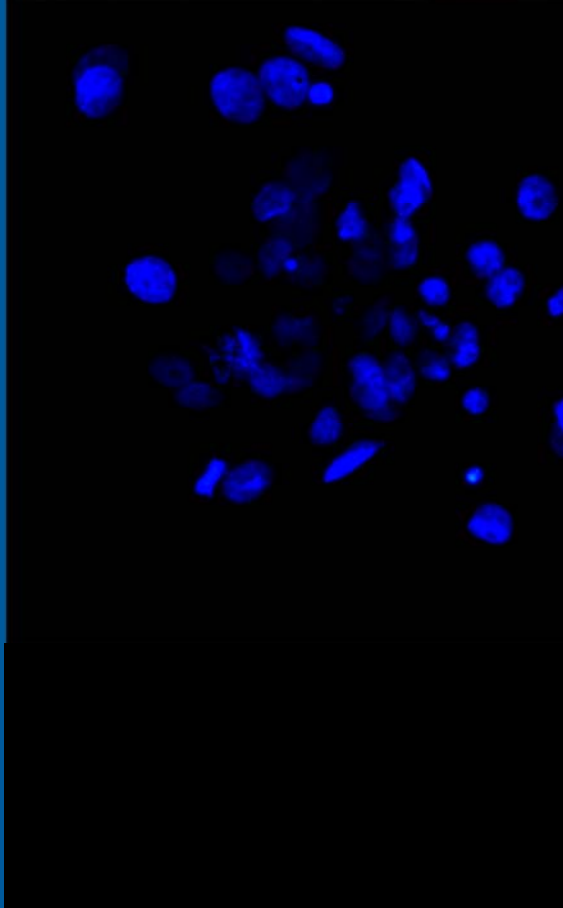
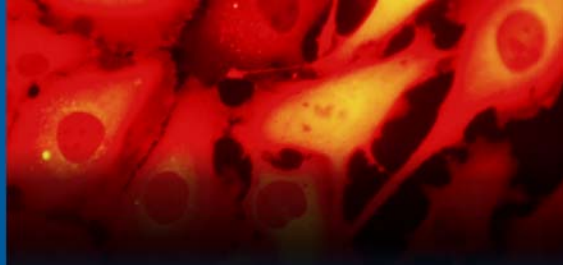


# Centre for Stem Cell

Honours, Masters &  
PhD  
Project Guide

2009



# MESSAGE FROM THE DIRECTORS

Dear Student

## Welcome to the 2009 Postgraduate Guide for the Centre for Stem Cell Research.

The focus of the Centre is on translating basic research into clinical and commercial outcomes via collaboration between its members, and with external partners.

The Centre is committed to conducting world

class research and providing excellent higher degree and research training opportunities.

We look forward to meeting you and discussing the many exciting projects on offer at the Centre,

Mark Nottle & Stan Gronthos

*Directors,*

*Centre for Stem Cell Research*

## CONTENTS

WELCOME & CONTENTS	1	PROJECTS	15
ABOUT THE CENTRE	2	Mesenchymal Stem Cell Group.....	16
GENERAL CONTACTS	2	Myeloma Research Program (MRP) and Regenerative Medicine Program (RMP).....	18
THE HONOURS PROGRAM	3	Periodontal Repair.....	21
Code of practice: Honours program.....	5	Developmental Genetics Group.....	22
ENTRY REQUIREMENTS FOR THE MASTERS & PHD PROGRAMS	6	Ovarian Biology.....	24
ABOUT THE MASTERS PROGRAM	6	Transplantation Immunology.....	26
ABOUT THE PHD PROGRAM	6	Acute Leukaemia Laboratory.....	28
Overview of the Masters & PhD programs.....	7	Molecular Immunology.....	30
Code of practice for University of Adelaide Masters and PhD programs.....	10	Cardiac Research Centre.....	32
CHOOSING A SUPERVISOR	11	Reproductive Biotechnology Group.....	33
STUDENT TESTIMONIALS	12	Stroke Research Programme.....	34
		SCHOLARSHIP OPPORTUNITIES	36
		EXPRESSION OF INTEREST: HONOURS	37

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## ABOUT THE CENTRE

The University of Adelaide's Centre for Stem Cell Research is a collaborative initiative comprising 18 research groups located at the University, the Women's and Children's Hospital, the Institute of Medical and Veterinary Sciences, and the Queen Elizabeth Hospital. The members of the Centre for Stem Cell Research undertake internationally recognised and awarded research on areas such as the isolation of adult and cord blood stem cells, clinical applications including potential cures for stroke damage and cardiac repair, as well as novel approaches to diseases such as cystic fibrosis and leukaemia.

*The Centre for Stem Cell Research offers cutting edge opportunities for students to undertake world-class research in the area of stem cell research.*

## GENERAL CONTACTS

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Molecular & Biomedical Sciences:

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Dentistry:

Professor Gary Slade, 8303 3291, gary.slade@adelaide.edu.au

# THE HONOURS PROGRAM

We offer an Honours enrolment through both the Faculties of Science and Health Sciences at the University of Adelaide, leading to the awards of , BSc (Hons), and BMedSci (Hons), BHSc (Hons) BDS (Hons). Students from any University who have completed a Bachelor of Science, Health Science, Biomedical Science, Arts or Agricultural Science degrees, or three years of the MBBS and BDS (or others as negotiated) are eligible for the course.

## Aims of the course

- To develop skills for independent critical thought and learning.
- To provide mentored training in scientific research methods.
- To encourage and develop interests in the science of stem cell biology.

Honours graduates of the Centre gain tangible experience in analytical thinking, written and verbal communication and working as a team member. These qualifications are highly sought by employers in all fields.

## What are the entry requirements?

The Centre does not have subject pre-requisites for entry into Honours. In past years, students with backgrounds in Physiology, Biochemistry, Microbiology and Immunology, Health Sciences, Genetics, Animal Sciences, Anatomy, Pharmacology, Psychology, Public Health, Medicine, Nutrition and others have been successful in the Honours program.

In general, students should have an aggregate credit level or higher in third year subjects, particularly in those subjects relevant to the proposed research area. However, students who have not achieved this level, but are highly motivated to become involved in research, can also excel in Honours and in their subsequent careers. If you fall into this category, you are encouraged to discuss the matter with the project manager of your Group or the Centre Manager.

The most important thing to do regarding possible enrolment in Honours is to identify a project or project area in this booklet that interests you. Then arrange to meet with the project supervisor to discuss the details of the project. If the supervisor agrees to take you on as an Honours student and your academic record is acceptable to the Centre and corresponding School, you will be invited to enrol in the course.

An expression of interest form can be found in the back of this booklet, and for further information regarding enrolment please contact us.



# THE HONOURS PROGRAM

What does the course involve?

(Example only from the School of Paediatrics & Reproductive Health)

The Honours course varies depending on Faculty & School that your chosen host group is based within, however it largely consists of one academic year of original research and structured training, primarily in an interactive relationship with one or two specific mentors (which may be from one or more groups). This culminates in the preparation and presentation by the candidate of a thesis outlining the conduct of the research project. The thesis is written in the form of a scientific paper written in the style of a journal article. The thesis is marked by 2 examiners with specific expertise in the research area and a general examiner from the Centre.

Some Honours programs (such as in the School of Paediatrics & Reproductive Health) also include participation in a series of tutorials on contemporary knowledge of physiology, methodology and philosophy in areas of research. Expansive reading around the tutorial topics and active contribution to group discussions are expected. Students' knowledge of these principles is assessed by written examination and is assessed by several examiners.

A critical assessment of relevant literature and research plan is usually submitted at the end of May.

Throughout the year, considerable emphasis is given to developing candidate's expertise in describing and presenting their projects to people with little specialist knowledge. The student gives three seminars during the year with the intention of building students confidence and presentation skills. Constructive feedback is given on performance in the non-assessed seminars:

- (1) an introduction/research proposal (Formative, not assessed) - early April
- (2) a progress seminar (Formative, not assessed) - mid August
- (3) a final seminar, two weeks after thesis submission (assessed) - end November

For a full summary of the requirements of the Honours program of the School which you will be enrolled through, please contact us.

## Assessment

As stated above, the requirements of the Honours year may vary depending on the School through which you are enrolled, but generally, the following assessment schedule can be followed:

Overview of Honours assessment components and relative weight in 2008 (School of Paediatrics & Reproductive Health)

Critical literature assessment	15%
Examination	15%
Tutorial contribution	5%
Thesis	50%
Final Seminar	15%
Total	100%

The University of Adelaide Research Education Programs Unit provided courses in

- Writing a Research Proposal
- Seminar Presentation Skills
- Reviewing Literature, plagiarism and Independent Research writing skills
- Producing a Thesis

## Reference

The above represents selective rewriting of the School of Paediatrics & Reproductive Health Honours Book, 2007.

# CODE OF PRACTICE FOR UNIVERSITY OF ADELAIDE HONOURS PROGRAMS

1. That senior undergraduate students are made aware of the personal development and career opportunities offered by Honours programmes.
2. That students have access to the grades of Honours awarded by the Discipline over the preceding 3 years
3. That a member of academic staff should have responsibility for the coordination of the academic programme and the welfare of the Honours students within the Discipline.
4. That commencing students are provided with full details of the Honours programmes. These details should include, but are not necessarily restricted to:
  - The detail of the academic programme such as course work and research components with relative weightings and contribution to the final result
  - Methods of assessment and timelines
  - Specification for theses and reports
  - Details surrounding seminar presentations
  - Facilities available for use during the year
  - Mechanisms for the resolution of complaints
5. That Disciplines commit to a guarantee of adequate supervision during the Honours programme and to the provision of adequate infrastructure for the research project.
6. That the proposed research project is appropriate for the specific academic programme.
7. That where necessary, Disciplines arrange ethical clearance for the project before the commencement of the Honours year, or take steps to ensure that the progress of the research is not delayed awaiting such clearance.
8. That the University's policies regarding Copyright and Intellectual Property are explained to students.
9. That opportunities are given to students to provide feedback and to contribute to the future development of Honours programmes in the Discipline.
10. That an appropriate procedure is established for dealing with unresolved conflicts between supervisor(s) and students, in line with institutional policy. The procedures should be designed to permit the investigation of problems arising during the candidature, and assist in formulating acceptable solutions.



# ENTRY REQUIREMENTS FOR THE MASTERS & PHD PROGRAMS

In order to gain admission to most postgraduate research programs in the University of Adelaide, it is necessary to have qualified for a four-year Australian university Honours degree (first or second class, division A Honours) or the equivalent from an approved overseas university. Some faculties may require students to enrol as a candidate for a Masters degree in the first instance, with the possibility of upgrading to a PhD at a later date if progress is deemed to be satisfactory.

If you are intending to apply for a Masters or PhD position, you must fill out an application form available from the following link:

[www.adelaide.edu.au/graduatecentre/scholarships/postgrad/pgforms.html](http://www.adelaide.edu.au/graduatecentre/scholarships/postgrad/pgforms.html)

Hard copies of these forms are also available from the Student Centre, Level 4 Wills Building. Ph: 8303 5208.

Email: [studentcentre@adelaide.edu.au](mailto:studentcentre@adelaide.edu.au)

## THE MASTERS PROGRAM

Masters' degrees involve one to two years of research for a full-time candidate and are similar in nature to the PhD, but do not necessarily require candidates to make a significant original contribution to research. Students are trained in research methodology and techniques and are engaged in the critical evaluation of literature and results in the substantive area of the thesis at an advanced level. Examiners of a Master's degree will be seeking evidence that the candidate has:

- a thorough understanding of the relevant techniques and methodologies in the field as demonstrated by a thorough critical review of the literature
- demonstrated competence in the chosen field through judicious selection and application of appropriate methodology to yield meaningful results
- demonstrated the capacity to evaluate critically these results and
- presented a clear and well-written thesis.

Whilst a number of Masters' degrees include an advanced coursework component, the focus is on research.

## THE PHD PROGRAM

The PhD is the basic qualification for a research career or academic position. The PhD involves two to four years of research for a full-time candidate or the equivalent in half-time candidature. In the course of completing the degree under appropriate supervision, candidates develop the capacity to conduct research independently at a high level of originality and quality and make a significant original contribution to knowledge in their chosen discipline.

A PhD thesis may comprise a conventional written narrative presented as typescript, or a combination of conventional written narrative presented as typescript and publications that have been published and/or submitted for publication and/or text in manuscripts, or a single major publication such as a book, or a portfolio of publications that have been published and/or submitted for publication and/or text in manuscripts, or creative or visual work(s).

Irrespective of the form of thesis presented, examiners will be looking for a candidate to:

- produce a clearly, accurately and cogently written thesis that is suitably illustrated and documented;
- demonstrate a deep knowledge of the research topic;
- relate the research topic to the broader framework of the discipline within which it falls;
- demonstrate an independence of thought and approach; and
- make a significant and original contribution to knowledge by the discovery of new facts, the formulation of theories, or the innovative reinterpretation of known data and established ideas.

# OVERVIEW OF THE MASTERS AND PHD PROGRAMS

## Provisional Candidature Requirements

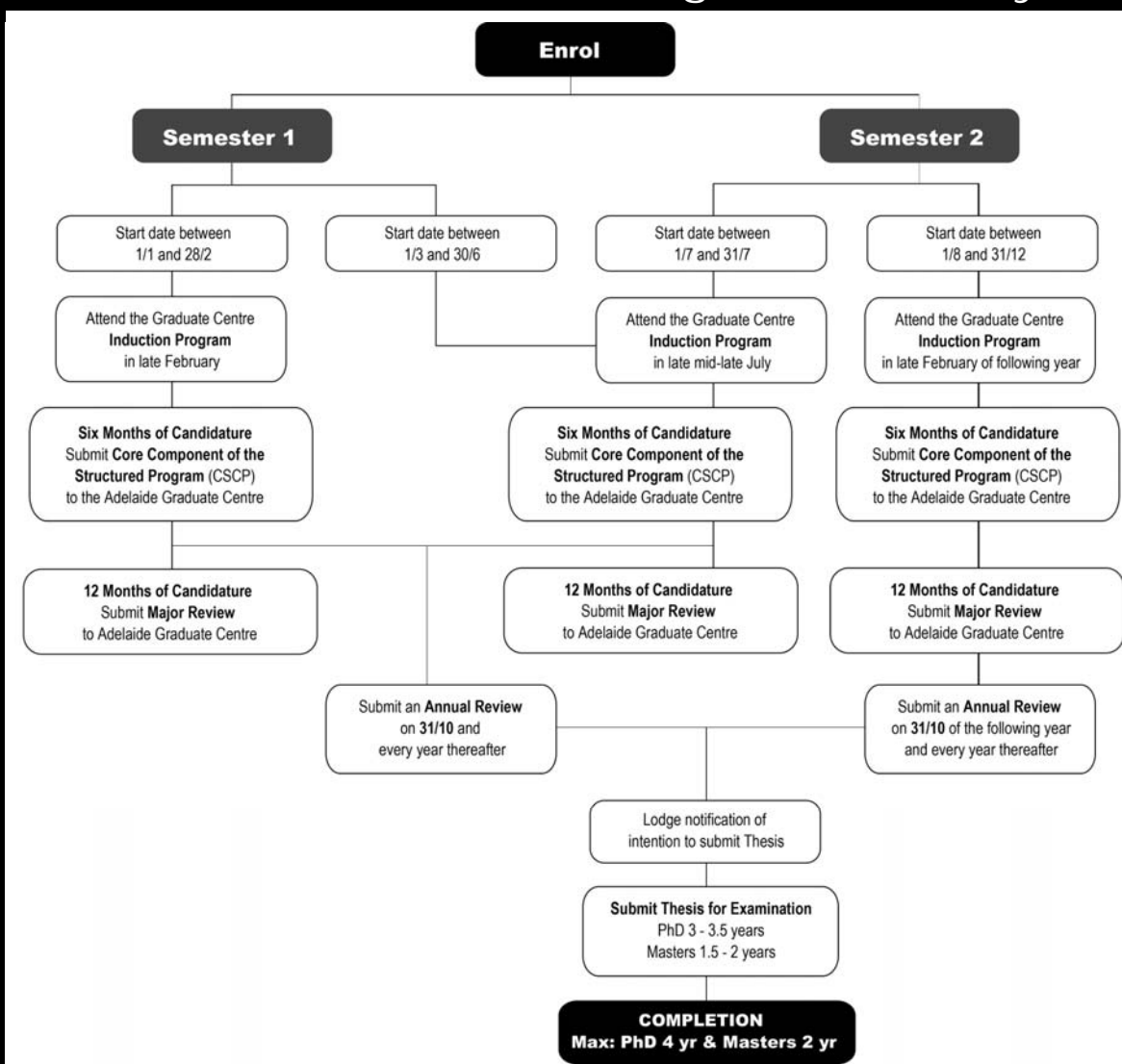
Formal acceptance as a higher degree by research candidate is a multi-stage process.

The first twelve months of candidature (or half-time equivalent) are provisional and during this time, you will undertake a number of milestones. These are:

- attendance at a local induction program
- attendance at the Adelaide Graduate Centre induction program
- completion of the core component of the structured program
- completion of an annual review of progress (note that you are exempted if you commence in candidature after the first of August in the year of the review) and
- completion of the major review of progress.

The number of milestones is greater during the period of provisional candidature than following confirmation, in order: to ensure that, irrespective of your discipline, you will receive a comprehensive induction to the facilities, services and professional development opportunities available to you; to introduce as much structure as possible into the first twelve months of your research program whilst you are adjusting to what is often a very different study environment and style; and to ensure that you formulate an academically sound and feasible research proposal in the early stages of your candidature

## Masters and PhD Program Pathway



# OVERVIEW OF THE MASTERS AND PHD PROGRAMS

## Adelaide Graduate Centre Induction Program

Each year, an induction program for commencing postgraduate research students is organised by the Graduate Centre. It is usually held on a Friday morning in late February and repeated in late July each year. The induction provides a valuable introduction to life as a research student at the University of Adelaide, and is intended to complement your School-level induction program. The Induction is run in two sessions over a half-day.

The first session introduces you to a range of topics such as the role of your Supervisor and how to keep your research on track, and services available such as computing and educational services. In the second session, students are divided into smaller discipline-focussed discussion groups where a panel comprising an experienced supervisor, a member of library staff and two later-year research students will talk about some of the important aspects of research candidature from their perspectives before inviting questions from the audience.

Attendance at a Graduate Centre induction program is a prerequisite for the confirmation of candidature (twelve months or half-time equivalent from commencement) and under normal circumstances all commencing higher degree by research students (including remote students) are expected to attend the first available induction program following enrolment.

For further information, to see the evaluations from previous inductions and to register your intention to attend the next induction, go to: <http://www.adelaide.edu.au/graduatecentre/induction/>

## Core Component of the Structured Program

The University of Adelaide structured program comprises "core" and "development" components. Further information about the development component of the structured program is provided later in this guide.

The core component must be completed within six months (or half-time equivalent) from the commencement of your candidature. Satisfactory completion requires that you have:

- attended a School induction program
- formulated a research proposal that is satisfactory to your School after explicit consideration of the ethical, intellectual property, and resource implications of your proposed research. The research proposal must be all your own work, except where there is clear acknowledgement and reference to the work of others
- presented your research proposal at a School seminar program
- regularly attended your School's seminar program and
- lodged the "Completion of the core component of the structured program" form and all other required documentation with the Graduate Centre by the due date.

In many Schools, students are also required to complete a literature review as part of their core component; your supervisors(s) or Postgraduate Coordinator will advise you where this is the case.

If your School has concerns about your progress these will be discussed with you and documented during your core component review and a recommendation may be made for the termination of your candidature or, where applicable, transfer to a Masters program.

Note that students who upgrade to doctoral candidature having already completed the core component during their prior Master's enrolment are exempted from undertaking the core component of the structured program in the doctoral program.

## Major Review of Progress

The major review of progress occurs twelve months or half-time equivalent from the commencement of candidature. It is 'major' in the sense that the outcome determines whether your candidature will be confirmed, or your provisional status extended, or, your candidature be transferred to the appropriate Master (If applicable), or a recommendation for termination of candidature on the grounds of unsatisfactory progress be considered by your Faculty's Higher Degrees Committee and the Research Education and Development Committee.

# OVERVIEW OF THE MASTERS AND PHD PROGRAMS

The Graduate Centre will advise you and your principal supervisor approximately one month in advance that your major review is due and direct you to the web site where you can download a copy of the form (a form will be mailed to you on request). The due date for return of your major review form is the first day of the thirteenth month (or half-time equivalent) from the commencement of your candidature. For example, if you are a full-time student who commenced between the 1st and the 31st of January, your major review of progress documentation must be returned to the Graduate Centre by the of 1st February of the following year.

To fulfil the requirements of the major review of progress, you must have:

- satisfactorily completed all the preceding milestones, including the Adelaide Graduate Centre Induction Program;
- regularly attended the School seminar program (remote students are exempted); and
- made satisfactory progress during the period of your provisional candidature.

In determining whether or not your overall progress has been satisfactory, your School may require additional tasks to be completed. Your supervisor(s) or Postgraduate Co-ordinator will advise you if this is the case in your School.

If your School recommended an extension of your provisional candidature at the Major Review, you will undertake an extended Major Review at the end of the extended provisional period. This review will confirm candidature, recommend conversion to the appropriate Master (if applicable) or recommend termination of candidature. No further extensions of the provisional status will be permitted.

## Annual Review of Progress

The annual review of progress, which occurs during September/October every year for all higher degree by research students who are active in candidature or on leave of absence, must be submitted to the Graduate Centre by the due date of 31 October. Note that if you commenced your candidature in August, September or October, you are exempt from undertaking an annual review in your year of enrolment.

Re-enrolment and the continuation of your scholarship (where applicable) are dependent upon satisfactory progress in the twelve months preceding the review or since the commencement of your candidature where this was less than twelve months ago.

The annual review is intended to be an open and frank appraisal of your rate of progress by both you and your supervisory panel. The review serves several purposes. It:

- ensures that you highlight your achievements during the preceding year so that you can clearly see the progress you have made both in your research and your professional development (it is common for students to underestimate their progress and the review process can provide some useful reassurance)
- provides you with an opportunity to formally set goals with your whole supervisory panel for the next stage of your project and in the next stage of your professional development
- is an important tool for identifying any problems that may be occurring in your candidature so that they can be documented and resolved. Documentation is very important, as the problems you report on your annual review form (which were beyond your control and have negatively affected your progress) will be taken into consideration if you submit an application for a candidature or scholarship extension in the future
- provides an opportunity to review and re-negotiate your access to resources and facilities
- provides an opportunity to review your supervisory arrangements, including the frequency and usefulness of meetings; and
- serves to ensure that your Postgraduate Co-ordinator, the Head of School and the Dean of Graduate Studies are kept fully informed of your progress.

# CODE OF PRACTICE FOR UNIVERSITY OF ADELAIDE MASTERS & PHD PROGRAMS

Students and staff members engaged in research are expected to be committed to exemplary standards of professional conduct and integrity. The broad elements that guide the conduct of research include:

- the maintenance of high ethical standards and intellectual honesty
- validity and accuracy in the collection and reporting of data
- appropriate storage and retention of data
- adherence to the Occupational Health & Safety requirements of the Discipline
- abiding by the University's guidelines for the authorship of publications
- avoidance of real or apparent conflicts of interest
- the appropriate recognition and assignment of intellectual property, copyright and technical/editing assistance and
- adherence to any confidentiality agreements and contractual agreements.

The University's 'Guidelines and rules for the responsible practice of research' ([Appendix 5](#)) summarise the standards of conduct and performance required of all those engaged in research at the University. Please also refer to the "Australian Code for the Responsible Conduct of Research 2007", which can be found at: <http://www.nhmrc.gov.au/index.htm>

If you are having difficulty interpreting the provisions of the Guidelines, you are encouraged to consult your supervisors, Post-graduate Coordinator or Head of School in the first instance. The Dean of Graduate Studies and the Deputy Vice-Chancellor and Vice-President (Research) are also available for consultation where required.

## Conflicts of Interest

A conflict of interest occurs when you have a private or personal interest or other external commitment, which may appear to an independent observer to be sufficient to influence and therefore compromise the validity of the research process by influencing impartial judgement. Disclosure of any actual or potential conflict of interest is essential for the responsible conduct of research. The University's policy on close personal relationships sets out the University's position on staff-student relationships and staff-staff relationships in regard to potential conflict of interest. A close personal relationship is defined as "one which gives rise to a real or potential conflict of interest and includes relatives and financial relationships".

If you are in a close personal relationship with a staff member, he or she is precluded from participating in any of the following with respect to you:

- selection for entry to the University
- selection for any undergraduate or postgraduate program offered by the University
- assessment procedures
- selection for any scholarship or prize
- honours or postgraduate supervision.

Close personal relationships must be disclosed to the Head of School or, if the Head of School is involved, to the Dean of the Faculty.

The policy is available at: <http://www.adelaide.edu.au/policies/138/>

## Paid Assistance for Undertaking Research

The Research Education and Development Committee has determined that it is acceptable for you to engage another person(s) (paid or otherwise) to assist in your research. The assistance may take the form of data collection (though not the manipulation of that data), preparation of routine chemicals and media or any similar tasks, provided that the proposed assistance is discussed with and approved by the School from the beginning and is appropriately acknowledged in your thesis.

# CHOOSING A SUPERVISOR

As an Honours student, you will be making the transition from assimilating existing knowledge to generating and disseminating new knowledge. What counts from now on is conceiving, conducting, documenting, interpreting, evaluating and communicating research.

Your supervisor is going to play a significant role in how well you succeed at these. You will become a researcher through the mentorship and guidance of your supervisor who will provide timely, constructive feedback regarding your understanding of the field you have selected to study. Your supervisor will also provide various resources such as space, equipment and supplies. On earning your degree your supervisor will likely also write vital letters of recommendation.

## Acquiring information about potential supervisors

Talk with current and former Honours and PhD students in the Centre, including those outside the potential supervisor's group. Use the Web of Science (<http://isiknowledge.com/wos>) and PubMed (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>) databases to see what the researcher has been doing and how the research has stimulated the work of others.

### *Face to face interaction*

meeting potential supervisors is essential, you must develop strong, positive self-presentation skills if you are to succeed. Meeting and familiarising yourself with potential supervisors offers you the opportunity to promote yourself as the best candidate for a project that interests you. Importantly you should also use the opportunity to gauge the supervisor, their group and research.

## Criteria for evaluating potential supervisors

### Whom to seek

#### *Someone with similar interests*

Seek someone with whom you share research interests; otherwise you may undertake a research project that you do not value highly and are therefore unlikely to complete satisfactorily.

#### *Someone with compatible interests*

All organisations offer people common means to diverse ends. Even if you cannot work in a group in which the research goals are similar to your own, their procedures may be relevant to your goals. It is quite probable of course that as you work in this "second choice" group, you may become interested in the research problems they are investigating.

#### *Scholars: renowned researchers*

Seek people who love science and are obsessive about research. They will document their work in articles, published in respected journals, that often describe a series of interlocking experiments concerned with a single problem. When researchers value their work and others agree, others will extend the work. Invited articles and presentations to professional societies suggest that a researcher's work is well received. You can check their publication records in the library.

Grant support from major research foundations such as the NHMRC, ARC or industry indicates that other scientists and/or the community judge this scientist to have made significant contributions to their discipline or society. Such grant support is allocated competitively; more competitively than the allocation of space in major journals. A history of grant support is therefore very impressive. Most impressive is a researcher who holds a special position where a university or granting body has granted the person long-term support.

There are potential problems working with renowned researchers. In areas where research costs require grant support, such supervisors may be unable to offer help because they are busy writing grant proposals, administering grants and supervising many other students and post-doctoral students.

#### *Scholars: less renowned researchers*

These researcher's records will have many of the attributes discussed above, but often a record of grant support may be absent or low. Where research costs are small, these people can also be excellent supervisors. Seek a supervisor who knows quite a bit about the area you are interested in, is enthusiastic about research, and of course, readily offers help.

# CHOOSING A SUPERVISOR

## *Someone you can respect*

If your supervisor is honest, ethical, loves doing science and is reasonably successful, it would also be nice if you liked your supervisor (and vice versa)! However, choosing a supervisor solely because he or she is nice is a mistake. A nice person may withhold frank evaluations of your knowledge, skills and progress. If you have an excellent supervisor, your feelings toward your supervisor might best be labelled as respect.

## **Whom to avoid**

### *Those not around the Lab much*

Be cautious with potential supervisors who structure research so that there are multiple layers of authority and who are rarely around the laboratory or group. Also consider with caution those whose duties take them away from the group for prolonged periods.

### *Reference*

The above represents selective rewriting of an article published in J. Chemical Education 70: 303, 1993.

# STUDENT TESTIMONIALS

Dr Peter Psaltis (FRACP)

**Research Focus:**

Cardiac reparative properties of mesenchymal stem cells (MSCs) from adult human and ovine bone marrow

**Study Background:**

MBBS (Honours) University of Adelaide, FRACP Clinical Cardiologist, Adelaide Cardiology /Royal Adelaide Hospital. NHMRC / NHF PhD Student, Department of Medicine



I graduated from The Adelaide University Medical School, with Honours in 1999 and was the recipient of both The Alumni University Medal and The University Medal. Following my internship, I undertook both Basic Physician Training and Advanced Training in Cardiology at the Royal Adelaide Hospital, receiving my FRACP at the end of 2005. Since 2006 I have been a Research Fellow at the Cardiovascular Research Centre, RAH and PhD student in the Department of Medicine, University of Adelaide. I am the holder of a co-funded NHMRC / NHF post-graduate scholarship, having ranked first nationally in my application for National Heart Foundation funding in 2006.

My PhD research is co-supervised by Associate Professors Stan Gronthos and Andrew Zannettino (Joint Heads of Mesenchymal Stem Cell Research Group, Division of Haematology, Institute of Medical and Veterinary Sciences and Hanson Institute) and Professor Stephen Worthley (Helpman Professor of Cardiovascular Medicine). Our project is investigating the cardiac reparative properties of immunoselected mesenchymal stem cells (MSCs) from both adult human and ovine bone marrow. This involves basic scientific experiments exploring the paracrine protective effects of MSCs on cardiac and vascular cells and the cardiomyocyte differentiative potential of MSCs, as well as the preclinical application of allogeneic MSCs in ovine models of heart failure. The latter studies are utilising both state-of-the-art stem cell delivery technology and cardiac magnetic resonance imaging.

In addition to my research commitments, I currently have a small clinical load in private cardiac practice and am actively involved in the teaching of Undergraduate medical students and post-graduate doctors, including those overseas-trained doctors preparing for their Australian Medical Council examinations. I have been an invited speaker at both national and international conferences.

## STUDENT TESTIMONIALS



**Danijela Menicanin**

**Research Focus:**

Characterisation of pluripotent stem cells in bone marrow, periodontal ligament and dental pulp

**Study Background:**

Bachelor of Laboratory Medicine (Honours), University of South Australia

After completion of the undergraduate degree, my interest in histopathology led to an honours project with Associate Professor Nicola Fazzalari, in the Bone and Joint Research Laboratories at the IMVS. The project focused on characterisation of osteoarthritic bone based on its immunophenotypic profile. Even though I found this field of research very interesting I felt the need to change direction and expand my knowledge. Due to extensive literature searching during my Honours year, I had become aware of the therapeutic potential in stem cell research and developed great interest in this area.

This led to my current joint project, in the Bone Cancer Research Laboratory at the IMVS and at Dental School, Health Sciences University of Adelaide, where for the past 20 months I have been doing my PhD under the supervision of Associate Professor Stan Gronthos and Professor Mark Bartold, respectively. My project involves the characterisation of pluripotent cells present in three types of stromal tissue, the bone marrow, periodontal ligament and dental pulp. Identifying the genetic differences between pluri-potent cell types and their mature counterparts will aid in our aim to gain a better understanding of fundamental cellular processes involved in cell development.

I have found my PhD to be a challenging, rewarding and a growing experience. I feel that I have benefited from it at a personal level, as well as a professional level, recently I was awarded a Royal Adelaide Hospital Dawes Scholarship. The independence and the responsibility gained during this project have enabled me to obtain time management and communication skills whilst acquiring the essential technical expertise. Most of all, I have found the past two years very enjoyable and look forward to a bright future in this field.



**Thomas Klaric**

**Research Focus:**

Stem Cell differentiation into neurons

**Study Background:**

Bachelor of Biotechnology (Honours), PhD Student, Discipline of Molecular and Biomedical Sciences, University of Adelaide. Major: Genetics.

I completed my Bachelor of Biotechnology at the University of Adelaide in 2004, majoring in Genetics. The following year I took up an Honours project in Dr Simon Koblar's laboratory investigating the function of a newly discovered gene, NPAS4. This is a gene that is expressed in the brain following various types of brain trauma, such as stroke and seizure. The focus of my project was to use stem cells to explore the role of NPAS4 in neural differentiation. I really enjoyed working on this project as, being a novel gene, very little was known about NPAS4 and so every discovery was new and groundbreaking. It was also good to gain experience working with stem cells and learning techniques to do with stem cell culture, as this is one of the most rapidly expanding fields in science today.

Having benefited from both an interesting project and a good relationship with my supervisor and other lab members, I returned in 2005 to commence my PhD and continue work on the NPAS4 project. I am now about to enter my third year and, though there have been some difficulties at times, I am still enjoying my work.

What I like most about research is that it stimulates the mind and constantly provides fresh challenges. It often requires some lateral thinking to come up with creative solutions to problems and when these problems are overcome, it provides a great sense of satisfaction. It is exciting to work in a cutting-edge field and make new discoveries that contribute to our understanding of natural biological processes. It also provides opportunities to travel to conferences and scientific meetings all around the world and I have been fortunate enough to be able to attend a number of major conferences already.

## STUDENT TESTIMONIALS

Kristie Pan Yu Lee

**Research Focus:**

SOX3 role in murine embryonic development and neural stem cells

**Study Background:**

Bachelor of Science (Honours). Majors: Genetics & Infection & immunity



During my last year of undergraduate studies, I took part in a 12 week research placement in Professor Robert Saint's laboratory in the Discipline of Genetics. I completed my Honours year with Associate Professor Robert Richards within the same discipline. His group studies genes at chromosomal fragile sites. My Honours project focused on the investigation of the interaction between WWOX and a stress response signaling molecule TRAF2.

The knowledge and experience I gained during my Honours year was invaluable. In the hope of becoming exposed to something different, I came across the work of Dr Paul Thomas, my current supervisor and whose research on the study of congenital X-linked disorder(s) through understanding the genetic and molecular networks during murine central nervous development has greatly interested me. We are currently investigating the role of the transcription factor, SOX3, in murine embryonic development. The Sox3 gene is active in neural stem cells in the primitive brain. My current research aims to elucidate the function of Sox3 in prenatal forebrain development and its relation to congenital hydrocephalus, which may ultimately lead to development of improved prognosis and treatment for this condition. My PhD experience so far has been most positive. I have made significant progress in understanding how hydrocephalus occurs in these mice. I have also mastered a number of skills as a developmental biologist and communicated my research findings to other scientists in the field. In return, I have learnt techniques from them and adapted these to my research. I am looking forward to meeting and presenting my work to researchers from a broader background at future conferences and to enjoy the next two years or so of my wonderful PhD life.



Sonya Diakiw

**Research Focus:**

The role of tumor suppressor genes in the development of acute myeloid leukaemia (AML)

**Study Background:**

Bachelor of Science (Honours - Molecular Biology), University of Adelaide. Major: Genetics.

I have always been interested in science but it wasn't until I had experienced several different fields of science at University that I became interested in molecular biology.

It has been fascinating for me to study how biological events occurring on a microscopic scale can result in a visible outcome, such as improved patient treatments for various diseases. After completing my undergraduate degree I undertook my Honours year with A/Prof Richard D'Andrea, focusing on identifying and characterising novel genes with potential involvement in the development of leukaemia. I enjoyed the challenges of laboratory research and developed an interest in cancer research in particular. I am now taking this area of interest further and doing my PhD with A/Prof D'Andrea, focusing on the characterisation of a potential novel tumour suppressor gene we believe may have a role in the development of acute myeloid leukaemia.

Leukaemia affects over 2500 Australians each year, and treatments often meet with limited success and can have debilitating side effects. Thus there is a distinct need for improved treatments however this can only be achieved with a clear understanding of the molecular processes involved. The work that I am undertaking as part of the D'Andrea laboratory focuses on these basic molecular processes, and by identifying new oncogenes or tumour suppressors involved with leukaemia we may one day be able to design treatments which specifically target these molecules.

Through my time in the laboratory I've developed critical thinking and various research skills, and have enjoyed being to apply my problem solving skills to the challenges at hand. It has also been a fantastic opportunity for me to attend several conferences both nationally and internationally which have allowed me to extend my knowledge and investigate further career opportunities once I

A fluorescence microscopy image of a plant root system. The roots are stained with multiple fluorescent dyes, resulting in a vibrant display of colors including green, purple, blue, and red. The central root is the most prominent, showing a clear purple segment. Other roots branch out from it, some showing green and red staining. The background is black, making the brightly colored roots stand out. The word "Projects" is overlaid in white text in the upper center, with a small red dot to its right.

# Projects •

# MESENCHYMAL STEM CELL GROUP

## About Us

We have previously identified different mesenchymal stem cell (MSC) populations that live in adult bone marrow, peripheral fat and dental pulp tissue. These stem cells have the capacity to differentiate into connective tissue cell types and form the tissues from which they were initially derived. However, the precise molecular signals responsible for maintaining these stem cell pools or inducing differentiation leading to the eventual formation of bone, fat, muscle, cartilage or dentin have yet to be determined.

We propose that primitive mesenchymal stem cells express critical genes that regulate maintenance of the stem cells pool and their differentiation into bone, cartilage and dentin.

We are currently analysing the gene expression profiles of highly purified mesenchymal stem cell populations derived from bone marrow and dental pulp tissue based on an isolation protocol they have patented. This work is conducted in collaboration with the Periodontal Repair Group (P 24), led by Professor Mark Bartold at the Colgate Australian Clinical Dental Research Centre.

We are also working on identifying genes uniquely expressed by these stem cells that will yield important clues for regulating cardiac, bone, fat muscle, ligament and dentin development.

Our group is also involved with several pre-clinical studies in Australia and the USA examining the efficacy of MSC to repair bone, cartilage, periodontal and cardiac defects using ovine large animal models in collaboration with Angioblast Systems Inc., New York, NY, USA and Mesoblast Ltd, Melbourne Vic Australia.

## Projects:

### 1: Mesenchymal stem cells in skeletal tissue regeneration

This work will investigate the molecular mechanisms controlling maintenance of osteo/chondrogenic precursor cells and skeletal tissue regeneration.

Projects will focus on stem cell biology and the use of microarray analysis and proteomic analysis for determining differences in the gene expression profiles of normal and genetically modified mesenchymal stem cell populations. In particular the role of the TWIST helix-loop-helix family of transcription factors, chemokines and Eph/ephrins in postnatal MSC maintenance and development of bone, cartilage, support of haematopoiesis and modulation of immune responses.

### 2: Dental mesenchymal stem cells for tissue regeneration

These studies involve the identification and characterization of human and ovine periodontal ligament stem cells (PDLSC) and dental pulp stem cells (DPSC). Studies will determine the efficacy of different stem cell preparations and biomaterials to repair alveolar bone, cementum, dentin and periodontal tissues using both ovine models representative of different dental defects.

### 3: Neural crest derived dental pulp source to repair neural tissue

This work will explore whether neural crest-derived primarily DPSC and PDLSC have the capacity to develop down a neural pathways. Studies will assess the capacity of human bone marrow, dental pulp and periodontal ligament derived MSC to form functional neural tissues in vitro and when transplanted into chick embryos and rodent brain tissue using a well established animal stroke model.

### 4: The use of mesenchymal stem cells for cardiac and vascular regeneration

These studies will identify factors produced by different MSC subpopulations and determine the effect of these molecules to stimulate angiogenesis and cardiomyocyte proliferation and differentiation.

# MESENCHYMAL STEM CELL GROUP

## Contact Us

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The Mesenchymal Stem Cell Group

Left to right: Sharon Paton, Peter Psaltis, Naohisa Wada, Danijela Menicanin, Krzysztof Mrozik, Stan Gronthos, Sandra Isenmann, Lachlan Cooper, Agnes Arthur, Tanya Henshall

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- (1) Gronthos S, Mankani M, Brahim J, Gehron Robey P, Shi S (2000). Post-Natal Human Dental Pulp Stem Cells In vitro and In vivo. *Proceedings of the National Academy of Sciences (USA)*, 97 (25): 13625-13630.
- (2) Gronthos S., Zannettino ACW, Kortesidis A, Shi S, Graves SE, Hay SJ, Simmons PJ (2003). Molecular and cellular characterisation of highly purified human bone marrow stromal stem cells. *Journal of Cell Science* 116: 1827-1835.
- (3) Shi S. and Gronthos S. (2003). Perivascular Niche of Postnatal Mesenchymal Stem Cells in Human Bone Marrow and Dental Pulp. *Journal of Bone and Mineral Research*, 18(4): 696-704.
- (4) Shi S, Gronthos S, Chen S, Reddi A, Counter CM, Robey PG, Wang CY (2002). Bone formation by human postnatal bone marrow stromal stem cells is enhanced by telomerase expression. *Nature Biotechnology*, 20(6): 587-591.
- (5) Kortesidis A, Zannettino ACW, Isenmann S, Shi S, Lapidot Tsvee L, and Gronthos S (2005). Stromal derived factor-1 promotes the growth, survival and development of human bone marrow stromal stem cells. *BLOOD*. 105(10):3793-3801.

# MYELOMA RESEARCH PROGRAM (MRP) AND REGENERATIVE MEDICINE PROGRAM (RMP)

## About Us

Multiple myeloma (MM) is an incurable haematological cancer of the antibody-producing plasma cell (PC). The estimated frequency of this disease in our community is estimated to be 5-6 new cases per 100,000 persons per year.

MM is unique amongst haematological malignancies in its capacity to cause massive destruction of the skeleton. The focal osteolytic lesions result in a range of debilitating clinical symptoms including bone pain, pathological fractures, spinal cord compression, hypercalcemia and renal failure.

The Myeloma Research Laboratory (MRL) was established in 2000 with the aim of identifying the molecular and cellular mechanisms responsible for the bone destruction.

Current projects are focused on:

- (a) identifying novel mediators of bone disease in MM;
- (b) identifying mechanisms of increased blood vessel density in MM;
- (c) developing aptamers (nucleic acid-based antibody-like molecules) against key target molecules involved in MM disease progression and (d) determining if tyrosine kinase inhibitors (and related compounds) represent suitable compounds to inhibit osteolytic bone resorption and promote bone formation.



The Myeloma Research Group

Left to Right: Dr Andrea Dewar, Dr Sharon Hampton-Smith, Dr Stephen Fitter, Ms Kate Vandyke, Dr Peter Diamond, Ms Jenny Drew, Ms Sally Martin, Ms Amanda Davis, A/Prof Andrew Zannettino.

## Contact Us

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# MYELOMA RESEARCH PROGRAM (MRP) AND REGENERATIVE MEDICINE PROGRAM (RMP)

## Projects:

### 1: The role of CXCL12/CXCR4 in pathological angiogenesis and osteolytic bone disease in Multiple Myeloma

Like solid tumours, the continued growth of the MM PC clone is dependent upon an adequate supply of oxygen and nutrients. In response to the increased metabolic demand, the MM tumour cells induce the formation of a new blood supply from the pre-existing vasculature ("angiogenesis"). Angiogenesis is critical in the progression of MM, and studies show that MM patients with active disease exhibit an increased BM angiogenesis when compared with those in remission or to subjects with a precursor of clinical MM (MGUS). In addition, increased angiogenesis is correlated with decreased overall survival in patients with MM. While the precise mechanisms by which MM cells induce angiogenesis are not completely understood, studies from our laboratory show that plasma levels of the potent chemokine, CXCL12, are elevated and positively correlate with BM angiogenesis. In addition to angiogenesis, our studies also suggest that CXCL12 also stimulates osteoclast (OC) precursor recruitment/activation and promotes osteolytic bone disease in MM patients.

As the growth of tumour cells is associated with a heightened need for nutrients and oxygen, the tumour microenvironment has reduced oxygen availability and is hypoxic. The central regulator of cellular responses to hypoxia is the transcription factor hypoxia-inducible factor-1 (HIF-1). Of significance to our work, recent studies show that the active HIF-1 complex can bind to the CXCL12 and CXCR4 promoters and activate their transcription in a variety of cell types.

#### Project work is aimed at:

- Examining if HIF expression co-localises with CXCL12 expression and is associated with heightened angiogenesis and osteoclastic bone resorption in the BM of patients with MM;
- Examining if hypoxia and cytokine-mediated upregulation of HIF expression in MM PC mediates aberrant CXCL12 expression in these cells;
- Examining if targeted disruption of HIF and the CXCL12/CXCR4 interaction, represent viable therapeutic modalities to inhibit osteoclastic bone resorption and pathological angiogenesis, using an established mouse model of MM PC-mediated osteolytic bone disease;
- Examining if bone turnover enhances colonisation and growth of the MM PC colony via a HIF-induced upregulation of CXCL12 expression in selected BM stromal cell "niches" using a mouse model of systemic human MM.

### 2: Development of a therapeutic aptamer that antagonises CXCL12 binding to CXCR4

One strategy to inhibit CXCL12 is the development of a functional blocker that will prevent the interaction of the factor with its cognate receptor. Historically, monoclonal antibodies (mAbs) have been developed for this purpose due to their high affinity and specificity binding. More recently, a novel approach to the isolation of target binding ligands has been developed with the realisation that single stranded nucleic acids can adopt complex three dimensional structures, or shapes. The folded nucleic acid structures are termed aptamers. Aptamers have been isolated to a wide range of targets of diverse size and chemistry that have no intrinsic nucleic acid binding properties. Aptamers bind with high affinity and specificity and offer significant advantages over mAbs in terms of their isolation, stability, immunogenicity and bioavailability resulting in their rapid development as novel diagnostics and therapeutics. Aptamers are isolated from random sequence libraries using an iterative selection and enrichment process known as SELEX or in vitro selection. Briefly, random sequence libraries with complexities of  $1 \times 10^{14}$  –  $1 \times 10^{16}$  unique sequences are mixed with the target and those sequences that fold into a shape that complements the target are partitioned from the gross excess of unbound sequences. Target bound aptamers are recovered by PCR and the process of target binding and recovery is repeated until those aptamers with the highest affinity and specificity for the target are enriched.

#### Project work is aimed at:

- Isolating nucleic acid aptamers from a random sequence library that bind CXCL12, using in vitro selection;
- Performing functional characterisation of the aptamers to determine how effectively the aptamers antagonise CXCL12 binding; and
- Performing biochemical characterisation of the CXCL12 aptamers to determine their binding affinity, identify the minimal binding sequence and map critical residues for binding using nuclease footprinting;
- Examining if an aptamer-mediated targeted disruption of the CXCL12/CXCR4 axis can limit MM disease progression in a mouse model of myeloma.

# MYELOMA RESEARCH PROGRAM (MRP) AND REGENERATIVE MEDICINE PROGRAM (RMP)

### 3: The effect of the PI3 kinase/mTOR Inhibitor, BEZ235, on osteoblast differentiation and function

Studies from our laboratory suggest that imatinib promotes osteoblast differentiation and function by inhibiting PDGF signaling (Fitter et al., 2008). An analysis of PDGF signaling pathways that are modulated by imatinib, in mesenchymal cells, revealed a potent inhibitory effect on Akt activation, a primary PI3 kinase substrate. PI3 kinase is an important transducer of PDGF signaling in mesenchymal cells, as demonstrated using phospho-tyrosine proteomics. Suppression of PI3 kinase activation using wortmannin and LY294002 promotes mineralised matrix formation in vitro. Furthermore, our studies have shown that LY294002 upregulates genes involved in osteogenic differentiation (BMP-2) and bone formation (BSP II, Osteopontin). These findings suggest that inhibitors of PI3 kinase activity may have potential effects on bone remodeling in vivo.

#### Project work is aimed at:

- Determining if the potent and specific inhibitor of PI3 kinase p110 subunits, BEZ235, modulates osteoblast differentiation and function in vitro and in vivo.
- Using complementary molecular genetic approaches, we will determine if PI3 kinase is a negative regulator of osteogenesis.
- Determining if inhibition of the PI3 kinase pathway represents a novel therapeutic approach to treat diseases characterised by bone loss.

### 4: Modulation of Bone Remodelling By Tyrosine Kinase Inhibitors (TKI)

The use of the tyrosine kinase inhibitors (TKIs) for the treatment of chronic myeloid leukaemia (CML) has demonstrated the success of rational pathway-specific therapeutic agents over traditional chemotherapy regimes. These TKI's achieve their specificity by targeting the CML-specific tyrosine kinase bcr-abl. In addition to bcr-abl, these drugs also displays activity against the M-CSF receptor (c-Fms), the platelet derived growth factor receptor (PDGF-R), stem cell factor receptor (c-Kit), c-abl, abl-related gene (ARG) and Lck. Of interest to our laboratory is the observation that the TKIs, imatinib, dasatinib and nilotinib inhibit the kinase activity of proteins involved in bone remodelling, including c-fms expressed on osteoclasts (OCs) and the PDGF-R expressed on osteoblasts (OBs). In vitro, we have shown that these tyrosine kinase inhibitors inhibit OC differentiation and function by blocking c-Fms, the receptor for M-CSF. In addition, we have shown that imatinib directs mesenchymal cell differentiation into osteogenic and adipogenic lineages via its affects on the PDGF-R.

#### Project work is aimed at:

- Examining the net skeletal consequences of imatinib and nilotinib therapy in vivo;
- Examining whether imatinib, dasatanib and nilotinib are effective anti-osteolytic agents in vivo using established murine models of myeloma;

## KEY PUBLICATIONS

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2. Martin SK, Dewar AL, Farrugia AN, Horvath N, Gronthos S, To LB, Zannettino ACW. Tumour Angiogenesis is Associated with Plasma Levels of SDF-1a in Patients with Multiple Myeloma. (2006). *Clin Cancer Res*. 12(23):6973-7.
3. Dewar AL, Farrugia AN, Condina MR, To LB, Hughes TP, Vernon-Roberts B, Zannettino AC. Imatinib as a potential anti-resorptive therapy for bone disease. *Blood*. 2006 Jun 1;107(11):4334-7. Epub 2006 Jan 31.
4. Zannettino AC, Farrugia AN, Kortesisid A, Manavis J, To LB, Martin SK, Diamond P, Tamamura H, Lapidot T, Fujii N, Gronthos S. Elevated serum levels of stromal-derived factor-1alpha are associated with increased osteoclast activity and osteolytic bone disease in multiple myeloma patients. *Cancer Res*. 2005 Mar 1;65(5):1700-9.
5. Dewar AL, Cambareri AC, Zannettino AC, Miller BL, Doherty KV, Hughes TP, Lyons AB. Macrophage colony-stimulating factor receptor c-fms is a novel target of imatinib. *Blood*. 2005 Apr 15;105(8):3127-32. Epub 2005 Jan 6.

# PERIODONTAL REPAIR

## About Us

To date repair of damaged periodontal tissues relies on implantation of structural substitutes with little or no reparative potential. More recently, tissue-engineering, based on an understanding of the cell and molecular biology of the periodontium, has emerged as an interesting alternative to existing therapies for periodontal regeneration.

We have established the presence of mesenchymal stem-like cells (PDLSC) in both human and ovine periodontal tissues capable of sustained renewal and tissue regeneration. We now hypothesize that PDLSC can be used for cellular based therapies to treat damaged periodontal tissues.

We collaborate extensively with the Mesenchymal Stem Cell Research Group, led by Associate Professor Stan Gronthos at the Hanson Institute/ Institute of Medical and Veterinary Sciences.

## Projects

### 1: Dental mesenchymal stem cells for tissue regeneration

These studies involve the identification and characterization of human and ovine periodontal ligament stem cells (PDLSC) and dental pulp stem cells (DPSC). Studies will determine the efficacy of different stem cell preparations and biomaterials to repair alveolar bone, cementum, dentin and periodontal tissues using both ovine models representative of different dental defects.

### 2: Neural crest derived dental pulp source to repair neural tissue

This work will explore whether neural crest-derived primarily DPSC and PDLSC have the capacity to develop down a neural pathways. Studies will assess the capacity of human bone marrow, dental pulp and periodontal ligament derived MSC to form functional neural tissues in vitro and when transplanted into chick embryos and rodent brain tissue using a well established animal stroke model.



The Periodontal Repair Group

Left to Right: Peter Zilm, Danijella Menicanin, Kris Mrozik, Stan Gronthos,  
Mark Bartold, Victor Marino, Nao Wada

## Contact Us

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# DEVELOPMENTAL GENETICS GROUP

## About Us

The development of the human brain into a complex structure containing one hundred billion cells is a fascinating process that requires thousands of genes. Mutations in genes that control brain development in humans cause common neurological disorders such as mental retardation.

Genetic studies performed in mice have demonstrated that the signaling systems and transcriptional networks that coordinate the differentiation of neuronal cell types are highly conserved throughout vertebrate evolution. Therefore, genetically modified mice provide an excellent system with which to investigate the genetic control of neurogenesis and to model human neurodevelopmental disorders.

Our laboratory has shown that duplication and mutation of the transcription factor gene SOX3 is associated with the mental retardation syndrome X-linked Hypopituitarism (XH). SOX3 is expressed in the stem cells of the developing brain and is a key regulator of neural differentiation. We have developed mouse models with altered dosage of SOX3 using gene knockout and transgenic technology. These mice exhibit abnormalities in brain development that resemble patients with XH. Our aim for the future is to understand how SOX3 controls the maintenance and differentiation of neural stem cells at the molecular and cellular level.

Our research uses a range of cutting-edge molecular genetic and cell biology techniques including microarray, fluorescence immunohistochemistry, proteomics and gene targeting in Embryonic Stem Cells.



## Projects

### 1: Identifying SOX3 target genes (Honours or PhD)

We have shown that SOX3 is a key regulator of neurogenesis in mice and humans. However, little is currently known about the genes/pathways that are regulated by this important transcription factor.

The aim of this project is to identify genes that are activated by SOX3 in the developing mouse brain. This project is based on microarray screens that we are currently performing using mouse embryos/neurospheres that lack SOX3 or overexpress SOX3.

Differentially expressed genes (ie putative SOX3 target genes) will be validated using Realtime-PCR and in situ hybridisation analysis of wildtype, knock-out and transgenic Sox3 embryos.

### 2: Identifying downstream targets of SOX3 (Honours or PhD)

We are also offering a complementary project using Difference in Gel Electrophoresis (DIGE) analysis to identify downstream targets of SOX3. This approach uses 2-D gel electrophoresis and mass spectroscopy fingerprinting to compare the proteome of SOX3 knock-out and transgenic embryos.

This is a fast moving area, so if you would like an update or further details please drop in for a chat!

# DEVELOPMENTAL GENETICS GROUP



Developmental Genetics Group  
(Dr Paul Thomas second from left)

## Contact Us

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## KEY PUBLICATIONS

1. Jacqueline T.T. Wong, Peter G. Farlie, Sebastien Holbert, Paul J. Lockhart and THOMAS PQ (2007) Polyalanine expansion mutations in the X-linked hypopituitarism gene *SOX3* result in aggresome formation and impaired transactivation. *Frontiers in Bioscience*, 12, 2085-2095
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4. Solomon, N. M., Nouri, S., Warne, G.L., Lagerstrom-Fermer, M., Forrest, S.M. and Thomas, P.Q. (2002) Increased gene dosage at Xq26-q27 is associated with X-linked hypopituitarism (XH). *Genomics* 79, 1-7

# OVARIAN BIOLOGY

## About Us

The primary function of the adult ovary is to mature and release eggs. Within the ovary eggs mature inside follicles and these in turn grow by replication of the cells of the follicle wall, namely granulosa and thecal cells. These cells produce the ovarian hormones, oestrogen and progesterone. Therefore replication of granulosa cells is critically important, both for hormone production and for maturation of eggs. In fact the number of eggs released and the timing of egg release is partially regulated via the cell fate decisions of the granulosa cells.

Our group focuses on the roles of extracellular matrix in regulating cell behaviour in the mammalian follicle. We were the first to identify that granulosa cells arise from a population of stem cells and to characterize them (reviewed in [1]). However limited studies have been conducted on these cells. They could be critical to understanding conditions such as premature ovarian failure, sterility induced by radiation treatment for cancer, infertility, hormone imbalances, as well as for developing new in vitro technologies for maturing eggs.

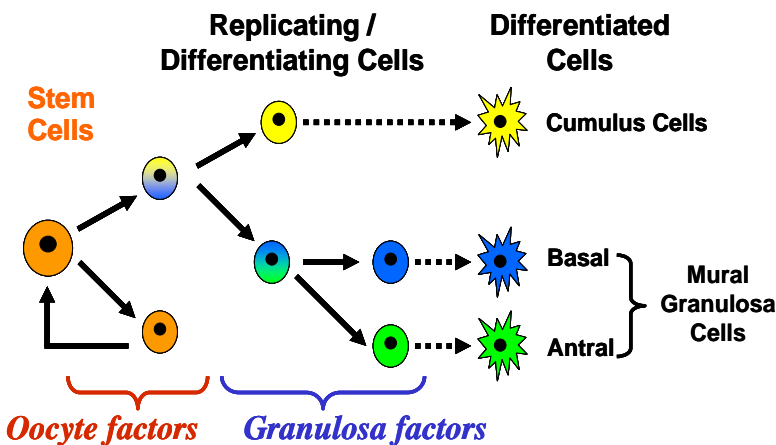


Fig 1: Ovarian Stem cells  
(Modified from [1])

## Projects

### 1: Stem Cells of Ovarian Follicles (Honours or PhD)

Our laboratory has shown that a proportion of granulosa cells isolated directly from antral follicles have a number of stem cell properties. These include the ability to divide under anchorage independent conditions [2], divide without contact inhibition [1] and express telomerase [3]. On this basis we proposed the model shown in the above figure [1].

It assumes pluripotentiality into at least cumulus cells (specialized cells surrounding the oocyte) and mural granulosa cells. The pluripotency of granulosa stem cells has yet to be demonstrated, however in mice expressing a dominant-stable mutant of beta-catenin, clonally derived granulosa cell tumours develop. These can be of granulosa, bone or neural phenotype [4], suggesting that tumours of granulosa cells are pluripotent. The goals of this project are to investigate the pluripotential of granulosa cells.

### 2: Thecal Stem Cells – Real or Not? (Honours or PhD)

In a recent PNAS article, 'thecal stem cells' [5] were reported in new born mice. However in this species follicles are still developing at birth.

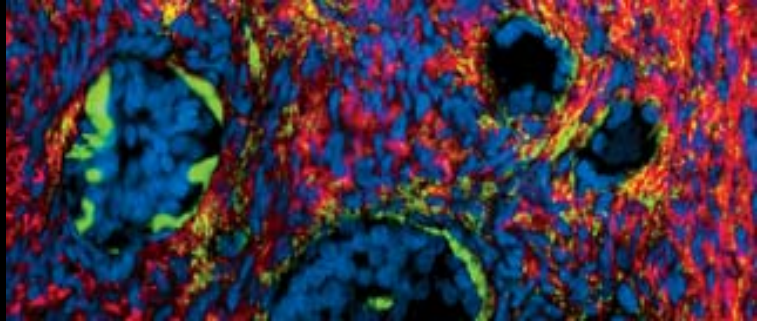
Whole ovaries were treated with collagenase and from this a heterogeneous mixture of cells was cultured and colonies of stem cells were identified in anchorage-independent culture. The authors identified expression of markers found in thecal cells, which in vivo are only expressed in the presence of granulosa cells. However they did not examine the colonies to see if all cells expressed the markers. Therefore it is possible that the colonies were of mixed cell type, containing granulosa stem cells and some thecal cells. Certainly the colonies bore a striking resemblance to granulosa stem cells [2].

The goal is to further investigate the existence of thecal stem cells. 'Thecal cell colonies' will be grown and harvested and processed for immunohistochemistry, and expression of thecal and granulosa cell markers will be examined for this purpose.

# OVARIAN BIOLOGY



Far Left: Prof Ray Rodgers (Group Head)  
Left: Dr Helen Irving-Rodgers



## Contact Us

### Supervisors:

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## KEY PUBLICATIONS

1. Rodgers RJ, Lavranos TC, van Wezel IL, Irving-Rodgers HF. Development of the ovarian follicular epithelium. *Mol Cell Endocrinol* 1999; 151: 171-179.
2. Lavranos TC, Rodgers HF, Bertoncetto I, Rodgers RJ. Anchorage-independent culture of bovine granulosa cells: the effects of basic fibroblast growth factor and dibutyryl cAMP on cell division and differentiation. *Exp Cell Res* 1994; 211: 245-251.
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4. Boerboom D, White LD, Dalle S, Courty J, Richards JS. Dominant-stable beta-catenin expression causes cell fate alterations and Wnt signaling antagonist expression in a murine granulosa cell tumor model. *Cancer Res* 2006; 66: 1964-1973.
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# TRANSPLANTATION IMMUNOLOGY

## About Us

The focus of this laboratory is on the molecular and cellular mechanisms of rejection of transplanted organs and the development of novel gene and cellular therapy approaches to treat rejection in organ transplantation.

The laboratory research program carried out by Dr Krishnan continues to investigate the role of inhibitory molecules in allograft rejection by the use of gene therapy vectors. Another aspect of Dr Krishnan's work examines the role of adult Mesenchymal stem cells as cellular therapeutic agents for modifying the alloimmune response to facilitate the acceptance

of transplanted organs with minimal immunosuppression. This work is being performed as a collaborative research project with the New York-based biotechnology company, Angioblast and Melbourne-based Mesoblast Ltd. This year Dr Krishnan has supervised two PhD students, Boris Fedorić and Darling Rojas, one Honours student, Jessica McIntyre and one international Master's student from China, Dongqing Yang.

## Dendritic cells

The dendritic cell from the donor organ is the major cell that initiates the rejection response by providing activation signals to the responding T cells from the recipient. The activation signals are provided by costimulatory molecules on dendritic cells, which interact with their appropriate ligands/receptors on T cells. The blockade of signals between these cells produces T cell unresponsiveness which facilitates organ transplant acceptance.

Our studies involve the genetic modification of dendritic cells using adenoviral 45 gene therapy vectors to delivery immunomodulatory molecules which belong to the immunoglobulin-like supergene family and the TNF-receptor-like supergene family members. Upon expression of these negative regulatory molecules in dendritic cells the effects on rejection responses and organ transplant acceptance will be studied in experimental models of transplantation.

## Mesenchymal stem cells

Adult mesenchymal stem cells are cells derived from bone marrow and can facilitate tissue repair of damaged or diseased tissue. Furthermore these cells have the distinct property of differentiating into bone, cartilage and adipose tissues and intriguingly under appropriate culture conditions can transdifferentiate into insulin producing cells.

Pancreatic islet transplantation is currently a clinical treatment for insulin replacement therapy in type 1 diabetics however the shortage of cadaveric pancreases is a limitation of this important treatment. Thus mesenchymal stem cells offer an expandable and readily available source of insulin producing cells.

## Projects (Honours, Masters and PhD levels)

### 1: Immunomodulatory properties of the immunoglobulin-like inhibitory molecule, CD200 in genetically modified dendritic cells.

The CD200 molecule is a transmembrane protein that interacts with its ligand CD200R expressed on T cells and induces T cell hyporesponsiveness. Dendritic cells will be modified with adenoviral vectors expressing CD200 and both in vitro and in vivo effects on modified immune responses will be studied. The project will involve a range of molecular biology and cell therapy techniques.

### 2: The immunomodulatory and differentiation properties of genetically modified mesenchymal stem cells.

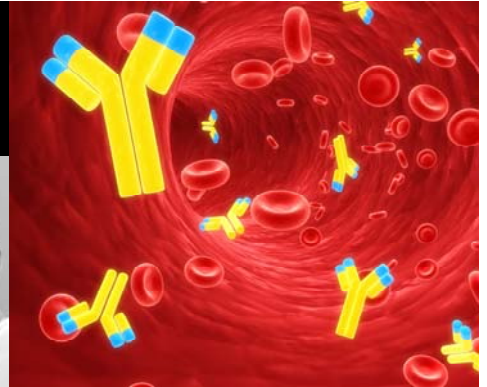
Since Mesenchymal stem cells can modify immune responses they may be further modified genetically to express therapeutic molecules that may facilitate organ transplant acceptance.

### 3: The characteristics of genetically modified mesenchymal stem cells that are transdifferentiated to insulin producing cells.

Mesenchymal stem cells can be converted to insulin producing cells under specific cell culture differentiation inducing conditions. The stability of the differentiated cells may be further enhanced by modifying the cells with selected genes.

# TRANSPLANTATION IMMUNOLOGY

Dr Ravi Krishnan (centre) with  
PhD students Boris Fedoric  
and Ashley Newland



## Contact Us

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Transplantation Immunology Laboratory,

28 Woodville Road, Woodville, South Australia, 5011

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Email: ravi.krishnan@adelaide.edu.au

## KEY PUBLICATIONS

1. Coates PT, Krishnan R, Kireta S, Johnston J, Russ GR.(2001) Human myeloid dendritic cells transduced with an adenoviral interleukin-10 gene construct inhibit human skin graft rejection in humanized NOD-scid chimeric mice. *Gene Therapy* 8(16):1224-33.
2. Klebe S, Sykes PJ, Coster DJ, Krishnan R, Williams KA. (2001) Prolongation of sheep corneal allograft survival by ex vivo transfer of the gene encoding interleukin-10. *Transplantation* 15;71(9):1214-20.
3. Newland A, Kireta S, Russ G and Krishnan R. (2004) Ovine dendritic cells transduced with an adenoviral CTLA4eEGFP fusion protein construct induce hyporesponsiveness to allostimulation. *Immunology* 113(3):310-7.
4. Klebe S, Coster DJ, Sykes PJ, Swinburne S, Hallsworth P, Scheerlinck J-PY, Krishnan R, Williams KA.(2005) Prolongation of sheep corneal allograft survival by transfer of the gene encoding ovine IL12-p40 but not interleukin 4 to donor corneal endothelium. *J Immunol* 175(4):2219-26.
5. Newland A, Russ G and Krishnan R. (2006) NK cells prime the responsiveness of autologous CD4+ T cells to CTLA4-Ig and IL10 mediated inhibition in an allogeneic dendritic cell-MLR. *Immunology* 118, 216-223.

# ACUTE LEUKAEMIA LABORATORY

## About Us

Our major focus is understanding the mechanisms underlying normal blood cell growth and differentiation, and the changes associated with myeloid leukaemia. We have used a number of molecular and biochemical approaches to investigate in detail the signaling responses and downstream events occurring during normal myelopoiesis, and with the aberrant growth associated with myeloid leukaemias. A significant research effort concerns analysis of cytokine receptor signaling. These receptors mediate stem and progenitor cell responses to a number of key cytokines and we are using novel systems to dissect pathways that control cytokine-induced cell survival, proliferation, differentiation and self-renewal. Aberrant cytokine receptor signaling occurs frequently in acute myeloid leukaemia (AML) and identification of key downstream events will allow development of targeted therapies with reduced toxicity.

Myeloproliferative disease (MPD) occurs as a result of changes acquired in the haemopoietic stem cell compartment which induce aberrant growth factor responses and over-production of mature myeloid cells. We have established a large cohort of patients with Polycythemia vera, and, through collaboration with Professor Tim Hughes and Prof Junia Melo at the Hanson Institute/IMVS, we have access to a larger number of patients with chronic myeloid leukaemia (CML). We aim to understand the nature of the changes that are associated with disease initiation and long-term maintenance of disease in these patients. Such changes are responsible for self-renewal of the disease stem cell and for survival of the disease stem cell during therapy. These pathways are also likely to be critical in the development of the leukaemic stem cell (LSC) in AML and by targeting these key pathways in leukaemia patients it may be possible to more effectively eradicate disease and prevent relapse. A key pathway that is important in CML is activation of beta-catenin and we will use patient material, unique delivery systems and animal models to investigate activation of this pathway in disease stem cell populations in CML and myeloid leukaemias.

## Project: Acute Myeloid Leukaemia

### 1: b-catenin target genes in Acute Myeloid Leukaemia (AML)

b-catenin is a central regulator of growth and self-renewal in multiple cell types, and mutations that cause activation of b-catenin activity have been found in many solid tumours (e.g. colorectal, lung, ovarian, breast). Self-renewal is a critical property of cancer stem cells that contributes to disease relapse and therefore targeting self-renewal regulators is an important new approach in cancer treatment. b-catenin is a transcriptional co-activator that is central to transmission of canonical Wnt signalling. Over the past several years evidence has been emerging that b-catenin protein stabilisation, which is essential for its transcriptional regulatory activity, has important roles in self-renewal of normal haemopoietic stem cells as well as some leukaemic stem cells. The mechanism associated with b-catenin stabilisation in haemopoietic cells is not well understood and importantly the transcription factor DNA-binding partners and direct targets of b-catenin are poorly defined. We hypothesise that the action of b-catenin in myeloid cells may not be solely through TCF/LEF family members (DNA binding members of the canonical Wnt signalling pathway) and propose here to analyse specific gene targets identified by chromatin immunoprecipitation and high-throughput sequencing (ChIP-seq) using b-catenin antibodies. This will characterise the function of the direct target genes and partner binding proteins for b-catenin in myeloid leukaemia.

## Projects: Polycythemia Vera (PV)

### Background

Polycythemia Vera (PV) is a late onset progressive haemopoietic disorders characterised by the clonal hyperproliferation of stem and progenitor cells and resulting in the expansion of erythroid, myeloid and megakaryocytic lineages. Most PV patients (>95%) carry the same base pair mutation in the key haemopoietic kinase Janus Kinase 2 (JAK2V617F).

JAK2 is the primary signalling, non-receptor tyrosine kinase associated with multiple, homodimeric or heterodimeric, type I cytokine receptors and is essential for activity of several key haemopoietic cytokines (eg Epo, Tpo, GM-CSF, IL3, IL5). Members of the heterodimeric type I cytokine receptor family are comprised of a ligand/cytokine specific alpha chain (GM-CSF R, IL3 R and IL5 R) and share a common beta chain (h $\beta$ c) which is involved in signalling. JAK2V617F is different from other constitutively activated kinases, such as TEL-JAK2 or BCR/ABL, in that it requires binding to unliganded type I cytokine receptors for constitutive signal transduction.

Although it has been shown that coexpression of JAK2V617F with either EpoR, TpoR, G-CSFR or prolactin-R allows these cells to proliferate in the absence of ligand, it is not known whether co-operation of JAK2V617F with the h $\beta$ c also confers a proliferative advantage in the absence of ligand.

### 1: Does JAK2V617F co-operate with the human common beta chain of type 1 cytokine receptors in myeloid proliferative disease?

This project aims to evaluate the contribution of the common beta chain to JAK2V617F – induced disease. To address this, proliferation and phosphorylation of downstream targets will be measured in cells coexpressing JAK2V617F and h $\beta$ c in the absence of ligand.

The ability of JAK2V617F to transform cell lines established from m $\beta$ c KO and wild type mice will be compared. The definitive role of h $\beta$ c will be evaluated in JAK2V617F positive primary human cells with h $\beta$ c siRNA, blocking anti-h $\beta$ c mAb and antisense h $\beta$ c oligonucleotide. (Publications 1&2)

### 2: Molecular genetics of Polycythemia Vera

The aim of this project, is to identify novel lesions in our JAK2V617F positive PV cohort, by comparison of paired disease and normal samples, on a high resolution Affymetrix Genome-Wide Human SNP array (600K).

Genes associated with chromosomal gains or losses will be over-expressed or downregulated respectively and their ability to alter growth factor responses of haemopoietic progenitor cells (eg BA/F3-EpoR and human CD34+ cells) measured.

Time permitting, the consequences of dysregulation of one candidate gene showing effects consistent with a role in early development of PV in these preliminary experiments will be tested in a bone marrow reconstitution model. (Publications 3&4)

## Contact Us

### Supervisors:

A/Prof Richard D'Andrea, Dr Anna Brown

Division of Haematology, IMVS or Division of Haematology and Oncology, The Queen Elizabeth Hospital  
Adelaide University, Discipline of Genetics, Faculty of Science

### Phone:

A/Prof Richard D'Andrea (8222 6363)

Dr Anna Brown (8222 6369);

Dr Petra Neufing (8222 6369)

### Email:

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anna.brown@imvs.sa.gov.au

petra.neufing@imvs.sa.gov.au



## KEY PUBLICATIONS

1. Levine RL, Pardanani A, Tefferi A, Gilliland DG. Role of JAK2 in the pathogenesis and therapy of myeloproliferative disorders. *Nat Rev Cancer* 2007 7(9): 673-83.
2. Morgan KJ and Gilliland DG. A role for JAK2 mutations in Myeloproliferative diseases. *An Rev Med* 2008 59: 231-222.
3. Butcher CM, Hutton JF, Hahn U, To LB, Bardy P, Lewis I, D'Andrea RJ. Cellular origin and lineage specificity of the JAK2(V617F) allele in polycythemia vera. *Blood* 2007 109(1):386-7.
4. Butcher CM, Hahn U, To LB, Gecz J, Wilkins EJ, Scott HS, Bardy PG, D'Andrea RJ. Two novel JAK2 exon 12 mutations in JAK2V617F-negative polycythaemia vera patients. *Leukemia*. 2008 Apr;22(4):870-3.

## About Us

Simon Barry's lab is focused on function based gene discovery. We are developing tools for gene discovery, gene delivery and gene ablation, and applying them in immunological cell settings. The lab uses cellular and molecular approaches to identify and characterize genes involved in the function of a specialized subset of T cells that are CD4+ CD25+ double positive and express the transcription factor FoxP3 (regulatory T cells). We aim to identify the target genes regulated by FoxP3 and gain insight into how these cells exert their suppressor function.

We are also attempting to identify novel proteins on the surface of regulatory T cells, which may be useful as diagnostic or functional markers for autoimmune diseases. Vectors based on the third generation self inactivating lentiviruses are being developed for stable gene delivery and stable delivery of shRNAi for gene ablation.

In addition we seek to generate Treg *de novo* from stem cells as an alternative approach for generation of cells for clinical intervention in autoimmune disease and in transplantation.

1. Defining the molecular basis of immune cell function using high content unbiased discovery technologies including micro arrays
2. Demonstrating functional roles for genes in immune cells using lentiviral gene delivery for over expression or ablation
3. Developing systems for in vitro differentiation of cord blood stem cells into cells of immune function

## Projects:

### 1: Analyse surface protein expression on Treg by flow cytometry and proteomics (Hons/Ph.D)

To separate regulatory T cells by flow cytometry based on three surface markers (CD4, CD25 and test antibody), and to investigate the expression of the transcription factor FoxP3 in the sub populations generated. This will be done by both antibody staining of permeabilised cells and by preparation of RNA for RT PCR.

The object is to identify a surface marker whose expression directly correlates with that of FoxP3 so that Tregs can be purified without the use of CD25. The rationale is that CD25 is a poor marker of Tregs as it is induced by activation of many T cells. Hence it is not exclusive to Tregs. Functional significance of any surface marker will be tested first in in vitro suppression assays and then in vivo.

### 2: To knockdown FoxP3 in Treg cells and test if it is required for suppressor function (Hons/Ph.D)

We aim to target genes required for regulatory function in T cells and examine their role by either over expression or gene silencing. For over expression studies, genes will be cloned into the lentiviral vectors and directly expressed in the target cells.

For gene ablation we will generate and screen shRNAi molecules against key transcription factors such as foxp3 and then transfer them to tet-inducible lentiviral RNAi vectors. The virus will be used to transduce primary T cell populations and validation of knockdown will be performed at the RNA level in the presence of tetracyclin. We have now generated lentiviral targeting constructs against FoxP3 and will test them in T cells to determine if FoxP3 expression is required to maintain Treg function, or is only required for the generation of Treg cells.

### 3: To optimise and characterise Treg differentiation from cord blood stem cells (Hons/Ph.D)

The clinical application of regulatory T cells is significantly hampered by the limited cell numbers that can be obtained from either cord or adult blood. Attempts to expand these purified Treg ex vivo have shown some promise, but there is some evidence that after extended culture ex vivo these cells lose their suppressive capacity. An alternative approach is to generate large numbers of T cells de novo from stem cells since these cells have the capacity to differentiate into all cells of the haemopoietic system.

We have established an ex vivo differentiation assay that can expand cord blood stem cells and induce their differentiation along the lymphoid pathway using a co-culture system giving notch signals via the Notch ligand Delta like 1. In this system we robustly observe 500-600 fold expansion of cell numbers and the generation of T cell subsets as defined by CD4/CD8 staining. We have successfully generated Treg cells using this culture system and are currently validating them functionally in vitro.

# MOLECULAR IMMUNOLOGY

## Contact Us

### Supervisors:

Dr Simon C Barry (Head Of Group & main contact)

Dr Timothy Sadlon

Dr Cheryl Brown

### Location:

Women's & Children's Hospital

University of Adelaide, Faculty of Health Sciences

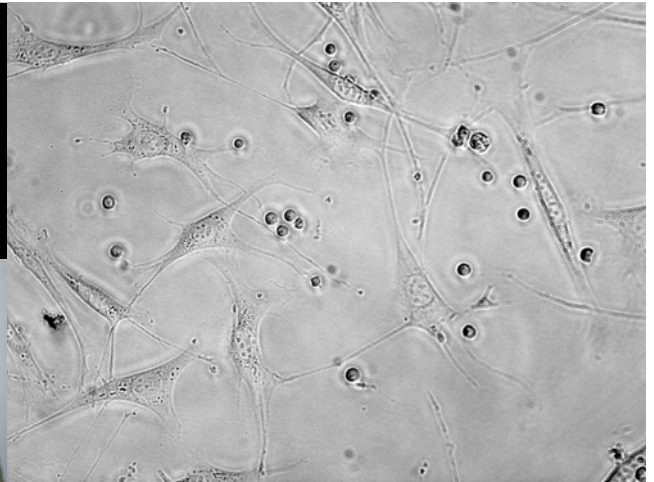
School of Paediatrics and Reproductive Health

Discipline of Paediatrics

Email: [Simon.barry@adelaide.edu.au](mailto:Simon.barry@adelaide.edu.au)

Phone: 8161 6562

Molecular Immunology Group  
Dr Simon Barry (Head)



## KEY PUBLICATIONS

1. Jonathon F. Hutton, Timothy J Sadlon, Suzanne Brezats, Richard J. D'Andrea and Simon C. Barry. Development of CD4+CD25+FOXP3+ Regulatory T cells from Cord Blood Haemopoietic Progenitor Cells. *Nature Medicine* in review
2. Barry SC and Coates PT, Retroviral escape using DC - that's what Friends are for *Blood* in press
3. Bresatz S Sadlon T, Millard D, Zola H, Barry SC. Purification and characterization of CD4+ CD25+ regulatory cells from Cord and peripheral blood. *J Immunol Methods* Jul 17; [Epub ahead of print]
4. Drabsch Y, Hugo H, Zhang R, Dowhan DH, Miao YR, Gewirtz AM, Barry SC, Ramsay RG and Gonda TJ. Mechanism of and Requirement for Estrogen-Regulated MYB Expression in Estrogen Receptor-Positive Breast Cancer Cells. *PNAS* Aug 21;104(34):13762-7
5. Zola H, Swart B, Banham A, Barry S, Beare A, Bensussan A, Boumsell L, D Buckley C, Buhning HJ, Clark G, Engel P, Fox D, Jin BQ, Macardle PJ, Malavasi F, Mason D, Stockinger H, Yang X. CD molecules 2006--human cell differentiation molecules. *J Immunol Methods*. 2007 Jan 30;319(1-2):1-5.

# CARDIAC RESEARCH CENTRE

## About Us

The Cardiac Research Centre and Mesenchymal Stem Cell Group are collaborating on research investigating the cardiovascular reparative properties of mesenchymal stromal/stromal cells (MSCs).

We are currently the only group in Australia (and one of only two groups in the Asia Pacific system) to be using state-of-the-art catheter-based stem cell delivery technology for the heart (NOGA™, Johnson & Johnson), while all of our in vivo projects utilise the gold standard for cardiac imaging (magnetic resonance imaging). We have collaborative ties to the University of Columbia, New York and Texas Heart Institute, Houston. Future projects will be an extension of this preclinical work investigating different delivery strategies, different cell types and different disease processes. In addition, several clinical projects are intended beginning in 2009.

## Projects:

Research opportunities range from basic science focused studies into the differentiative and reparative qualities of adult derived MSCs to preclinical and clinical in vivo studies.

The MSC group, headed by Assoc Profs Andrew Zannettino and Stan Gronthos have world-class expertise in the isolation of MSCs using special immunoselection techniques, from a range of tissues (eg bone marrow, adipose, dental pulp and periodontal ligament). Together with Prof Steve Worthley and Dr Peter Psaltis (Cardiologists), we are performing collaborative projects both (1) at the bench exploring the paracrine effects of these cells in supporting cardiac and vascular relevant cells and (2) at the preclinical level. The latter has involved the development of novel models of cardiomyopathy in large animals and the evaluation of immunoselected MSC therapy in this disease context.

## Contact Us

Cardiovascular Research Centre (CRC), Royal Adelaide Hospital, in collaboration with the Mesenchymal Stem Cell (MSC) Group, Institute of Medical and Veterinary Science

Contact person:

Ms Angela Hooper (PA to Prof Worthley), Email: [angela.hooper@adelaide.edu.au](mailto:angela.hooper@adelaide.edu.au), Phone: 8222 5608

Supervisors: Prof Stephen Worthley (Head, CRC), A/Prof Stan Gronthos, (Head, MSC Group), A/Prof Andrew Zannettino (Head, MSC Group), Dr Peter Psaltis

Locations: Level 3, Bone and Cancer Laboratory, Institute of Medical and Veterinary Science and Level 5, & Cardiovascular Research Centre, McEwin Building, Royal Adelaide Hospital, University of Adelaide, Faculty of Health Sciences, Discipline of Medicine

**Professor Worthley (front) and his team**

*Photo courtesy of Randy Larcombe*



## KEY PUBLICATIONS

1. Psaltis PJ, Zannettino ACW, Worthley SG, Gronthos S. Mesenchymal Stromal Cells – Potential for Cardiovascular Repair. *Stem Cells*. 2008. E-pub Jul 3.
2. Psaltis PJ, Carbone A, Nelson A et al. An ovine model of non-ischaemic cardiomyopathy – validation by cardiac magnetic resonance imaging. *Journal of Cardiac Failure* 2008. In press.
3. Zannettino ACW, Psaltis PJ, Gronthos S. Home is where the heart is: via the FROUNT Cell Stem Cell. 2008 Jun 5;2(6):513-4
4. Gronthos S, Fitter S, Diamond P et al. A novel monoclonal antibody (STRO-3) identifies an isoform of tissue non-specific alkaline phosphatase expressed by multipotent bone marrow stromal stem cells. *Stem Cells Dev*. 2007 Dec;16(6):953-63.

# REPRODUCTIVE BIOTECHNOLOGY GROUP

## About Us

The Reproductive Biotechnology Group has an international reputation in the development of cutting edge reproductive biotechnologies for use in biomedical and agricultural research .

These include the development of somatic cell nuclear transfer or cloning, as it is more commonly known. The Group's research is increasingly focused in the area of embryonic and adult stem cells and uses the pig as a model for humans in these fields. The following topics are being offered as Honours projects in 2009. These projects will expose candidates to leading edge research equipping them with a wide range of skills in the general areas of embryology, molecular and cellular biology.

## Projects (Honours)

### 1: Effect of oxygen tension on ES cell isolation

The aim of this study is to investigate effect of oxygen concentration on the efficiency with which mouse ES cells can be isolated. Plating efficiency, cell cycle duration and pluripotent gene expression will be examined.

### 2: Effect of LIF on ES cell progenitor number

The aim of this study is to duplicate in vitro "delayed blastocyst" conditions using Leukaemia Inhibitory factor (LIF) . The effect of different concentrations of LIF on the number of ES cell progenitors and the efficiency with which ES cells can be isolated in mice will be examined.

### 3: Effect of oxygen concentration on inner cell mass (ICM) outgrowth formation

The aim of this study is to investigate effect of oxygen concentration on inner cell mass composition. The effect of oxygen concentration on ICM outgrowths formation in mice will be examined.

### 4: Effect of plating method and culture medium on embryonal outgrowth formation and ES cell isolation

The aim of this study is to compare the ability of mouse immunosurgically isolated ICMs, zona pellucida-free blastocysts or blastocysts embedded into feeder layers, and cultured in different medium to form embryonal outgrowths from which ES cells are isolated from.

### 5: Embryonal outgrowth formation using extra-cellular matrix

The aim of this study is to develop feeder free condition for the isolation of porcine ES cells. The use of extra-cellular matrix for ES cell isolation will be compared with mouse embryonic fibroblast (MEF) feeder layers. The study will also investigate the ability of extra-cellular matrix to support the growth of porcine ES cell lines.

## Projects (MSc/PhD)

### Directed differentiation of porcine ES cells into definitive endoderm derivatives.

The aim of this project is to develop a protocol for the directed differentiation of porcine ES cell lines into precursors of liver, pancreas etc. This is unique opportunity for young investigator(s) to work with an unique large animal model for human ES cells.

## Contact Us

### Supervisors:

Associate Professor Mark Nottle (Right)

8303 4087, mark.nottle@adelaide.edu.au

Dr Ivan Vassiliev (Far right)

8303 3372, ivan.vassiliev@adelaide.edu.au

### Location:

Medical School, University of Adelaide  
School of Paediatrics & Reproductive Health  
(Discipline of Obstetrics & Gynaecology)



# STROKE RESEARCH PROGRAMME

## About Us

Each year 53,000 Australians suffer a stroke and one third have significant residual functional disabilities; indeed, stroke is the leading cause of disability in the Australian community. The financial burden is estimated to be greater than \$2 billion per annum and the psychological and emotional burden is immeasurable.

Stem cell therapy may provide a therapeutic strategy to overcome this burden.

In collaboration with Prof. Richard Faull, Auckland University, NZ, we will investigate the neural stem cell response of the human brain following stroke. To our knowledge we have set-up a world first initiative under the auspices of the SA Brain Bank to have patients who die from stroke donate their brain for investigation.

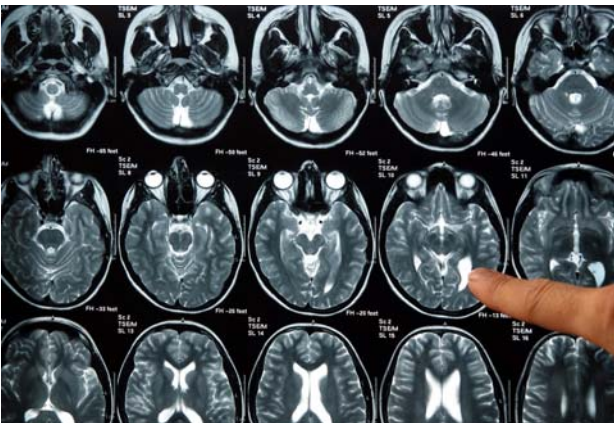
## Projects

### Neural stem cells in the adult human brain and dental pulp stem cells

Our main research objective is to understand the biology of neural stem cells (NSC) and how these unique cells may be used in cellular therapies to improve clinical outcome after stroke. Over the last ten years we have investigated the factors that generate neurons and how they wire-up the brain to form a functioning nervous system during embryonic development and disease.

Such new research is essential and, when turned into practical applications, our student's discoveries may help with prognosis, management, treatment and prevention.

We are investigating the potential of these two types of stem cells to promote brain repair after a stroke.



## KEY PUBLICATIONS

1. Leung E, Hamilton-Bruce A, Koblar S, Price C. TIA Assessment. *Australian Family Physician* 2008;37(3):103.
2. Barry C, Koblar SA, O'Carroll D. Frontier Technologies for Brain Repair. *Australasian Science* 2007;28(7):16-18. (Feature article with Front cover illustration).
3. Stokowski A, Shi S, Barthold M, Gronthos S\*, Koblar SA\*. EphB/ephrin-B interaction mediates adult stem cell attachment, spreading, and migration: Implications for dental tissue repair. *Stem Cells* 2007;25(1):156-164. \*Co-senior authorship.
4. Jannes J, Hamilton-Bruce MA, Pilotto L, Smith BJ, Mullighan CG, Bardy PG, Koblar SA. Tissue Plasminogen Activator – 7351C/T Enhancer Polymorphism Is a Risk Factor for Lacunar Stroke. *Stroke*. 2004; 35:1090-1094.
5. Flood WD, Moyer RW, Tsykin A, Sutherland GR, Koblar SA. Nxf and Fbxo33: novel seizure-responsive genes in mice. *Eur J Neurosci*. 2004;20(7):1819-26.

# STROKE RESEARCH PROGRAMME

## The Role of NPAS4 in neuronal brain formation & repair.

We propose formation of the forebrain is mediated by a critical and novel transcription factor NPAS4, which plays a role in neurogenesis both during development and following brain injury. NPAS4 is known to be induced following brain injury in the adult brain; however, preliminary data from our lab indicates NPAS4 also plays a role in forebrain development. Our interest and this proposal concern the developmental role of NPAS4 in brain formation, which to date has not been reported.

This class of transcriptional regulators involved in a diverse range of developmental and physiological roles contain the basic Helix-Loop-Helix/Per-Arnt-Sim (bHLH/PAS) domains. The family includes NPAS4, the hypoxia-inducible-factors (HIF-1a, HIF-2), single-minded (SIM1, SIM2) and the dioxin receptor to name a few. The bHLH domain well characterised in developmental transcription factors, allows dimerisation and DNA binding. PAS domains enable sensing of environmental or metabolic states, and are found in cytoplasmic proteins involved in signal transduction.

*The Three projects on offer are:*

1. Expression profiling embryonic stem cells with regard to NPAS4 expression during differentiation into neurons.
2. Manipulation of NPAS4 expression in the zebrafish model organism.
3. Characterising the neuronal cell stresses that induce NPAS4 expression

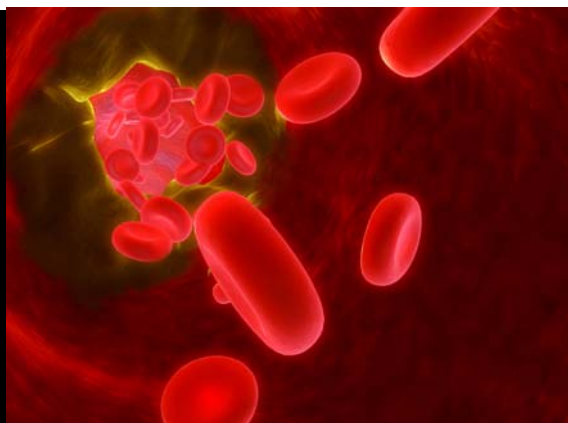
## Contact Us

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Discipline of Medicine,  
The University of Adelaide & The Queen Elizabeth Hospital



## KEY PUBLICATIONS

1. Flood WD, Moyer RW, Tsykin A, Sutherland GR, Koblar SA. 2004. Nxf and Fbxo33: novel seizure-responsive genes in mice. *Eur J Neurosci* 20:1819-1826.
2. Moser M, Knoth R, Bode C, Patterson C. 2004. LE-PAS, a novel Arnt-dependent HLH-PAS protein, is expressed in limbic tissues and transactivates the CNS midline enhancer element. *Brain Res Mol Brain Res* 128:141-149.
3. Ooe N, Saito K, Mikami N, Nakatuka I, Kaneko H. 2004. Identification of a novel basic helix-loop-helix-PAS factor, NXF, reveals a Sim2 competitive, positive regulatory role in dendritic-cytoskeleton modulator drebrin gene expression. *Mol Cell Biol* 24:608-616.
4. Shamloo M, Soriano L, von Schack D, Rickhag M, Chin DJ, Gonzalez-Zulueta M, Gido G, Urfer R, Wieloch T, Nikolich K. 2006. Npas4, a novel helix-loop-helix PAS domain protein, is regulated in response to cerebral ischemia. *Eur J Neurosci* 24:2705-2720.

# SCHOLARSHIP OPPORTUNITIES

## Honours

Honours Scholarships up to \$5000 are available from various Faculties, Schools and Groups associated with the centre.

## Masters/PhD

Are you a citizen or a permanent resident of Australia or a citizen of New Zealand looking for an Honours or Postgraduate scholarship or project?

Postgraduate scholarships currently available:

[www.adelaide.edu.au/graduatecentre/scholarships/postgrad/pgcurrent.html](http://www.adelaide.edu.au/graduatecentre/scholarships/postgrad/pgcurrent.html)

More information is also available from:

Student Centre, level 4, wills building

Phone: 8303 5208, Email: [student.centre@adelaide.edu.au](mailto:student.centre@adelaide.edu.au)

## Other Scholarships (extensive list)

[http://www.adelaide.edu.au/graduate centre/scholarships/links/](http://www.adelaide.edu.au/graduate%20centre/scholarships/links/)

## International Honours & Postgraduate Students

Information for International Students who are interested in Honours, PhD and Masters study at the University of Adelaide, is available on the University's [International Students](#) web site.

Here you will also find the Postgraduate [Research Prospectus](#) (pdf 2MB) pages 28 to 31 has information about application and scholarships.

Click on the links for specific information about the Research Programs available in [Dentistry](#) and [Medicine & Health Sciences](#) where you can find out about the pre-requisite qualifications and international fees 2009.

There are a number of international postgraduate [scholarship](#) opportunities, including:

Endeavour International and Adelaide Scholarships International (*Please note the closing date for complete EIPRS/ASI applications for entry in 2009 is likely to be on or before 31 August 2008.*)

Joint China Scholarship Council (CSC) and University of Adelaide Scholarships for students from the People's Republic of China. (*More details will be available soon.*)

Several scholarship programs are available to support AusAID Scholars in the Asia-Pacific region.

[DAAD](#) scholarships for students from Germany (Contact: [Christian Gericke](#) or [Christiane Niess](#))

If you are searching for a PhD supervisor and project in your area of research interest, we suggest you browse the University and Faculty Research [Centres & Institutes](#) page as well as the School [Research Areas](#). There are links on this site to the individual Schools and Disciplines where you can discover experienced staff who may be able to provide supervision in your field of research interest.

*Should you be unable to locate either your specific area of research interest or a potential supervisor please [contact](#) us for assistance.*

Forms must be submitted to: Adelaide Graduate Centre, Level 6, 115 Grenfell St, University of Adelaide SA 5005.

Email: [graduatecentre@adelaide.edu.au](mailto:graduatecentre@adelaide.edu.au).

# EXPRESSION OF INTEREST: HONOURS

## CENTRE FOR STEM CELL RESEARCH

Discuss your intention to apply for the project with the appropriate supervisor, then complete the form below including obtaining the supervisors signature.

**Return this form together with a copy of your current academic transcript by Monday the 17<sup>th</sup> of November 2008 to:**

*Dr Sarah List  
Manager, Centre for Stem Cell Research  
Level 6, Medical School North  
Frome St. University of Adelaide 5006*

**Your complete transcript is required once official exam results are released.**

**If you are accepted, you will receive a Letter of Authority to enrol in the relevant Honours Course [BSc (Hons), and BMedSci (Hons), BHSc (Hons) or BDS (Hons)] course signed by the Head of the School administering your program and instruction on the enrolment process.**

The enrolment of students will be conducted online mid to late January 2008 – (Ring the appropriate Faculty that your Group belongs to)

### HONOURS at the Centre for Stem Cell Research in 2009 STUDENT RETURN SLIP

STUDENT NAME: .....

STUDENT NO: .....UNDERGRADUATE DEGREE.....

STUDENT POSTAL ADDRESS: .....

.....P/Code ..... TELEPHONE NO: .....

EMAIL ADDRESS:.....

- CITIZENSHIP:
- AUSTRALIAN CITIZEN
  - NEW ZEALAND CITIZEN
  - HOLDER OF PERMANENT VISA
  - HOLDER OF A PERMANENT HUMANITARIAN VISA

HONOURS PROJECT: .....

SUPERVISOR SIGNATURE: .....