunometabolism interact in asthma, and establish whether this varies by asthma severity and by T2/non-T2 phenotype, and identify novel therapeutic strategies for severe and non-severe asthma that harness hormone-mediated effects on immunometabolism.

I) Laboratory Location

HMRI Building – Level 2 East

A) Project Title: The discovery of cardioprotective drugs in Carfilzomib-induced cardiotoxicity

B) <u>Supervisory Details (must be completed)</u>:

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** Up to 2 additional co-supervisors can be included (maximum 4 supervisors in total), please copy and paste the above information for each additional co-supervisor **

C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach: *(MAX HALF-PAGE).*

Background: Increased cancer survivorship represents a remarkable achievement for modern medicine. Unfortunately, though, cancer treatments have inadvertently contributed to cardiovascular damage, significantly threatening the health and quality of life of patients living with, through and beyond cancer. The wide spectrum of anti-cancer drugs and the range of their cardiovascular side effects make clinical detection of cardiotoxicity challenging without targeted and individualized approaches to monitoring and risk management. Cancer cells depend on proteasome function as they have a higher protein synthesis rate compared to normal healthy cells, in which is specifically targeted in cancer cells. Carfilzomib (Cfz) is a proteasome-inhibiting chemotherapy drug that inhibits the cell's proteolytic activity and leads to misfolded protein accumulation, triggering cell death (apoptosis). CFz is an effective chemotherapy and is widely used for multiple myeloma. However, there have been reports on Cfz causing cardiotoxic effects including heart failure, arrhythmias, hypertension, and such. One of many theories proposed for Cfz-induced cardiotoxicity is that cardiomyocytes also exhibited similar proteolytic activity as cancer cells, hence becoming Cfz's target. The cardiotoxicity profiles of Cfz and other proteasome inhibitors (e.g., bortezomib) are limited to date. Consequently, these have led to early disruption or discontinuation of potentially life-saving anti-cancer therapy and restricted cancer survival rates. The discovery of potential cardioprotective drugs may help to discover ways to alleviate cardiotoxicity induced by cardiotoxic anti-cancer drugs.

Hypothesis & Aim: Therefore, we hypothesised that novel cardioprotective therapies are necessary to mitigate Cfz-induced cardiotoxicities while preserving Cfz's effectiveness. This

study aims to screen and identify potentially novel cardioprotective agents from FDA-approved anti-cancer drug panels (more than 1,000 drugs).

Experimental Approach: A series of combinations of Cfz and anti-cancer drugs from an FDA-approved anti-cancer drug panel (co-treatment experiments) will be conducted on primary human cardiomyocytes (HCM) and cancer cell lines. The effectiveness of the anti-cancer drugs mitigating Cfz cardiotoxicity will be assessed by measuring the HCMs viability (Cell-Titre Glo kit), lactate dehydrogenase (LDH), Caspase 3/7 and proteasomal activities. Simultaneously, the potential cardioprotective co-treatments will be tested on cancer cells to ensure that the drug does not compromise Cfz's effectiveness in killing cancer cells.

D) Laboratory Location

Hunter Medical Research Institute, Level 3 East, New Lambton Heights

A) **Project Title: Investigating changes in antigen presentation between types of vaccines.**

B) **<u>Supervisory Details (must be completed)</u>:**
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** Up to 2 additional co-supervisors can be included (maximum 4 supervisors in total), please copy and paste the above information for each additional co-supervisor **

C) **Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach: *(MAX HALF-PAGE).***

Vaccines are one of the most cost-effective tools in animal and human health to reduce the burden of infectious diseases and rely on activation of the adaptive immune system and development of long-lived memory responses. Although a large variety of vaccines platforms are now available (ie mRNA, protein, viral vector) capable of inducing different types of immune responses (ie antibodies and T cells, it is still not clear how this diversity in immune responses occurs.

Central to activation of the adaptive immune system is antigen presentation, a process which involves uptake, processing and presentation of foreign proteins by antigen presenting cells (APCs). These APCs must then migrate from the site of exposure to lymph nodes where they are able to activate antigen specific T and B cells, a process triggered by innate immune signals.

It is hypothesised that the way vaccine antigens are processed and presented shapes the type of adaptive immune response induced. As differences in immunity between vaccines could be due to changes in antigen presentation, this study aims to use multi-parameter flow cytometry to study the early events in immune activation in mice following vaccination.

Aim 1: Develop a flow cytometry panel to measure and phenotype antigen presenting cells.

Aim 2: Use flow cytometry to track antigen uptake and APC activation following vaccination.

Aim 3: Compare antigen uptake and APC activation between different vaccine platforms.

D) **Laboratory Location: HMRI**

A) Project Title: Elucidating the Mechanism that Initiates Premature Birth

B) Supervisory Details:

Primary-Supervisor Name: Jon Hirst
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Co-Supervisor Name: Tamas Zakar
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C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach:

Background: The mechanisms that initiate premature birth is one of the biggest mysteries of human physiology: why are some babies are born prematurely. About 7% of all babies are born prematurely in Australia, and these babies are highly susceptible to complications causing death, permanent disabilities, and chronic diseases later in life. Determining the physiological mechanism leading to birth and its dysregulation causing premature delivery is urgently needed and is of enormous health importance. This project investigates key mechanisms that programme contractile processes toward vulnerability for early birth.

The project hypothesis is: That remodelling of regulatory (enhancer) chromatin regions occurs in the gestational tissues before preterm labour, which changes gene expression patterns and establishes a labour-inducing inflammatory state.

Aims:

1. Isolate amnion epithelial and mesenchymal cells from human placentae after preterm and term birth and perform genome-wide screens of gene expression and chromatin modifications to identify preterm labour-associated changes in gene activity and chromatin structure.

2. To use using primary amnion cell culture models to examine the genomic changes observed from the genome wide screening.

3. To utilize the cell culture system to demonstrate the effect of novel drugs for reverseing the labour-associated changes in expression.

These studies will generate key preclinical data on targets for blocking the upregulation of labour associated genes and lead to establishing new therapies for preventing premature birth.

D) Laboratory Location: HMRI, Level 3E (Mothers and Babies Research Program).

A) Project Title: Improving IVF outcomes by enhancing sperm production

B) <u>Supervisory Details (must be completed)</u>:

Primary Supervisor Name: A/Prof. Mark Baker
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C) Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach: *(MAX HALF-PAGE).*

Title: Improving the rate of IVF success rates for infertile men.

Assisted conception, including in-vitro fertilisation and intracellular injection, is responsible for around 5% of all birth rates. Unfortunately, the technology has a low success rate, with around 18% of all cycles resulting in a live birth. In the case of male-factor infertility, despite using otherwise pristine eggs, success rates are even lower. As such, in cases where only the male is at fault, the female bears the burden of treatment. This includes twice daily hormone injections one month prior to the invasive procedure of having eggs harvested, fertilised, then embryos are placed back through the cervix into the uterus one at a time.

Increased testicular heat stress appears to be a major issue for many men and their fertility. We have developed an advanced understanding of the impact of testicular hyperthermia and the biochemical response germs cells undergo. In this case, a testis specific organelle, known as the chromatid body, undergoes changes in response to increasing temperature. This project will investigate the impact of testicular heat stress and the biochemical changes seen within the chromatid body. Further, this project will work with IVF industry to industry to study the impact of scrotal cooling and determine if we can increase the rates of per-cycle embryo outcomes by improving semen quality in men.

D) Laboratory Location

Ls4.42

A) Project Title: Development of New Therapeutics for the Treatment of Preeclampsia

B) <u>Supervisory Details:</u>

Primary Supervisor Name: Kirsty Pringle
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Co-Supervisor Name: Saije Endacott
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***C)* Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach:**

Preeclampsia affects 3-5% of all pregnancies and causes more than 60,000 maternal and over 500,000 fetal deaths annually. Preeclampsia is associated with maternal hypertension, vascular injury, kidney and liver dysfunction, haemolysis, and seizures. It also increases the risk of fetal growth restriction and preterm birth. Inadequate placentation and subsequent maternal endothelial dysfunction underly the pathogenesis of preeclampsia but the development of new effective therapies are essential.

We have shown that a newly identified molecule, the soluble prorenin receptor (sPRR) causes hypertension, kidney, and endothelial dysfunction, thus contributing to the pathogenesis of preeclampsia in a rodent model. Therefore, inhibiting the activity of the sPRR could be effective in the treatment for preeclampsia. This project will test the effectiveness of novel compounds that target the sPRR as potential new therapies for preeclampsia.

Aims:

1. To test the effectiveness of novel compounds, that are predicted to target the sPRR, to prevent sPRR-induced endothelial dysfunction *in vitro*.
2. To show that novel compounds that are effective at blocking sPRR-induced endothelial dysfunction are also effective at preventing endothelial dysfunction induced by serum from women with preeclampsia.

D) Laboratory Location: HMRI

A) Project Title: Characterising placentas from women with gestational diabetes

B) <u>Supervisory Details:</u>

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***C)* Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach:**

In Australia, diabetes affects approximately 10% of pregnancies worldwide and 13% of pregnancies nationally. Of these, about 9% of women develop gestational diabetes mellitus (GDM), and 1% have pre-existing (type 1 or type 2) diabetes mellitus. The placenta, which separates the maternal and fetal circulations, is sensitive to hyperglycaemia. Alterations in placental structural development and subsequent vascular dysfunction are present in over 85% of pregnant women with diabetes. It is these placental morphologies that alter transport of nutrients wastes and oxygen across the placenta and hence impact fetal growth in women with GDM. The mechanisms that underpin the placental abnormalities associated with GDM are poorly understood, despite their impact on transplacental transport and fetal development.

Aims:

1. To examine differences in the molecular pathways involved in tissue injury, oxidative stress and glucose transport/metabolism in the placentas of women with GDM or with normal glucose tolerance.
2. To assess the impact of hyperglycaemia on the placental expression of molecular pathways involved in tissue injury, oxidative stress and glucose transport/metabolism in placental explants *in vitro*.

Experimental Approach:

Aim 1: Placentae from pregnant women with normal glucose tolerance and from women with GDM (n=40/group) have already been collected and stored. Using these stored samples, the expression/localisation of markers of tissue injury, oxidative stress and glucose transport/metabolism will be examined by qPCR, IHC or immunoblotting.

Aim 2: Placental explants will be isolated from placentae of uncomplicated normal glucose tolerance pregnancies and cultured in normoglycaemic [5 mM glucose] or hyperglycaemic [25 mM glucose] conditions. Explants and supernatant will be collected to quantify the expression of markers of tissue injury, oxidative stress and glucose transport/metabolism as outlined in Aim 1.

This project will improve our understanding of the mechanisms underlying the structural and functional changes observed in the placentae of women with GDM.

D) Laboratory Location: HMRI

A) Project Title: Trends in Stillbirth in Hunter New England Local Health District

B) <u>Supervisory Details (must be completed)</u>:

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C)* Background and Summary of Proposed Research, including a clear hypothesis, aims and experimental approach: *(MAX HALF-PAGE).

There has been a decline in the rate of stillbirths across our Hunter New England Local Health District over the last 10 years but the mechanisms behind this decline have not been evaluated. There are a number of recognisable risk factors for stillbirth and dedicated practice changes have been developed to address these risk factor. However, we neither have a grasp on which type of stillbirths have been reducing in number nor do we understand which type of stillbirths remain prevalent at our unit. Without this information, we cannot reliably assess which service initiatives have been most impactful on the rate of stillbirth in our unit, and which areas of need remain unmet.

Aim:

1. Has there been a change in the incidence of stillbirth in the Hunter New England Local Health District over the last 12 years?
2. Has the types of stillbirth changed (based on PSANZ classification) changed over the last 12 years?
3. Does the change in 'pattern' of stillbirths relate to any system changes/education packages etc. over the last 12 years?

Methods: This retrospective cohort study will extract data from the Obstetrix and eMaternity databases across HNELHD over the past 12 years. Stillbirths will be classified by PSANZ criteria and trends over time will be assessed.

D) Laboratory Location: HMRI