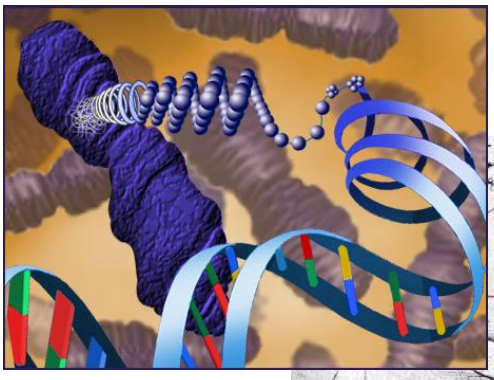
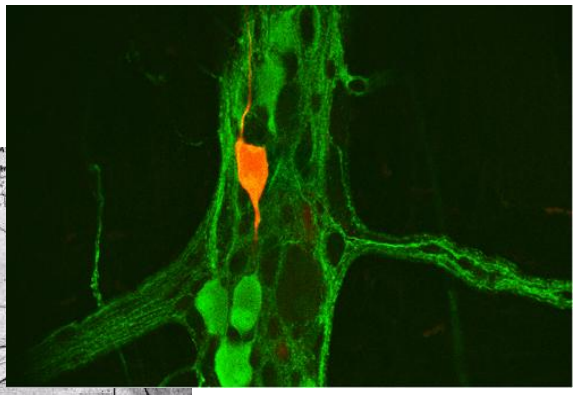
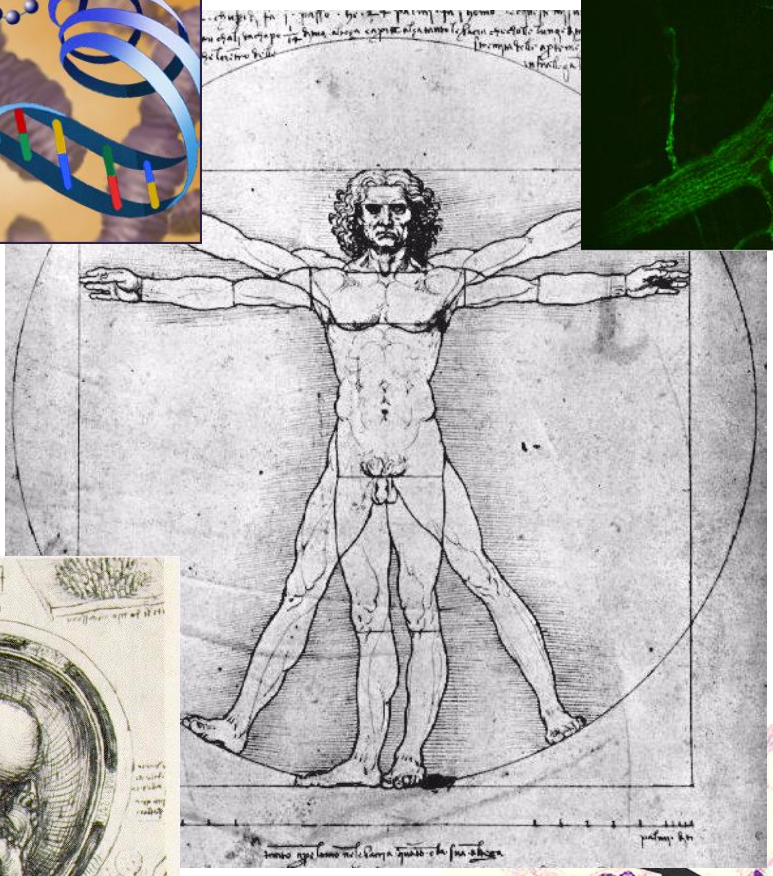
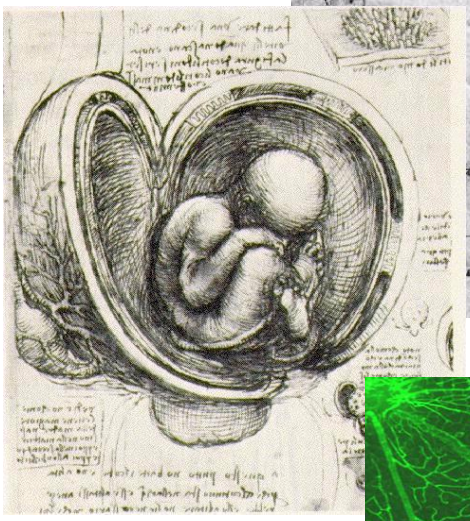
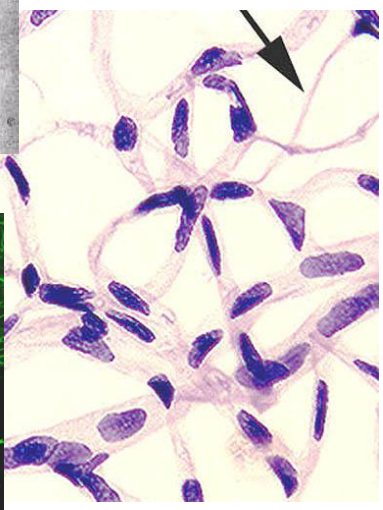
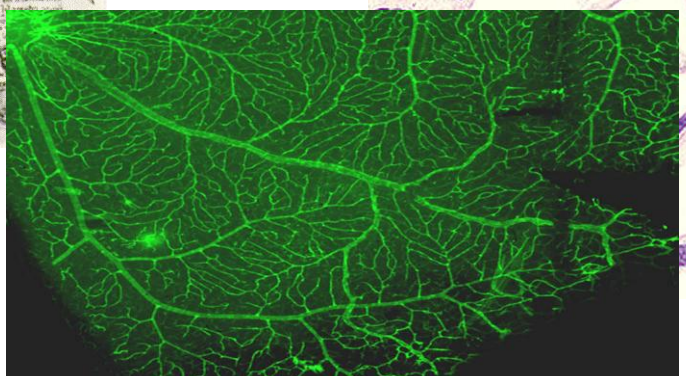
THE UNIVERSITY OF MELBOURNE

## Department of Physiology

# MBiomedSc / BBiomed(Hons) / BSc(Hons) Information Booklet 2016

Edited by
Ms Lesley Robinson
September 2015

Cover graphics: Department of Physiology, The University of Melbourne.
DNA graphic: Roche Pharmaceuticals
Drawings by Leonardo Da Vinci – http://www.visi.com/~reuteler/leonardo.html

# Interested in research in Physiology ?

The characters above represent the Chinese pictographs for the word Physiology, written in an archaic form as used several thousand years ago. The first character represents a tree with a new leaf and came to mean life. The second character is a composite of a dissecting tool and a person deciding the natural plane along which to split a previous stone. This came to mean structure or logic. The third symbol is a combination of child beneath an ornate (school) roof and came to mean study. Thus taken together, the three characters can be translated as "The Study of The Logic of Life".

Welcome to the Department of Physiology

Information dates and places

Overview of Master of Biomedical Science and Honours

The Master of Biomedical Science Program
(and how to apply)

The Honours Program
(and how to apply)

Summer Studentships

Research Supervisors & Projects

**Convenors**

**Honours:** Dr René Koopman
Tel. 8344-0243 Room N422
rkoopman@unimelb.edu.au

**Masters**: Prof Lea Delbridge
Tel: 8344 5853 Room N525
lmd@unimelb.edu.au

# Welcome to the Department of Physiology

## In many ways the decision to undertake an Honours year or a Masters degree is one of the most important you will make.

It is often the first step towards an independent scientific career when you get the chance to pursue a research area of interest. The extra qualification will also help set you apart from competitors when seeking employment or entry into other courses or specialities.

There are many things to consider – the research topic; your need and desire to undertake additional, advanced coursework, the laboratory and its resources, the potential supervisor and the departmental support of students.

The Department of Physiology has a strong record of award-winning research training and mentorship with our graduates securing leadership roles in universities, institutes, industry and in the private sector. A recent winner of the highly prestigious 'Premier's Award for Health and Medical Research', Dr. Stefan Gehrig, trained as an undergraduate and graduate researcher in the Department of Physiology.

We are very proud of our students and have developed a carefully structured program of coursework to complement your developing laboratory and analytical skills. The Department environment provides support in a number of ways for our Honours and Masters students, but perhaps none is more important than the friendship, advice and mentoring they receive from our graduate students.

This booklet provides information that will help you decide on a potential research project in Physiology at Honours and Masters levels.

Our research is focussed on themes related to cardiovascular health, neurophysiology, and muscle and exercise. Take your time and look at the different projects on offer. Identify projects that appeal to you and contact potential supervisors for more information and visit their laboratories. Ask lab heads, staff and students about the projects and your potential career options with the new qualification.

Physiology offers many exciting research opportunities and we welcome the chance to discuss these with you.

Best of luck!

Professor Gordon S. Lynch
Head of Department

## Information Sessions you can attend.

Information specifically about the Department of Physiology Master of Biomedical Science / Honours programs :

**Department of Physiology Information Session:**
**- Friday 11th September - 11.30am – 12.45pm**

This is an ideal opportunity to meet supervisors, and to gain a quick overview of the Master of Biomedical Science and Honours Programs – what they involve and how they compare.

*Department of Physiology, Level 3 Prac Labs, north wing, Medical Building.*

Other University general information sessions include:

- **How to Apply for Honours Information Session**
  - Wednesday 2nd September, 5.15pm to 6.15pm – Kenneth Myer Building - aka Brain Centre (ground floor lecture theatre – Ian Potter Auditorium)

- **MDHS Honours Expo - Information Session**
  -Friday 4th September, 2.00pm-4.30pm Kenneth Myer Bldg, Ground Floor

## Places to find additional Faculty & Departmental Information

MDHS Honours Information
http://www.sc.mdhs.unimelb.edu.au/why-honours

Faculty of Science regulations and further information governing Master of Biomedical Science and Honours degrees : http://www.science.unimelb.edu.au/

How to apply
http://www.mdhs.unimelb.edu.au/future_students/honours/application_process

BBiomed/BSc (Hons) in Physiology – information on the structure of the current course:
http://www.physiology.unimelb.edu.au/

Research in Physiology:
http://www.physiology.unimelb.edu.au/research/research.asp

# An overview of Master of Biomedical Science and Honours Programs

The **Master of Biomedical Science** program offered by the **School of Biomedical Sciences** is a postgraduate specialty degree, which has been created to provide an alternate pathway into a research career and/or PhD studies, and to offer additional professional training for a career in science. In the Masters program, you are able to undertake a more substantial research project, and also select coursework subjects to develop your technical, communication, business and professional skills. A variety of 'Discipline' and 'Professional' subjects are offered across the University from which you can select.

**Honours** is a fourth-year undergraduate program which gives you the opportunity to draw together your previous studies and focus your knowledge and skills on an original research project. The Honours program is a one year extension of your undergraduate degree, which gives you a taste of what working as a scientist would be like as a career, allows you to demonstrate academic excellence in an area of special interest to you, and provides an entry point for further research higher degree study (ie PhD).

The Department of Physiology offers a **range of research projects which can be tailored to fit the Masters or Honours** context. Discussions with individual potential supervisors will be helpful for you in determining how a project might take shape if it is configured to fit within the Masters or Honours framework.

In the Department of Physiology the **Masters or Honours students interact extensively** and **share some core coursework components**. The course outlines are summarized in the Table below.

Overall, **Masters students complete 200 points** of coursework / project work over 4 semesters and **Honours students complete 100 points** of coursework / project work over 2 semesters. Both student groups take the core Discipline Subjects 'PHYS90008 Advanced Seminars in Physiology' and 'BIOM40001 Introduction to Biomedical Research'. Usually Masters students will take these subjects in the first semester of their course enrolment. Masters students complete a research project which comprises 125 points and Honours students complete a project comprising 75 points (including Literature Review and Oral Presentation tasks). During their enrolment, Masters students will take additional 'Professional Skills' subjects and other 'Discipline Subjects' (to complete the 200 points as indicated in the table below).

| Program Component | Description | Masters (points/200) | Honours (points/100) |
|---|---|---|---|
| Core Discipline subject | Advanced Seminars in Physiology PHYS90008 | 12.5 | 12.5 |
| Core Discipline subject | Introduction to Biomedical Research BIOM40001 | 12.5 | 12.5 |
| Research Project | Literature Review, Thesis, & Oral Presentations | 125 | 75 |
| Other Discipline subjects | | 25 | Not Applicable |
| Professional Skills | | 25 | Not Applicable |
| **Total** | | **200 points** | **100 points** |

Details of the Core Discipline subjects are provided on the following page. Information specific to the Masters and Honours programs and application processes then follows.

As a Physiology Masters or Honours student, you will take two core 'Physiology Discipline' subjects. These subjects are foundational Discipline research subjects – training you in contemporary Physiology experimental approaches and engaging you in the fun process of research debate and discussion. Both these subjects are available during Semester 1. Usually Masters students will take these subjects in the first semester of their program also (but if a second semester start has been agreed with your Supervisor then you will defer taking these subjects for a semester).

## BIOM40001 Introduction to Biomedical Research (12.5 points)

This subject uses a structured approach to introduce students to processes and strategies at the core of modern biomedical research. In a series of 10 x 2hr tutorials, students are guided through the need for – and tools of – testable hypothesis formulation, data management and evaluation, data presentation, and research outcome communication. Specific case examples of experimental design and statistical testing techniques are considered. In the course of this, students are introduced to appropriate statistical approaches and software. Ethical practices relevant to both animal and human experimental biomedical research are reviewed and inculcated. Broad issues relating to research conduct and management are addressed in the context of Discussion Workshops. These topics include critical reading skills, management of intellectual property, scientific integrity and fraud, conflict of interest, e-research, publication production, reference management and archiving of data. Additional Workshops deal with advanced techniques utilised in contemporary medical research.

The objectives of this subject are

- To develop a mature understanding of experimental design, experimental implementation, data evaluation and communication as it relates to modern biomedical research, in a broad ethical context.
- To acquire competency in statistical analysis, hypothesis testing and data presentation.
- To generate awareness of, and appropriate behaviours relating to, ethical conduct of animal and human experimental ethics, including regulatory requirements.
- To appreciate the need for the active management of intellectual property issues, scientific integrity and conflict of interest in a contemporary biomedical research context.
- To become aware of the scientific and technical basis of selected advanced techniques in biomedical research.

## PHYS90008 Advanced Seminars in Physiology (12.5 points)

This subject uses Research Seminars as a vehicle to learn about the experimental approach to contemporary physiological questions. Seminars are presented by a mixture of Physiology Department faculty, invited speakers from outside the department, and postgraduate students chosen to cover each of the three main research areas of the department. These seminars cover a diverse range of physiological questions and the experimental strategies used to address them. You will learn to critique seminars and to focus on the scientific essentials, i.e. what question is being addressed? What led up to this question? What strategies are being used to answer the question, and how well have they succeeded? Three seminars will receive particular attention. Questions and recommended reading will be distributed several days in advance to get you thinking before each of these three seminars and you will be involved in workshops after the seminars to dissect the science and the questions which arise.

The objectives of this subject are

- To increase students' knowledge of the experimental approaches and strategies used in different areas of physiology, and to think of ways that these could be applied to their own research projects;
- To teach students to think critically about the limitations and weaknesses that are associated with virtually all experimental strategies;
- To encourage students to conceptualize their own experimental strategies and approaches to physiological questions.

The Master of Biomedical Science is an important step into the world of Postgraduate study. You have increased independence to direct and manage your learning and training program to suit your career goals – in research and professional realms. The program, with extended time allocation for research, allows you to tackle a project at greater depth and possibly to employ more technically demanding techniques.

As the program extends over 2 years, your opportunities to be involved in detailed planning of your project and moving your work through to publication are increased. You will achieve a postgraduate qualification of recognized Discipline relevance to take you on the road confidently into further higher degree research. You will also develop competence in a range of professional skill areas relevant to science which might include technical, business, planning and communication strengths. Course structure information is available at:

http://mdhs-study.unimelb.edu.au/degrees/master-of-biomedical-science/overview

## Entry Requirements

A Bachelor degree with a major in an appropriate biomedicine/bioscience discipline (ie Physiology or related discipline) with at least an H3 (65%) in the third year Major subjects or equivalent relevant to the selected Project.

Students may commence a MBiomedSc program in Semester 1 or Semester 2, with Supervisor agreement, although Semester 1 is preferred.

## Masters Research Project and non-core subject selection

The program is designed to combine professional training with completion of a substantial original research project. You need to identify and arrange provisional acceptance from a supervisor. Some advice about how to find a supervisor and some possible project areas is available at:

http://mdhs-study.unimelb.edu.au/degrees/master-of-biomedical-science/entry-requirements#nav

Along with your research project, you will be taking the ***two core Physiology Discipline subjects*** (Introduction to Biomedical Research BIOM40001 and Advanced Seminars in Physiology PHYS90008), and you will select a range of other 'Professional Skills' units and 'Discipline Subjects' to complete a total of 200 points over 4 semesters. Depending on available subjects and selections, some students may be able to gain credit for Discipline or Professional Skills subjects taken over the summer. Introduction to Biomedical Research (BIOM40001) is a two week intensive program taken prior to the commencement of Semester 1 which provides flexibility for involvement in other subjects and early progress with your research project in the first year of enrolment.

Non Core Discipline Subjects (select 2 = 25 points)
In addition to the two core Physiology Discipline subjects required (25 pts, BIOM40001 & PHYS90008), you may select an additional 2 Discipline subjects. These additional Discipline subjects could be selected from Masters programs offered by other Departments or Schools or could be undergraduate subjects related to your research project.

You may select:
- Other relevant Department subjects (offered at 500 and 600 level)
- Other relevant undergraduate subject (offered at 300 level)

Professional Skills (select 2 = 25 points)
Beyond your Research project and the core and selected Discipline subjects, you will also select 2 'Professional Skills' subjects. These subjects provide you with broad professional training in areas of communication, social context of science, and business management.

A list of available subjects is at https://handbook.unimelb.edu.au/view/2015/MC-BMEDSC

## How to apply for MBiomedSc

*Course Code MC-BMEDSC*

1. Applications for the Masters are made directly via the University online application system from September. Timely applications close on 30 November (domestic applications). Late applications can be considered for admission (but may not eligible for competitive fee places or bursaries) until 31 January 2016.

2. Talk with academic staff offering projects you are interested in. Find out what is involved. Talk to the students in the labs. Talk with the Masters Physiology Coordinator if you have questions about the overall course structure.

3. When you are ready to make a formal application, you must lodge an online application via the School of Biomedical Sciences Course www site at:

   http://mdhs-study.unimelb.edu.au/degrees/master-of-biomedical-science/enquire-now#nav

   Link for Domestic students:
   http://futurestudents.unimelb.edu.au/admissions/applications/grad-com
   Applications close 30 November 2015. Late applications can be considered until 31 January 2016.

   Link for International students:
   http://futurestudents.unimelb.edu.au/admissions/applications/grad-int
   Applications close 31 October 2015. Late international applications will not be considered for this course.

   After the initial receipt of your application you will be required to nominate a Department, Supervisor and Project.

4. Wait for your email letter of offer early-mid December.

5. Complete the acceptance process as outlined and follow enrolment instructions.

As for Honours, Commonwealth supported places (CSP) are competitively available for eligible Masters students and HECS funding arrangements for fees apply. Overseas and Australian Fee places are also offered (and Fee Help support is available for local students). Students entering the Masters program need to check the banding classification of specific subjects to determine overall fees payable as some selected Discipline and Professional Skills subjects may be in fee bands which are different (possibly lower) than fee bands which apply to natural and physical sciences, mathematics and statistics fee band subjects. Some students may qualify for scholarship funding.

http://mdhs-study.unimelb.edu.au/degrees/master-of-biomedical-science/fees-scholarships#nav

Local students applying for the Masters may be eligible for financial support
http://www.centrelink.gov.au/internet/internet.nsf/payments/youth_allow.htm

## Enquiries

**Masters Coordinator**
Prof Lea Delbridge
Department of Physiology

lmd@unimelb.edu.au

**School of Biomedical Sciences**
**Graduate Team**

biomedsci-gradstudent@unimelb.edu.au

Honours is very different from earlier undergraduate years, allowing and requiring a greater degree of independence and flexibility that will help develop the maturity and skills for transition to employment in a range of occupations and industries or a research higher degree. Overall the Honours year adds value to your basic degree, provides you with an additional undergraduate year to demonstrate academic excellence and sets you apart as a student with extended experience of research methodology and with practical research credentials.

## Entry Requirements

There are two Faculty entry requirements which must be satisfied.

Applicants must hold a Bachelor of Biomedicine (BBiomed), Bachelor of Science (BSc) or equivalent qualification. Applicants currently enrolled in a BSc combined course at the University of Melbourne are not required to have completed their combined course to be eligible for Honours. These combined course applicants are required however, to have completed sufficient points to be eligible for the single BSc.

Weighted Average Mark (WAM) of at least 65%. The WAM weights subjects to reflect their credit value. This is calculated by multiplying the mark received for each subject against that subject's credit point value (i.e. 12.5 for most undergraduate subjects offered at the University of Melbourne). Each multiplication is then added together and then divided by the total amount of credit points for subjects undertaken (i.e. 300 for the B-BMED and B-SCI).

Entry into an Honours program is subject to the capacity of the department(s) or schools(s) offering the program to provide adequate supervision in a project appropriate to the interests and preparation of the individual student.

Honours students commence studies in Semester 1.

## Honours Research Project

The Honours Research Project in Physiology is designed to:

- Provide an introduction to the process and practice of physiological research;
- Enhance understanding of biological and medical sciences across a wide area;
- Strongly develop the ability to critically analyse and independently evaluate experimental data;
- To develop oral and written communication skills to levels expected of a practising scientist;
- To enhance the process of life-long independent learning.

The Honours Research Project (total 75 points) comprises three assessment components:

- Two oral presentations covering Project background, methods & research outcomes (20%)
- A literature review of less than 5,000 words on a nominated topic in Physiology (15%)
- A written report (Thesis) at the end of the year, not exceeding 10,000 words (65%).

To successfully complete the Honours program in Physiology, students must obtain an overall weighted average of 65% or better for all course components combined..

## Enquiries

**Honours Coordinator**
Dr René Koopman
Room N422
Department of Physiology

Tel: 61 3 8344 0243
Email: rkoopman@unimelb.edu.au

**Honours Administration**
Ms Lesley Robinson
SBS Academic Services

Tel: 61 3 8344 7755
Email: lesleyr@unimelb.edu.au

FREQUENTLY ASKED QUESTIONS
http://sc.mdhs.unimelb.edu.au/honours-faq

## How to Apply for Honours

**STEP 1**: Decide which departments, institutes, supervisors and projects you wish to apply for and make contact with the relevant supervisor. Applicants must contact potential supervisors before submitting an online application for entry to an MDHS Honours course.

Department and Institute Honours project booklets and websites, the MDHS Honours Expo and individual information sessions held by departments and institutes are ways of helping you to make contact with potential Honours supervisors.

**IMPORTANT NOTE:**
Students wishing to undertake Honours in the Departments or Schools of Genetics, Veterinary Science or Zoology must contact those departments or schools directly for guidance on their Honours application procedures. The Faculty of Medicine, Dentistry and Health Sciences does not manage Honours applications for these departments

**STEP 2**: Lodge an online application between Friday 28 August and Friday 13 November 2015

**Currently enrolled University of Melbourne students and alumni**
1. Apply online and select the *Returning Applicants, Current Students and Previous Students* option.
2. Provide original or certified transcript(s) for any study not undertaken at The University of Melbourne. You are not required to provide transcripts for study undertaken at this university.

**External Applicants**
1. **Apply online** and select the *First Time Applicants* option. Do not select this option if you have previously completed study or applied to a program at The University of Melbourne.
2. Provide original or certified transcript(s) for any study not undertaken at The University of Melbourne.

**Supporting documentation may be submitted to:**

Honours Admissions Team
Learning and Teaching Unit
Level 1, Brownless Biomedical Library
The University of Melbourne
VIC 3010 Australia

Please include your University of Melbourne Applicant ID or Student ID on all items and correspondence.

**STEP 3:** Lodge your project preference application in the *Honours Application and Tracking System (HATS).* NOTE: This step is only for applicants for 2016 start-year entry.

HATS will open on Monday 7 September 2015 and close at 5pm on Friday 27 November 2015.
You may select up to ten projects preferences via HATS. You must only preference projects after making contact with the relevant supervisor. HATS usernames / passwords are issued once a week (usually on a Monday) to applicants whose applications are submitted properly in the previous week.

**STEP 4: OFFERS**
Round one offers for entry into 2016 will be made from Friday 18 December 2015. Students must accept their offer by the Offer Lapse Date noted in their offer letter. Students who meet the minimum entry requirements but are not made a Round 1 offer may be considered for Round 2 in mid-January.

It is the responsibility of all applicants to ensure they make appropriate arrangements for their mail and email during December and January. The Faculty of Medicine, Dentistry and Health Sciences is not responsible for correspondence that has not been received due to applicants being unavailable during the offer period.

**IMPORTANT NOTE:** Not all students who meet the minimum entry requirements and make contact with Supervisors will be offered a place in an MDHS Honours course. Entry is conditional upon selection by the Departmental Selection Committee and is academically competitive.

# Summer Studentships

Are you a third year student interested in undertaking Honours or a Master of Biomedical Science degree within the Department of Physiology in 2016? If so, consider a Summer Studentship to work on a supervised research project. The following is available :

R D Wright Summer Studentship
Application forms available from the Department of Physiology
Please contact Lesley Robinson lesleyr@unimelb.edu.au to request copy or check relevant LMS site.

Deadline 31 October

The purpose of the Summer Research Studentships is to provide an opportunity for undergraduates to gain first-hand experience in research. Students currently enrolled in the Third Year of the science or biomedical science courses at this University are eligible to apply. Applications from students interested in Honours will be given special consideration. Please note that you must discuss a project with the appropriate supervisor before applying.

The Physiology Department identifies several broad areas of research emphasis. These include:

**Cardiovascular Health**

| | |
|---|---|
| Prof Lea Delbridge | - Cardiac Phenomics |
| Prof Mary Wlodek | - Fetal, Postnatal & Adult Physiology and Disease |
| Dr Deanne Skelly | - Health and Lifestyle Diseases |
| Prof Stephen Harrap | - Genetic Physiology |

**Muscle and Exercise**

| | |
|---|---|
| Prof Gordon Lynch | - Basic & Clinical Myology |
| Dr René Koopman | - Clinical Nutrition and Muscle & Exercise Metabolism |

**Neurophysiology**

| | | |
|---|---|---|
| Prof Andrew Allen | - | - Central Neurogenesis Regulation |
| Prof Joel Bornstein | | - Enteric Neuroscience |
| Prof David Williams | | - Neurodegeneration |

Unless otherwise indicated, all projects listed are suitable for students undertaking Masters or Honours.

Projects are managed by the Primary Supervisor within that area of Research. In some instances they are co-supervised as indicated.

**CARDIAC PHENOMICS**

Prof Lea Delbridge
Dr James Bell
Dr Claire Curl

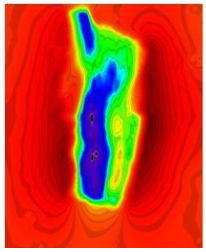
lmd@unimelb.edu.au

www.physiology.unimelb.edu.au/research/cardiovascular_health/cardiac_phenomics

The Cardiac Phenomics Laboratory research is about understanding how the heart response to stress can be managed to minimize the damaging impacts of a variety of disease conditions. We investigate responses of the working 'pumping' heart, of specialized muscle tissues and cells from different regions of the heart and of molecular signaling processes. As our name suggests, we look at how the cardiac '*genome*' (the genetically defined heart) is translated in different stressor situations to create the '*phenome*' (the structurally and functionally defined heart).

Our pre-clinical work focuses on cardiac pathology arising from Type 1 and Type 2 diabetes and on the factors which determine how female and male hearts respond differently to stress and disease challenges. These areas of heart health are of critical significance in shaping the demographics of cardiovascular disease. We use experimental models to mimic human disease conditions, and we look for links between the performance of single muscle cells and the functioning heart. Our goals are to inform the development of new treatments for diabetic cardiomyopathy and to understand how for women and men, cardiac 'difference' may be managed with optimized therapeutic tools.

Student projects in the Cardiac Phenomics lab could incorporate a range of methodologies including animal dietary and pharmacologic treatments, instrumented working heart preparations, immunohistochemistry, cell culture and adenoviral expression manipulation, cell kinetic imaging, biochemical assay, confocal microscopy, microarray gene profiling, realtime PCR, and western blot techniques. Projects are particularly suitable for MSc students, as there is scope for progression to publication within the degree time frame and research work is supported by complementary skills development coursework.

***DIABETIC CARDIOMYOPATHY – AN EPIDEMIC DISEASE***

Globally, diabetes is an epidemic disease with a specific cardiopathology independent of vascular and other cardiovascular risk profile. In the diabetic heart, one of the first signs of pathology is deterioration in the capacity of the heart to relax (in diastole) – and later signs of active pump failure (in systole) emerge.

Our work focuses on understanding the mechanisms of both diastolic and systolic dysfunction, examining how circulating and locally produced hormones impact on cardiopathology and identifying potential molecular targets for intervention. Using genetic and experimental models of type 1 and type 2 diabetes, we are investigating the structural bases for relaxation abnormality in the diabetic heart – evaluating active and passive components of stiffness which reflect both cardiac muscle cell and extracellular matrix pathology.

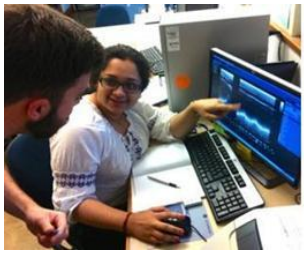
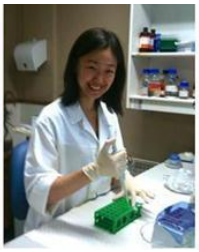
**Projects:**

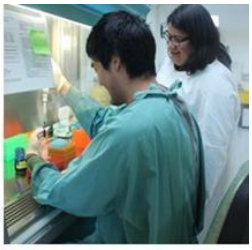
**1) Glycogen handling pathology in diabetic cardiomyopathy** With Dr Kimberley Mellor, (University of Auckland) *An investigation of the cellular mechanisms which underlie energy storage defects in muscle cells from the diabetic heart.*

**2) Defining mechanisms of cardiac muscle cell death in the diabetic heart**. *How are cardiac muscle cells dying in the diabetic heart – and what are they most important pathways for cell death?*

**3) New strategies to rescue diabetes-induced cardiac dysfunction**. With A/Prof Rebecca Ritchie, Baker IDI Heart & Diabetes Institute *Looking at interventions to deliver small molecules with potential therapeutic benefit in rescuing function in the diabetic heart.*


- Delbridge LM, Mellor KM, Taylor DJ, Gottlieb RA. Myocardial autophagic energy stress responses – macroautophagy, mitophagy and glycophagy. Am J Physiol –Heart 308:H1194-204, 2015
- *Reichelt ME, *Mellor KM, Curl CL, Stapleton D, Delbridge LM. Myocardial glycophagy - a specific glycogen handling response to metabolic stress is accentuated in the female heart. J Mol Cell Cardiol. 65:67-75, 2013.
- Mellor KM, Wendt IR, Ritchie RH, Delbridge LM Fructose diet treatment in mice induces fundamental disturbance of cardiomyocyte Ca2+ handling and myofilament responsiveness. . Am J Physiol Heart Circ Physiol. 15:302:H964-72, 2012.



***STEROID HORMONES AND HEART FAILURE – SEX PERSPECTIVES***

Important differences exist between women and men with regard to cardiovascular disease. Sex differences have been reported in left ventricular hypertrophy, cardiac remodeling with aging, arrhythmogenic activity, and post-infarct myocardial salvage. In recent years there has been controversy about the use of steroid therapies in men and women – and the cardiovascular problems of anabolic steroid abuse have become apparent. Therapies involving mineralocorticoid block have differential cardiac effectiveness in men and women. The molecular bases for sex-related differences in myocardial disease and response to steroids are poorly understood.

The goal of this research is to determine how sex steroids ( testosterone & estrogen) and mineral/glucocorticoid steroids (aldosterone, cortisol & corticosterone) regulate heart growth and function under normal and metabolic stress conditions. We investigate the early developmental origins of progression to failure in males and females– and have demonstrated that cell loss in the neonatal transition period is linked with life-long cardiac muscle cell deficit and susceptibility to autophagy.

**Projects:**

**4) Discovering the importance of cardiac aromatase in converting androgens to estrogen – new therapeutic targets**. *Following up our exciting new lead in discovering that the heart can make it's own estrogen – for better or for worse!*

**5) Making and breaking hearts – tracing the journey to heart failure back to early developmental influences** With Prof Stephen Harrap and Prof Fadi Charchar, (Federation University) *Exploring the mechanisms during development which condemn enlarged heart muscle cells to lose mechanical effectiveness and succumb to early death.*

**6) Sex differences in cardiac stress resilience – why are female hearts protected?** *An experimental project to understand why, although women are less likely to experience heart attack, when they do the consequences are likely to be more dire.*

- Bell JR, Bernasochi GB, Varma U, Raaijmakers AJ, Delbridge LM. Sex and sex hormones in cardiac stress--mechanistic insights. J Steroid Biochem Mol Biol. 137:124-35, 2013.
- Aromatase transgenic upregulation modulates basal cardiac performance and the response to ischemic stress in male mice. Bell JR, Bernasochi GB, Varma U, Boon WC, Ellem SJ, Risbridger GP, Delbridge LM. Am J Physiol Heart Circ Physiol. 306:H1265-74, 2014.
- Bell JR, Raaijmakers AJ, Curl CL, … Harrap SB, **Delbridge LM.** Cardiac CaMKIIδ splice variants exhibit target signalling specificity and confer sex-selective arrhythmogenic actions in the ischemic-reperfused heart. Int J Cardiol.181:288-296, 2015.

## CARDIOVASCULAR HEALTH

Professor Mary Wlodek
Room N619
Level 6 north wing, Medical Building

Tel. 61 3 8344 8801
m.wlodek@unimelb.edu.au

Dr Deanne Skelly
Room N526
Level 5 north wing, Medical Building

Tel. 61 3 9035 9923
deanne.skelly@unimelb.edu.au

## FETAL, POSTNATAL & ADULT PHYSIOLOGY AND DISEASE

Small size at birth for gestational age occurs in 10% of human pregnancies in developed societies. This results from restricted growth of the fetus, which primarily reflects a poor environment within the uterus, commonly due to uteroplacental insufficiency. Recent human studies have confirmed that being born small is associated with the increased risk of developing adult diseases. Our results have proved pivotal to shifting programming research paradigms to now include the postnatal lactational environment.

We are exploring how a reduction in the number of functioning units of the kidney (nephrons), heart (cardiomyocyte) and pancreas (beta cell) program rat offspring born small to develop renal, cardiovascular and metabolic disease and the transgenerational transmission of diseases. We aim to identify developmental stages during which nutritional, exercise or other lifestyle interventions may have beneficial consequences. We are now exploring how these programmed diseases can be passed to the next generation. We are currently studying the impact of maternal stress, obesity and exercise during pregnancy on disease development of the next generation. These studies will enable us to identify individuals at increased risk of developing later life diseases that can be transmitted to the next generation. Our studies will provide the scientific basis for the design and testing of appropriately targeted lifestyle interventions to reduce adverse health effects of pregnant mothers and their babies. Identification of groups of individuals at risk of developing diseases will become increasingly important due to the ever-increasing incidence and earlier age at onset of these diseases.

### PROJECTS

*(All projects for Honours or Masters unless otherwise stated)*

#### 7) Benefits of exercise training in pregnancy for overweight females born small: role of leptin

*With Dr Deanne Skelly (deanne.skelly@unimelb.edu.au)*

Many experimental and human studies worldwide have shown that babies born small for gestational age or are light at birth are strongly and consistently at increased risk of developing disease as adults and that this risk is passed onto subsequent generations. We have also shown that in rats born small there is a leptin deficit, and that exercise training can normalise programmed F1 pathologies. However, the ability of leptin to increase the risk of programmed pathologies is unknown. This proposal addresses the likelihood that a mother born small who becomes overweight will develop serious pregnancy complications, affecting growth of her baby. The aim of this study is to identify whether exercise training during pregnancy, in normal and overweight females, alters placental growth and development causing deregulated placental leptin signalling pathways influencing fetal growth.

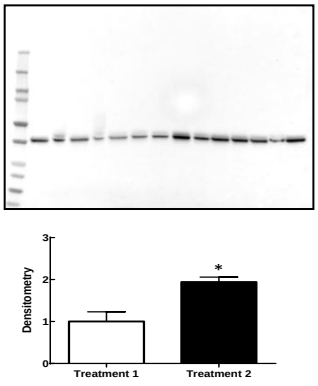



*Figure 1: Western blot of Leptin protein expression in the rat kidney.*

**8) Benefits of exercise training in pregnancy for overweight females born small: cardiovascular transgenerational effects** *(Masters project only)*

Many experimental and human studies worldwide have shown that babies born small for gestational age or are light at birth are strongly and consistently at increased risk of developing disease as adults and that this risk is passed onto subsequent generations. We have also shown that exercise training can normalise programmed F1 deficits. This proposal addresses the likelihood that a mother born small who becomes overweight will develop serious pregnancy complications, affecting growth of her baby. The aim of this study is to identify whether exercise training during pregnancy, in normal and overweight females, can prevent the likelihood of developing cardiovascular and renal diseases in offspring.

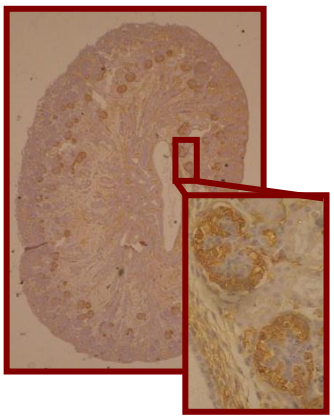


*Figure 2: Fetal rat kidney prepared for nephron counting.*

**9) Benefits of exercise training in pregnancy for overweight females born small: metabolic transgenerational effects** *(Masters project only)*

Many experimental and human studies worldwide have shown that babies born small for gestational age or are light at birth are strongly and consistently at increased risk of developing disease as adults and that this risk is passed onto subsequent generations. We have also shown that exercise training can normalise programmed F1 deficits. This proposal addresses the likelihood that a mother born small who becomes overweight will develop serious pregnancy complications, affecting growth of her baby. The aim of this study is to identify whether exercise training during pregnancy, in normal and overweight females, can prevent the likelihood of developing metabolic diseases in offspring.

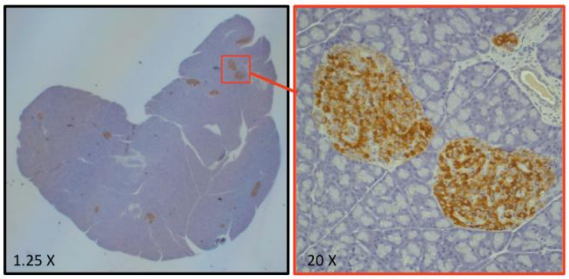



*Figure 3: Rat pancreas as viewed under a Light Zeiss microscope after immunohistological staining.*

**10) Role of being overweight in paternal line in transgeneration transmission of cardiovascular disease**

Many experimental and human studies worldwide have shown that babies born small for gestational age or are light at birth are strongly and consistently at increased risk of developing cardiovascular and metabolic diseases as adults and that this risk is passed onto subsequent generations. Being overweight or obese can exacerbate these consequences. The relative role of paternal transmission is less well understood. We have demonstrated in our model of uteroplacental insufficiency that the fetal growth restriction in the first generation is associated with hypertension, a nephron deficit and metabolic dysfunction. The aim of this study is to determine whether cardiovascular dysfunction and nephron deficits transmitted to the next generation are exacerbated if the growth restricted father is overweight or obese.

**11) Role of being overweight in paternal line in transgeneration transmission and the influence on sperm**

Many experimental and human studies worldwide have shown that babies born small for gestational age or are light at birth are strongly and consistently at increased risk of developing cardiovascular and metabolic diseases as adults and that this risk is passed onto subsequent generations. Being overweight or obese can exacerbate these consequences. The relative role of paternal transmission is less well understood. We have demonstrated in our model of uteroplacental insufficiency that the fetal growth restriction in the first generation is associated with hypertension, a nephron deficit and metabolic dysfunction. The aim of this study is to determine whether F1 germ cell and sperm mRNA and microRNA levels are perturbed thereby programming altered F2 phenotypes in males born small and whether exacerbated if the male is overweight or obese.

**12) Placental and pregnancy complications for obese women**
*With A/Prof Joanne Said (Sunshine Hospital) (jsaid@unimelb.edu.au )*

Many experimental and human studies worldwide have shown that babies born small for gestational age or are light at birth are strongly and consistently at increased risk of developing diseases and obesity as adults and that this risk is passed onto subsequent generations. Obesity in pregnancy has adverse consequences for a mothers pregnancy and her children's later life health. This proposal addresses the likelihood that a mother born small who becomes obese in pregnancy will develop serious pregnancy complications, affecting placental function and growth of her baby. The aim of this study is to characterise pregnancy outcomes and altered placental function (including gene and protein expression) in obese women (Sunshine Hospital) that were either born small or of normal weight.

**13) A mouse model of pre-eclampsia with intervention strategies**
*With A/Prof Joanne Said (Sunshine Hospital) (jsaid@unimelb.edu.au )*

Pre-eclampsia is characterized by new onset hypertension and proteinuria occurring after 20 weeks gestation, and is accompanied by a range of other multisystem effects and adverse pregnancy outcomes (placental abruption, fetal growth restriction, prematurity and stillbirth). What is known is that the placenta plays a pivotal role in the development of pre-eclampsia. Despite a worldwide research effort, the aetiology of this devastating condition remains unknown and treatment strategies are elusive. The aim of the project is to use a mouse model of pre-eclampsia and characterise gene and protein expression changes in the placenta that have already been established in our human studies. In addition, pharmacological agents will be administered to determine whether the molecular changes in the placenta can be improved to prevent pre-eclampsia.

**Selected Recent References of Professor Wlodek and colleagues**


Briffa, J.F., McAinch, A.J., Romano, T., **Wlodek, M.E.** and Hryciw, D.H. Leptin in pregnancy and development: a contributor to adulthood disease. *Am. J. Physiol.* 308:E335-E350, 2015.

van der Linde, S., Romano, T., Jefferies, A., **Wlodek, M.E**. and Hryciw, DH. Growth restriction in the rat alters expression of cardiac JAK/STAT genes in a sex-specific manner. *J DOHaD* 4:314-321, 2014.

Gallo, L.A., Tran, M., Cullen-McEwen, L.A., Denton, K.M., Jefferies, A.J. Moritz, K.M. and **Wlodek, M.E**. Transgenerational programming of fetal nephron deficits and sex-specific adult hypertension in rats. *Reprod. Fertil. Develop.* 26:1032-1043, 2014.

Tran, M., Gallo, L.A., Jefferies, A.J., Moritz, K.M. and **Wlodek, M.E**. Transgenerational metabolic outcomes associated with uteroplacental insufficiency. *J. Endocrinology* 217:105-118, 2013.

Gallo, L.A., Tran, M., Master, J.S., Moritz, K.M. and **Wlodek, M.E**. Maternal adaptations and inheritance in the transgenerational programming of adult disease. *Cell. Tissue. Res.* 349:863-880, 2012.

Gallo, L.A., Tran, M., Moritz, K.M., Jefferies, A.J. and **Wlodek, M.E**. Pregnancy in aged female rats born small: cardio-renal and metabolic adaptations and second generation fetal growth restriction. *FASEB. J.* 26:4337-4347, 2012. *Our article is featured on the October 2012 cover*

Gallo, L.A., Tran, M., Moritz, K.M., Mazzuca, M.Q., Parry, L.J., Westcott, K., Jefferies, J., Cullen-McEwen, L., **Wlodek, M.E**. Cardio-renal and metabolic adaptations during pregnancy in female rats born small: Implications for maternal health and second generation fetal growth. *J. Physiol*. 590:617-630, 2012. *Subject of "J Physiol Perspectives" 590.5:1019, 2012.*

Laker, R.C., **Wlodek, M.E**., Wadley, G.D., Gallo, L.A., Meikle, P.J. and McConell, G.K. Exercise early in life in rats that were born small does not normalize reductions in skeletal muscle PGC-1α in adulthood *Am. J. Physiol.* E1221-E1230, 2012.

Laker, R.C., Gallo, L.A., **Wlodek, M.E**., Siebel, A.L., Wadley, G.D. and McConell, G.K. Short-term exercise training early in life restores deficits in pancreatic β-cell mass associated with growth restriction in adult male rats. *Am. J. Physiol.* 301:E931-E940, 2011.

Chui A, Murthi P, Brennecke SP, Ignjatovic V, Monagle PT, Said JM. The expression of placental proteoglycans in pre-eclampsia. Gynecol Obstet Invest. 2012;73(4):277-84.


.

**MUSCLE AND EXERCISE**

Prof. Gordon S. Lynch

Tel. 61 3 83440065
gsl@unimelb.edu.au

Dr. Kristy Swiderski

Tel. 61 3 8348503
kristys@unimelb.edu.au

Dr. James Ryall

Tel. 61 3 83443672
ryalljg@unimelb.edu.au

## *BASIC AND CLINICAL MYOLOGY*

Our group investigates the mechanisms underlying skeletal muscle wasting and weakness and develops and tests therapies to counteract muscle wasting disorders.

Our research is focused on ageing (sarcopenia), muscle diseases (such as the muscular dystrophies), and cancer cachexia. We also investigate novel approaches for improving muscle repair after injury.

We are testing the efficacy of pharmacological interventions to counteract muscle wasting and hasten muscle repair after injury

Our work has application for many other muscle wasting conditions including: sepsis and other forms of metabolic stress; denervation, disuse, inactivity, unloading or microgravity; burns, human immunodeficiency virus (HIV)-acquired immunodeficiency syndrome; chronic kidney or heart failure; and chronic obstructive pulmonary disease.

Our studies involve investigation of molecular pathways regulating muscle size and function with a translational approach of cell culture experiments complemented by studies utilizing different animal models for these muscle wasting conditions.

# PROJECTS

## *14) Inhibition of stem cell commitment via metabolic reprogramming*

Despite the success of hematopoietic stem cell transplant, almost all other stem cell therapies have proven disappointing, with most still considered experimental and in various stages of preclinical testing. One of the major limitations of transplantation (particularly with regards to skeletal muscle stem cells) is premature specification and the rapid loss of "stemness" of cells to be transplanted. Recent work has identified a process of stem cell metabolic remodelling that occurs during changes in cell fate, with a shift in metabolism occurring during stem cell specification and differentiation. Interestingly, preliminary evidence suggests that by forcing stem cells into a different metabolic state (a new approach termed "metabolic reprogramming") it is possible to prevent or even reverse the process of stem cell specification. These exciting results suggest that metabolic reprogramming may provide a new avenue for improving stem cell transplant therapy. The current application seeks to make use of metabolic reprogramming to improve the process of stem cell transplantation, using adult skeletal muscle stem cells as a treatment for muscle injury. The results from this study have important implications for patients suffering from one of a multitude of muscle injuries and/or muscle disorders.

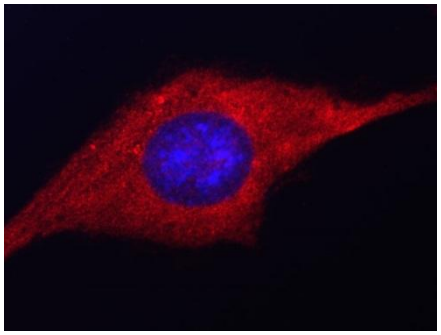


Figure 2.a

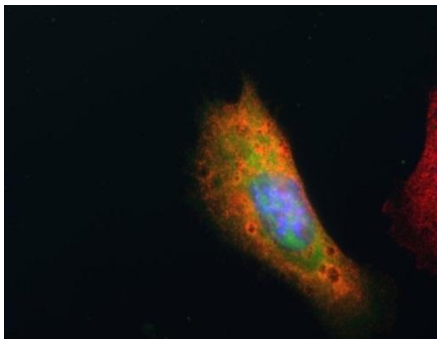


Figure 2.b

***Figure 2:*** *Images of C2C12 skeletal muscle cells. Nuclei have been stained with Dapi (blue), the red staining indicates the endogenous expression of PKM2. PKM2 is an enzyme involved in the glycolytic pathway and appears to play an important role in the metabolic remodelling seen during myogenesis. Figure 2b has also been tagged with Green Fluorescent Protein (GFP).*

## 15) The role of heat shock proteins for improving skeletal muscle structure and function in dystrophic mice

The heat shock proteins (Hsp) are a family of molecular chaperone proteins known to be involved in the cell stress response. We have recently revealed how induction of one member of this family, heat shock protein 72 (Hsp72) (through transgenic manipulation, heat therapy and drug-induction) can protect dystrophic muscle against functional decline and improve lifespan in severely affected dko mice (Gehrig et al., 2012) This project aims to further examine the role of other heat shock proteins and the therapeutic potential of Hsp induction in the skeletal and cardiac muscles of various models of muscular dystrophy, with the ultimate aim to develop a novel treatment to improve both skeletal and cardiac muscle function and quality of life for patients with muscular dystrophy.

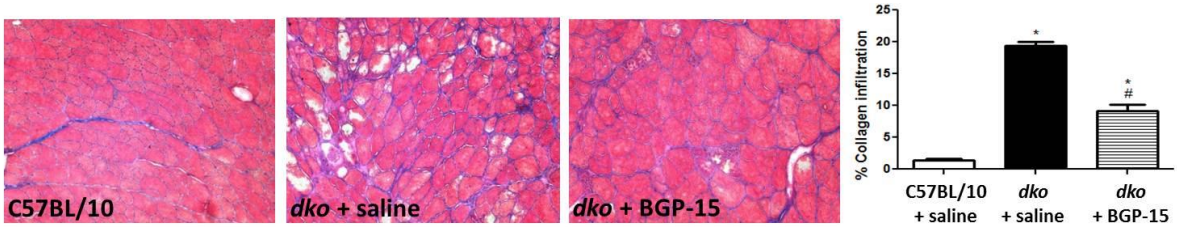



***Figure 2.*** *Pharmacological up-regulation of Hsp72 by BGP-15 reduces fibrosis (collagen infiltration) in the severely dystrophic dko mouse.*

## References (Prof G Lynch)


1. Koopman R, Ly CH and Ryall JG (2014). A metabolic link to skeletal muscle wasting and regeneration. Front Physiol 5,32.

2. Ryall JG (2013). Metabolic reprogramming as a novel regulator of skeletal muscle development and regeneration. FEBS J 280, 4004-4013.

3. Murphy KT, Chee A, Gleeson BG, Naim T, Swiderski K, Koopman R and Lynch GS. (2011). Antibody-directed myostatin inhibition enhances muscle mass and function in tumor-bearing mice. Am J Physiol 2011; doi:10.1152/ajpregu.00121.2011

4. Murphy KT, Lynch GS. (2009). Update on emerging drugs for cancer cachexia. Expert Opin Emerg Drugs 14: 619-632.

5. Gehrig SM, Koopman R, Naim T, Tjoakarfa C, Lynch GS (2010). Making fast-twitch dystrophic muscles bigger protects them from contraction injury and attenuates the dystrophic pathology. *Am J Pathol.* 176: 29-33.

6. Koopman R, Gehrig SM, Leger B, Trieu J, Walrand S, Murphy KT, and Lynch GS (2010). Cellular mechanisms underlying temporal changes in skeletal muscle protein synthesis and breakdown during chronic beta-adrenoceptor stimulation in mice. *J Physiol*: 4811-4823,.

7. Ryall JG, Church JE, Lynch GS (2010). Novel role for beta-adrenergic signalling in skeletal muscle growth, development and regeneration. *Clin Exp Pharmacol Physiol*. 37: 397-401.

**MUSCLE AND EXERCISE**

Dr. René Koopman

Level 4 north, Medical Building

Tel. 61 3 83440243
rkoopman@unimelb.edu.au

## *CLINICAL NUTRITION AND MUSCLE & EXERCISE METABOLISM*

We specialise in basic and translational (bench-to-bedside) research programs focussing on (nutritional) interventions to improve muscle protein and carbohydrate metabolism in health and disease. The main fields of interest include skeletal muscle protein and carbohydrate metabolism in response to food intake and exercise in health and disease, exercise metabolism, clinical nutrition, type 2 diabetes and aging. Working together closely with Gordon's Basic and Clinical Myology Laboratory, we also examine the metabolic mechanisms underlying skeletal muscle wasting in mammals.

Our research aims to increase knowledge that will enable us to define the most effective interventions to improve the anabolic response to food and exercise in acute and chronic metabolic diseases and ageing.

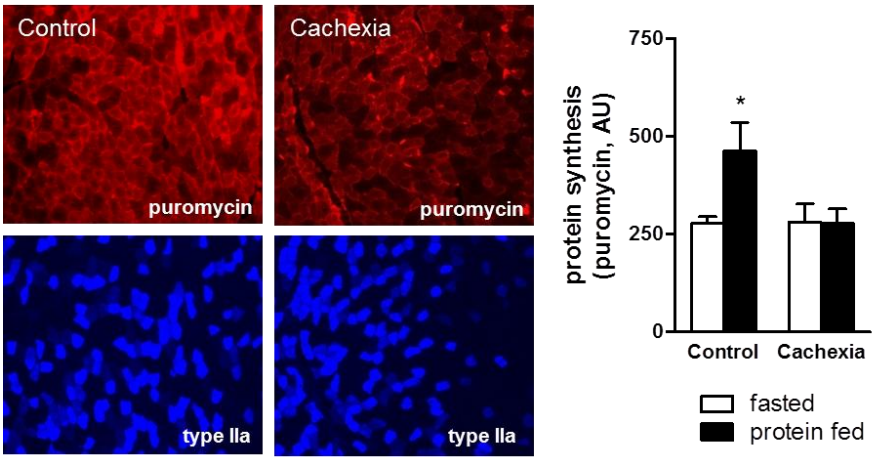



***Figure 1.*** *The anabolic (protein synthesis) response to protein feeding is impaired in skeletal muscle of tumour bearing mice.*

## PROJECTS

### *16) Establish the effect of glycine/serine metabolism on skeletal muscle cell growth*

Skeletal muscle cell proliferation and growth require the production of building blocks for new cellular components (proteins, lipids and nucleic acids) as well the maintenance of cellular redox status. Observations in other cells suggest that the metabolism of the amino acid L-serine and its intermediate glycine can provide carbon units that satisfy many of these requirements. However, the cellular demand for L-serine is much greater than its uptake suggesting that the de novo production of L-serine is of critical importance to sustain cellular growth. Surprisingly, to date no detailed investigation of the role of L-serine biosynthesis in skeletal muscle has been performed and whether L-serine can support the production of biomass in growing muscle cells remains to be established.

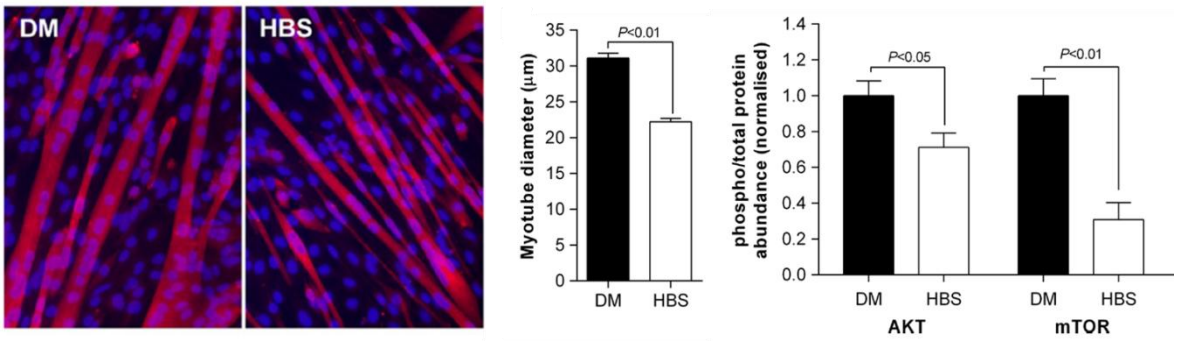



***Figure 2.*** *Nutrient and growth factor deprivation rapidly induces wasting by reducing muscle protein synthesis and signalling through mTORC1. (Ham et al. Amino Acids 2014)*

### *17) Glycine: a novel modulator of skeletal muscle endurance and performance*

Our preliminary studies in mice clearly show that glycine administration enhances exercise capacity and our published work demonstrates that glycine supplementation preserves whole-body function during conditions of increased inflammation and oxidative stress. Combined with the observation of enhanced loss of adipose tissue during caloric restriction, these results suggest that glycine may act as an ergogenic aid, but studies testing any performance effects of glycine in humans are not available. Our goal is to test the potential for glycine to modulate fuel utilisation and increase exercise performance capacity using a practical dosing regimen, and performance-based assessment.

*References:*


1. Ham DJ, Kennedy TL, Caldow MK, Chee A, Lynch GS, **Koopman R**. Citrulline does not prevent skeletal muscle wasting or weakness in limbcasted mice. *J Nutr* (2015).145:900-6.
2. Ham DJ, Caldow MK, Lynch GS, **Koopman R**. Leucine as a treatment for muscle wasting: a critical review. *Clin Nutr*. (2014). 33:937-45
3. Ham DJ, Caldow MK, Lynch GS, **Koopman R**. Arginine protects muscle cells from wasting in vitro in an mTORC1-dependent and NO-independent manner. *Amino Acids* (2014). 46, 2643-2652
4. Ham DJ, Murphy KT, Chee A, Lynch GS, and **Koopman R**. Glycine administration attenuates skeletal muscle wasting in a mouse model of cancer cachexia *Clin Nutr*. (2014). 33:448-458.
5. Stapleton DI, Lau X, Flores M, Trieu J, Gehrig SM, Chee A, Naim T, Lynch GS, and **Koopman R**. Dysfunctional muscle and liver glycogen metabolism in mdx dystrophic mice. *PloS One* (2014). March 13. doi: 10.1371/journal.pone.0091514.
6. **Koopman R**, Ly CH, and Ryall JG. A metabolic link to skeletal muscle wasting and regeneration. *Frontiers in Physiology* (2014). 5; doi: 10.3389/fphys.2014.00032.
7. **Koopman R**. Dietary protein and exercise training in ageing. *Proc Nutr Soc* (2011). 70:104-113.
8. **Koopman R**, Gehrig SM, Leger B, Trieu J., Walrand S., Murphy KT and Lynch GS. Cellular mechanisms underlying temporal changes in skeletal muscle protein synthesis and breakdown during chronic β-adrenoceptor stimulation in mice. *J Physiol* (2010). 588:4811-4823.
9. **Koopman** R, Walrand S, Beelen M, Gijsen AP, Kies AK, Boirie Y, Saris WH, van Loon LJ. Dietary protein digestion and absorption rates and the subsequent postprandial muscle protein synthetic response do not differ between young and elderly men. J Nutr. (2009).139:1707-13.
10. Witard OC, Tieland M, Beelen M, Tipton KD, van Loon LJ, **Koopman** R. Resistance exercise increases postprandial muscle protein synthesis in humans. Med Sci Sports Exerc. (2009).41:144-54.

**NEUROPHYSIOLOGY**

Prof Joel Bornstein
Room N604
Level 6 north wing, Medical Building

Tel. 61 3 83445850
j.bornstein@unimelb.edu.au

Dr Elisa Hill

Tel. 61 3 90456407
elhill@unimelb.edu.au

Dr Jaime Foong

Tel. 61 3 83444543
jpfoong@unimelb.edu.au

**ENTERIC NEUROSCIENCE**

My major research interest is in the neural mechanisms that control intestinal motor functions underlying the digestive process, including both muscle movement and the secretion of water and salt by the mucosa, and how these are disturbed by bacterial toxins and in neuropsychiatric disease. This work involves a range of experimental methods ranging from electrophysiological analysis of synaptic transmission in reflex pathways, to immunohistochemical analysis of enteric neural circuits, to measurements of intestinal movements and secretions both in vitro and in vivo and computer simulation of the networks of neurons that mediate these functions.

Much of this work, especially that involving interactions between intestinal movements and secretion, is carried out in close collaboration with Prof Henrik Sjovall of Goteborg's University in Sweden and Dr Tor Savidge of Baylor College of Medicine in Texas. Other international collaborations include studies of GI disorders in autism with Dr Kent Williams of Ohio State University in the USA,.

Melbourne collaborators include Prof Heather Young of the Department of Anatomy and Neuroscience in a study of the functional development the enteric nervous system of the mouse and Dr Tony Hannan of the Florey Neurosciences Institute in studies of autism. .

**PROJECTS**

**18) Mechanisms by which cholera toxin and *Clostridium difficile* toxin A affect intestinal movements**
(with Dr Jaime Foong)

Our recent data indicate that cholera toxin and toxin A, bacterial exotoxins, in addition to causing massive diarrhoea due to over-secretion of water and salt across the intestinal mucosa, also modify the neural circuitry that controls the movements of the intestine (motility). This set of projects will address the mechanisms responsible. Two distinct studies are needed.
***(suitable for Hons/Masters)***

(a) Pharmacological analysis of the role of serotonin and other mucosal mediators in coupling the actions of cholera toxin and/or toxin A to intestinal movements recorded using video-imaging. Interactions of the toxins and nutrients that independently activate intestinal motility patterns will be a specific focus.

(b) Electrophysiological analysis of site of action of cholera toxin or toxin A in the reflex pathways that regulate intestinal movements. This will use extracellular recordings from contracting preparations in multi-chambered organ baths to dissect whether the toxin acts via sensory neurons, interneurons or motor neurons, or a combination of all three.

**19) Autism in the gastrointestinal tract – why do autistic patients get constipated?**
(with Dr Elisa Hill)

Gastrointestinal disorders, especially constipation, are believed to be a characteristic feature of autism, but this is often thought to be secondary to dysfunctions in the brain. Our recent studies have shown that mice carrying a mutation of a synaptic protein that is associated with autism in some patients have disordered gastrointestinal movements due to a change within the enteric nervous system, however the mechanisms responsible for this are unclear. In this project, you will use immunohistochemical, molecular and electrophysiological methods to determine which synaptic proteins in the enteric nervous system are modified in these autistic mice and how this affects the neural circuits that control colonic motility. ***(suitable for Hons/Masters)***

**20) Modelling nerves and networks**

Modelling is an essential form of inquiry in the quest to understand how the nervous system performs its tasks. We are engaged in a number of modelling projects that examine aspects of the nervous system from constructing models of synaptic transmission and detailed biophysical models of single cells through to elucidating emergent properties of large networks. The main techniques are computer simulation and some mathematical analysis. We concentrate on the enteric nervous system, which controls reflexes and motor patterns of the intestine, but the insights gained are also applicable to the brain and we are developing models that directly test some central nervous functions. ***(suitable for Masters)***

**21) Development of the enteric nervous system in the mouse – what is the role of the intestinal microbiota?**
***(suitable for Hons/Masters)***
(with Dr Jaime Foong)

The cells that make up the enteric nervous system are derived from neural crest cells that migrate along the path that will become the vagus nerve and enter the upper gut at about embryonic day 9. By embryonic day 14.5, these neural crest cells and their derivative neurons and glia have completely colonised the intestinal tube. However, our data indicate that neural control of intestinal function does not become completely mature until at least 6 days after birth. Immediately after birth the intestinal is colonised by various microbes that proliferate and ultimately reach adult proportions and composition some time after weaning. Virtually nothing is known about the interactions between these microbes and the developing enteric nervous system, although it is known that the intestinal microbiota can alter activity of enteric neurons in adult gut. This project will address this question by using antibiotics and probiotics to modify the maturing microbiota during critical periods of enteric nervous system development and maturation and then measuring the consequences for neuron number, neurochemistry and function. Methods used will include immunohistochemistry, video-recording of contractile activity and measurement of water and electrolyte secretion across the intestinal mucosa.
Masters students will also be able to pursue functional aspects of the question using electrophysiological analyses of the development of synaptic and neuromuscular transmission.

**References**


Gwynne RM, Ellis M, Sjövall H, Bornstein JC (2009) Cholera toxin induces sustained hyperexcitability in submucosal secretomotor neurons in guinea pig jejunum. *Gastroenterology* **136**, 299-308

Neal K, Parry L & Bornstein J. 2009. Strain-specific genetics, anatomy and function of enteric neural serotonergic pathways in inbred mice. *Journal of Physiology*. **587** (3): 567-586.

Chambers JD, Bornstein J & Thomas E. 2008. Insights into mechanisms of intestinal segmentation in guinea pigs: a combined computational modeling and in vitro study. *American Journal of Physiology - Gastrointestinal and Liver Physiology*. **295**: G534-G541.

Larsson M, Sapnara M, Thomas E, Bornstein J, Lindstrom E, Svensson D & Sjovall H. 2008. Pharmacological analysis of components of the change in transmural potential difference evoked by distension of rat proximal small intestine in vivo. *American Journal of Physiology - Gastrointestinal and Liver Physiology*. **294**: G165-G173.

Monro R, Bornstein J & Bertrand P. 2008. Synaptic transmission from the submucosal plexus to the myenteric plexus in Guinea-pig ileum. *Neurogastroenterology and Motility*. **20** (10): 1165-1173.

Neal K & Bornstein J. 2008. Targets of myenteric interneurons in the guinea-pig small intestine. *Neurogastroenterology and Motility*. **20** (5): 566-575.

**NEUROPHYSIOLOGY**

Prof Andrew Allen
Room N502
Level 5 north wing, Medical Building

Tel. 61 3 83445838
a.allen@unimelb.edu.au

## 22) Central Regulation Of Cardiovascular Function

The focus of our research is to understand how neural circuits generate and regulate sympathetic activity to the cardiovascular system. Our evidence suggests that this activity is a critical component in the development of hypertension, and subsequently cardiovascular diseases.

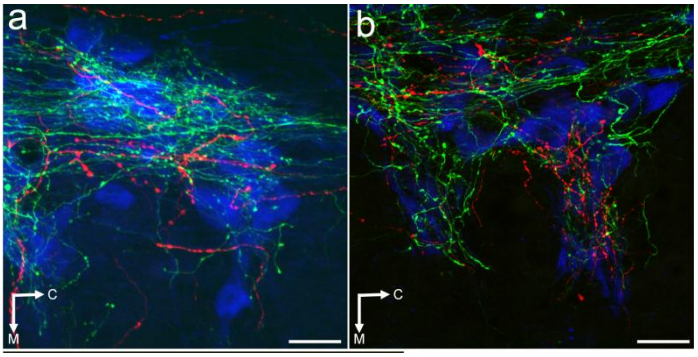



*Figure: Using viral transduction we have labelled one group of neurons with a red fluorophore and a different group with a green fluorophore. These neurons are located in the medulla oblongata. Their axonal projections are seen here in the vicinity of sympathetic preganglionic neurons in the spinal cord (blue neurons). These projections are many centimetres away from the cell body.*

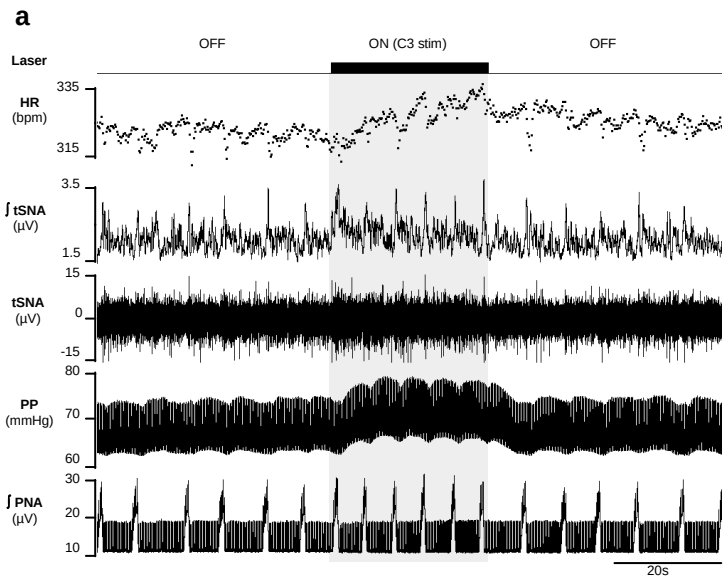



*Figure: Using viral transduction we have expressed the excitatory ion channel, channel rhodopsin, in a group of neurons whose function was not known. Channelrhodopsin is opened by blue light (heavy bar at top) leading to increased activity of just this cell group. Here we show that this group of neurons regulates heart rate and sympathetic nerve activity (tSNA) and increases blood pressure (PP).*

Key to deciphering how neural circuits generate particular outputs is knowing how different cell groups interact anatomically, and how the activity of one group affects that of others. We utilize cutting edge viral approaches to introduce transgenes into specific cells so that we can trace their axonal projections and connections (Sevigny et al., J. Comp. Neurol. 2012) or receptor expression (Simonds et al., Cell 2015). Using this same approach we also introduce activity-modifying proteins that enable us to remotely alter the activity of particular neurons – this technique is called opto- or pharmaco-genetics (Marina et al., Cardio. Res. 2011; Menuet et al., J. Neurosci. 2015). Using these approaches we are re-defining our understanding of the neural circuits involved in complex behaviours.

We tailor projects towards the interests of the student with emphasis on experimental physiology, electrophysiology, neuroanatomy or molecular biology approaches. In addition the scope of the projects can be modified to enable sufficient experimental work for Honours, Masters or PhD level degrees. Interested students are invited to discuss the projects, see similar experimental work in progress and meet the other members of the laboratory. To organize this, please contact Andrew Allen.

*Cited References.*

Marina N, Abdala AP, Korsak A, Simms AE, Allen AM, Paton JF, Gourine AV. Control of sympathetic vasomotor tone by catecholaminergic C1 neurones of the rostral ventrolateral medulla oblongata. Cardiovascular Research, 2011; 91: 703-710

Menuet C, Sevigny SP, Connelly AA, Bassi JK, Jancovski N, Williams DA, Anderson CR, Llewellyn-Smith IJ, Fong AY, Allen AM. Catecholaminergic C3 neurons are sympathoexcitatory and involved in glucose homeostasis. J. Neuroscience 2014; 34: 15110-15122

Sevigny CP, Bassi JK, Thomas WG, Williams DA, Anderson CR, Allen AM. Efferent projections of C3 adrenergic neurons in the rat central nervous system. J. Comp. Neurol. 2012; 520: 2352-2368

Simonds SE, Pryor JT, Ravussin E, Greenway FL, Dileone R, Allen AM, Bassi J, Elmquist JK, Keogh JM, Henning E, Myers MG, Licinio J, Brown RD, Enriori PJ, O'Rahilly S, Sternson SM, Grove KL, Spanswick DC, Farooqi IS, Cowley MA. Leptin mediates the increase in blood pressure associated with obesity. Cell 2014; 159: 1404-1406

**NEUROPHYSIOLOGY**

Prof David Williams
Room N523
Level 5 North wing, Medical Building

Tel. 61 3 83445845
d.williams@unimelb.edu.au

My special interest has been in the regulation of ionic balance in normal and diseased cells and tissues.

I was fortunate to publish some of the first work on fluorescent biosensors for physiologically important ions. This work set the tone and analytical framework for numerous papers that followed and contributed to the birth of a field that has impacted on the study of cell physiology and other disciplines of life sciences research.

New and improved methods have been developed for the detection of $Ca^{2+}$ and other ions in living cells and we were among the earliest to merge this technology with digital imaging microscopy. These new methods have been applied to a body of work on the $Ca^{2+}$ metabolism of skeletal and cardiac muscle that has earned international recognition. In recent years the focus of the lab has turned to the Neurosciences and to develop a better understanding of cell-to-cell communication in the central nervous system. In particular, we are interested in the interactions of microglial cells with other cells of the brain including neurons. Microglia and now being viewed as an essential ingredient in maintenance of normal brain function but their myriad of functions are not well understood.

Research training is a priority and approximately 40 honours and PhD students, many of whom are currently thriving in independent scientific careers, have graduated from my laboratory. My laboratory also has a high profile in the Australasian Region running practical skills workshops for Biomedical imaging throughout Australia, New Zealand and South Korea that have trained over 200 research scientists and graduate students.

PROJECT

**23) The role of microglia in the neurodegenerative process**

Numerous neuroinflammatory conditions such as Alzheimer's disease, multiple sclerosis, prions disease, and ischemic brain injury show enhanced expression of the purinergic (ATP-activated) P2X7 receptor (P2X7R) in the neuroinflammatory foci, where increased microglial activation is a co-existing feature. Recently we have reported that simple P2X7R-overexpression is sufficient in driving microglial activation and proliferation. Once activated, microglia are known to release a number of bio-active substances that include the proinflammatory cytokine interleukin 1β (IL-1β). Previous studies have linked P2X7R stimulation to the processing and release of IL-1β, but whether P2X7R channel or P2X7R pore is the predominant entity driving that release is unknown.

Using primary hippocampal cultures, we have evidence that release of IL-1β is critically dependent on P2X7R pore activity. In addition, we found the trophic effects of P2X7R pore (in particular microglial activation and proliferation) to be mediated by IL-1β. Inhibition of IL-1β production and inhibition of its function resulted in a significant decrease in P2X7R pore-induced microglial activation and proliferation. Our results indicate that P2X7R stimulation is important in induction of microgliosis and inflammation, and that impairment of IL-1β release due to specific blockade of P2X7R pore may be of significant therapeutic benefit in neuroinflammatory and neurodegenerative conditions where excessive IL-1β is evident. We aim to identify other bioactive factors important in the neuroinflammatory cascade and learn more about the mechanisms that mediate this involvement. Ultimately, these projects are aimed at identifying ways in which to interfere with the inflammatory cascade evident in many neurodegenerative diseases

**Relevant Publications**

Monif M, O'Brien TJ, Drummond K, Reid CA, Liubinas SV, Williams DA. 2014. P2X7 receptors are a potential novel target for anti-glioma therapies. *Journal of Inflammation* (in press, July)

Monif M, Reid CA, Powell KL, Smart ML, Williams DA. 2009 The P2X7 receptor drives microglial activation and proliferation: a trophic role for P2X7R pore. Journal of Neuroscience ***29*** (12): 3781-91.