The information in this publication is correct as at 13th October 2011, but is subject to change from time to time. In particular the University reserves the right to change the content and/or the method of presentation and/or the method of assessment of any unit or study, to withdraw any unit of study or programme, and/or to vary arrangements for any programme.
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INTRODUCTION

The Bachelor of Medical Science (BMedSc) degree provides the opportunity for medical students and biomedical science graduates to spend a year studying in depth an aspect of medicine, which is of particular interest to them. It enables students to gain experience in experimental design and techniques, and to savour the excitement, which comes from original research. Students who successfully complete the course requirements are awarded the BMedSc degree with honours of the appropriate class (e.g. First Class Honours).

The degree is of particular value to those students contemplating a career in research or teaching, enabling them to assess their personal suitability for medical research while providing the basic training, which is required for future enrolment in a research degree and to acquire funding.

It is also useful to those students planning to undergo postgraduate training in one of the medical specialities. Given the current competition for specialist training positions, it is becoming increasingly necessary for trainees to undertake research activities prior to or during their specialty training. Successful completion of the BMedSc provides both evidence of a student's research capabilities and an insight into the research methods through which scientific progress in the specialities is achieved.

This booklet summarises the regulations governing the BMedSc degree, the nature of the course, scholarships available to BMedSc candidates and suggested research projects, which may be undertaken in each School.

ADMISSION OPTIONS

There are three pathways for entry into the BMedSc degree:

1. MBBS students who have shown special aptitude in their studies in the MBBS course and are recommended by the Head of School concerned as suitable for advanced work may be permitted to interrupt their studies in the MBBS course for one year and enrol in the BMedSc degree. Students must have completed at least the third year of the medical course and are guaranteed a place in the appropriate year of the medical course after they have completed their BMedSc year.

2. Successful completion of the requirements for the Bachelor of Science pass degree of this University or its equivalent with a relevant major in the area of biomedical science, and have achieved an average of at least 65 percent in the Level 3 (third year) units of the relevant major or equivalent, and have completed within the previous four years the final units or units of the major subject in which they intend to proceed to honours, unless the Faculty approves otherwise in recognition of exceptional circumstances.

3. MBBS students who have completed at least the Level 1 requirements of the MBBS course at this University or equivalent and have achieved a final weighted average of at least 65% in those units may be accepted as students in the combined course of BMedSc and MBBS. Students must have a proposed research project which is longitudinal in nature and would suit research over a three year period.

THE BMEDSC COURSE

The BMedSc degree consists of an approved course of advanced study and research to the value of 48 points in any subject offered by the Faculty of Medicine, Dentistry and Health Sciences. The course involves at least 36 weeks as a full-time student (or part-time equivalent for students in the combined course) in one of the schools of the Faculty (or approved schools not within the Faculty). The Faculty may permit a student to undertake some of this study and research at an approved institution either interstate or overseas. In such cases the principal supervisor must nonetheless be a UWA-based researcher. Students must present a dissertation based on their work. Students may also be required to undertake additional assessments such as a research seminar presentation or literature review. In some schools, the only formal components of the BMedSc course are the research project and submission of the thesis. However, in all schools, these are the major components of the course. Other schools require additional commitments, which may be assessed as part of the overall grading of the student. These include presentation of one or more seminars based on the student's research activities, submission of a review of relevant literature in the field of study, an oral examination of the thesis and related areas of research, and participation in formal courses which will be of value for the student's research activities. Intending BMedSc candidates should obtain information on the requirements of an individual school from the School Honours Co-ordinator/Academic Advisor or the Head of School before submitting an application.

Students should be aware that some research projects may require ethics approval from the Research Integrity Office which is responsible for administration and policy issues relating to experimentation on human participants and animals, and for biological safety. Approval should be sought as early as possible in the planning stages as it might take some time to obtain formal approval.
Students must, no later than 31 OCTOBER following their first enrolment in the course submit to the School a dissertation on the work done.

An example of an honours dissertation guide is presented on Page 6. Please note that this is only an example and students are required to consult their supervisor regarding specific requirements of the School. The dissertation is examined by at least two experts in the field of study who will make an assessment of the quality of the student's research and thesis via a written report to the school.

Each candidate will be under the principal supervision of one or two staff members who will help in the design of the research project; provide the necessary training in experimental methods; be a sounding board for the testing of ideas; encourage independent thought; be an accessible, organised, enthusiastic advisor; and provide advice on ethical issues, and how to overcome any difficulties which may arise from these. The supervisor(s) should assist in the planning and development of work but are not responsible for the details of research. Candidates must co-operate closely with their supervisor(s) but must also demonstrate a commitment to their research and a willingness to participate in the life of the University as fully as their programme permits. It is essential that the potential supervisor(s) and candidates agree upon their aims, objectives and expectations before a selection is formalised.

Students should discuss their possible BMedSc candidature and suitable research projects with supervisors of projects which interest them chosen from among the topics listed in this booklet. It is important that candidates also discuss their suitability for the project concerned. Heads of Schools must also be informed since they are required to recommend enrolment of BMedSc candidates.

AWARD OF DEGREE
The Bachelor of Medical Science degree is awarded with honours of the appropriate class when a student successfully completes all the requirements of the course. The honours classification is as follows:
- 80 – 100% First Class Honours
- 70 – 79% Second Class Honours (Division A)
- 60 – 69% Second Class Honours (Division B)
- 50 – 59% Third Class Honours

COMBINED BMedSc / MBBS COURSE
This option has been available since 2007 where eligible students may elect to undertake the combined course of Bachelor of Medical Science and the MBBS. This may appeal to students who are interested in pursuing a BMedSc without having to take a year away from their MBBS studies. The course is considered quite intensive and will only be offered to students who are achieving above average standards in their MBBS course.

The course consists of units to a total value of 320 points comprising a Bachelor of Medical Science component to a value of 48 points (as described in the section above) and a Bachelor of Medicine and Bachelor of Surgery (MBBS) component to the value of 272 points.

Students wishing to undertake the combined course must have a research project which is longitudinal in nature and would suit research over a three year period. The majority of the research is undertaken during the summer vacation periods following second, third and fourth year, with minor research components during the second and third year in place of the MBBS Level 2 and 3 option units.

Students in the combined course must, no later than 31 OCTOBER of their fifth year of enrolment, submit to the School a dissertation on the work done.

Students who successfully complete the course are awarded the degree of Bachelor of Medical Science (with honours of the appropriate class, as noted above) and the degree of Bachelor of Medicine and Bachelor of Surgery.

COURSE RULES
The complete official Rules for the Bachelor of Medical Science degree and the combined BMedSc / MBBS course can be found in the Undergraduate Handbook (www.handbooks.uwa.edu.au) and on Pages 8-10 of this handbook.
APPLICATION PROCEDURES
Current UWA students (domestic and international) are required to apply online via Student Connect (click on the “Apply for Honours” link in the left-hand menu bar) by the published closing date. See http://www.studyat.uwa.edu.au/undergrad/australian/honours for further information.

If you have studied elsewhere please see http://www.studyat.uwa.edu.au/undergrad/australian/honours for information about the application process. Note that there is a separate system for domestic versus international students. See the website for details.

In addition to the application form, students must also submit a broad outline (500-700 words) of the research to be undertaken, together with confirmation from the relevant School that general facilities are available to support the project.

SCHOLARSHIPS AND PRIZES
Various scholarships are available on a competitive basis for students undertaking the full-time BMedSc course.

Foundation Professors Bachelor of Medical Science Scholarships –
These scholarships are awarded in various disciplines to commemorate the Foundation Professors of the Faculty of Medicine, Dentistry and Health Sciences. The awards have a value of $6,000 each and are available to medical students of the Faculty.

- The Robert A. Milne BMedSc scholarship in honour of Professor David Sinclair, Foundation Professor of Anatomy
- The John and Rosemary Pearman BMedSc scholarship in honour of Professor Neville Stanley, Foundation Professor of Microbiology
- The Women and Infants Research Foundation BMedSc scholarship in honour of Prof Gordon King, Foundation Professor of Obstetrics and Gynaecology
- The John Harriott BMedSc scholarship in honour of Professor Mary Lockett, Foundation Professor of Pharmacology
- The Dawkins BMedSc scholarship in honour of Professor Rolf ten Seldam in pathology, Foundation Professor of Pathology
- The BMedSc Scholarship in honour of Professor Cecil Lewis, Foundation Professor of Surgery
- The BMedSc Scholarship in honour of Professor Eric, Foundation Professor of Medicine

Jean Rogerson Undergraduate Studentships in the Faculty of Medicine, Dentistry and Health Sciences
An award of not less than $1,000 for a student undertaking the degree in any approved area of research.

Robert Collin Prize for the Bachelor of Medical Science (in Physiology)
The Robert Collin Prize for the Bachelor of Medical Science (in physiology) comprises not less than $2000 provided from the annual income after capitalisation in accordance with Senate policy on a sum provided by Robert and Dorothy Windus Collin. To be eligible for consideration for the prize a student must be conducting advanced study and research in physiology for the Bachelor of Medical Science. Information regarding other non-faculty scholarships can be found at www.scholarships.uwa.edu.au/home/undergrad these have varied closing dates. You may also wish to approach areas related to your discipline or research to determine whether they may provide you with funding. These scholarships are subject to confirmation by the donors and are advertised by the Faculty of Medicine, Dentistry and Health Sciences. The Faculty gratefully acknowledges the support provided by the donors of BMedSc Scholarships.

YOUTH ALLOWANCE
Students who have queries about their Youth Allowance or Austudy entitlements should contact their local Centrelink Office or call 13 2490. www.centrelink.gov.au
EXAMPLE OF AN HONOURS DISSERTATION GUIDE

Please note this is only an example. Students are required to consult their supervisor in regards to specific formatting requirements of the school.

Typing and Diagrams

It is recommended that A4 paper be used and a 4.5 cm allowance made in the left-hand margin. Twelve-pitch typescript is recommended and 1.5 spacing between lines is suggested. Once the style for drawing and labelling the diagrams has been decided upon, it should be adhered to throughout the thesis. Recommended Subdivisions:

(i) Standard Title page
   Acknowledgments
   Summary
   A list of standard abbreviations
   Table of contents
   Introduction
   (a) Statement of the aims of the project
   (b) Introductory review of the literature
   Methods
   Results
   Discussion
   References

(ii) Optional Appendices: a presentation of material that is relevant but does not flow within the general standard structure of the thesis; a presentation of raw data so that readers can evaluate your analyses and interpretations.

(iii) Length The following is a general guide.
    The summary should be 400 words or less. The statement of the aims of the project should be less than two pages and the overall introduction should be 20 pages or less. The combined length of the methods, results and discussion should be 50 pages or less. However, it will be left to your supervisor to decide how long the individual sections should be and set an upper limit on the overall length of the thesis.

Style

Instruction to authors, Br. J. Pharmac., 50: 3-23, provides a good guide to the style desired for the presentation of the thesis. This article should help in the preparation of the summary, methods, results and discussion. It also describes the recommended manner for citing and arranging the references used and indicates an acceptable use of abbreviations and symbols.

While writing the thesis, a suitable dictionary should be readily available to determine the meaning of words not known or not fully understood. For example, while "disinterested" and "uninterested" may appear to be synonyms, an examination of the dictionary indicates that they are not; disinterested means "free from personal bias" while uninterested means "not interested".

Corrections to the thesis

Following the final examination, corrections may be required before the thesis is bound. These corrections must be submitted to the Honours Coordinator. You will be given the option of either doing detailed corrections, or preparing an "erratum" sheet. This sheet should be completed, in consultation with your supervisor, and inserted into each copy of the thesis prior to binding.

After the thesis has been marked and final corrections have been made by the stipulated date, at least 4 copies of the thesis should be produced and bound. Forward the copies (copied single sided) of your thesis to the relevant School Administrative Officer, who will arrange the permanent binding. The school requires lodgement of the thesis for binding before a final grade will be submitted to the Faculty. One copy will be given to you, a copy will be provided to your supervisor(s), the School library and the Faculty (all paid for by the School - $32.50 per copy). You must meet the cost of any additional copies you may require for family, etc. ($35.75 per copy). It can take 2-3 weeks for the bound copies to be returned to the School. You will be advised when this occurs.

The school requires one bound copy of the thesis before a final grade will be submitted to the Faculty of Medicine and Dentistry and Health Sciences.

Declaration

You are required to place a "declaration" page in your thesis acknowledging all persons who have materially assisted you in completing any aspect of the thesis, e.g.: methods, practical work, writing and the extent of their contribution. This will be verified with the supervisor at the time of the examiner's meeting.
COURSE ENROLMENT QUERIES

Students may contact the Faculty Office regarding enrolment queries:

Faculty of Medicine, Dentistry and Health Sciences
Mr Neil Bryan  Ph: 6488 4853  email: neil.bryan@uwa.edu.au

For enquiries about research projects, supervision or specific course and dissertation requirements please contact:

BMEDSC/HONOURS COORDINATORS/ACADEMIC ADVISORS

Faculty of Medicine, Dentistry and Health Sciences

School of Dentistry
Professor Linda Slack-Smith  Ph.9346 7874  email: linda.slack-smith@uwa.edu.au

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School of Paediatrics and Child Health
R/Assoc Professor Sunalene Devadason  Ph.9340 8452  email: sdevadason@meddent.uwa.edu.au

School of Pathology and Laboratory Medicine
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School of Population Health
Professor Niyi Awofeso  Ph.6488 1282  email: niyi.awofeso@uwa.edu.au

School of Primary, Aboriginal and Rural Health Care
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School of Psychiatry and Clinical Neurosciences
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School of Surgery
Professor Barry Iacopetta  Ph.9346 2085  email: barry.iacopetta@uwa.edu.au

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Faculty of Life and Physical Sciences

School of Anatomy and Human Biology
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Associate Professor Silvana Gaudieri  Ph. 9224 2137  email: silvana.gaudieri@uwa.edu.au
Professor Don Robertson  Ph: 6488 3291  email: don.robertson@uwa.edu.au

School of Chemistry and Biochemistry
Winthrop Professor Alice Vrielink  Ph: 6488 3162  email: alice.vrielink@uwa.edu.au
Applicability of the University General Rules for Academic Courses

8.2.3.1 The rules in 1.1 and 1.2 of the University General Rules for Academic Courses in this handbook apply to the course for the degree of Bachelor of Medical Science except as set out in the rules which follow.

Applicability of the Faculty General Provisions for Bachelor’s Degrees

8.2.3.2 The Faculty General Provisions for Bachelor’s Degrees in 8.2.1 apply to the course for the degree of Bachelor of Medical Science.

Admission

8.2.3.3 To be considered for entry into the Bachelor of Medical Science course applicants must—

(1) (a) (i) have completed at least the Level 3 requirements of the course for the degree of Bachelor of Medicine and Bachelor of Surgery of this University, or equivalent as recognised by the Faculty; and (ii) have shown special aptitude in their studies; and (iii) be recommended by the head of the school concerned as suitable for advanced work;

or

(b) have completed the course for the degree of Bachelor of Medicine and Bachelor of Surgery of this University, or equivalent as recognised by the Faculty, with a course weighted average mark of at least 65 per cent;

or

(c) (i) have completed the requirements of the course for the Bachelor of Science (50110) pass degree of this University, or equivalent as recognised by the Faculty, with a relevant major in the area of biomedical science; and (ii) have achieved an average of at least 65 per cent in the Level 3 units of the relevant major, or equivalent as recognised by the Faculty; and (iii) have completed within the previous four years the final units or units of the major subject in which they intend to proceed to honours, unless the Faculty approves otherwise in recognition of exceptional circumstances.

(2) Those described in (1)(a) who are accepted into the Bachelor of Medical Science course will be permitted by the Faculty to interrupt their studies for the degree of Bachelor of Medicine and Bachelor of Surgery to enrol in the Bachelor of Medical Science course.

Course Structure

8.2.3.4 Students must—

(a) complete an approved course of advanced study and research to the value of 48 points in any subject approved by the Faculty; and

(b) work for at least 36 weeks as a full-time student in the school concerned.

External Study

8.2.3.5 The Faculty may permit a student to undertake an approved course of advanced study and research at an institution either interstate or overseas.

Assessment

8.2.3.6

(1) A student must, no later than 31 October following their first enrolment in the Bachelor of Medical Science course—

(a) submit to the school a dissertation on the work done; and (b) sit for such written, practical and oral examinations as may be required.

(2) A school must, for each dissertation, appoint no more than two examiners who, following their examination of the dissertation, provide a written report to the school.

Award of Degree

8.2.3.7 The degree is awarded with honours of the appropriate class when a student completes the course described in Rule 8.2.3.4.
11.1.55 BACHELOR OF MEDICAL SCIENCE HONOURS AND BACHELOR OF MEDICINE AND BACHELOR OF SURGERY (90170)

Applicability of the University General Rules for Academic Courses

11.1.55.1 The rules in 1.1 and 1.2 of the University General Rules for Academic Courses in this handbook apply to the combined course for the degrees of Bachelor of Medical Science and Bachelor of Medicine and Bachelor of Surgery except as set out in the rules which follow.

Applicability of the Faculty of Medicine, Dentistry and Health Sciences Rules

11.1.55.2 The Faculty of Medicine, Dentistry and Health Sciences Rules 8.2.2.6 to 8.2.2.20 apply to the Bachelor of Medicine and Bachelor of Surgery component of the combined course except as set out in the rules which follow.

Admission

11.1.55.3 The Faculty of Medicine, Dentistry and Health Sciences may accept as a student in the combined course an applicant who—

(a) has completed at least the Level 1 requirements of the course for the degree of Bachelor of Medicine and Bachelor of Surgery of this University, or equivalent as recognised by the Faculty; and
(b) has achieved a final weighted average of at least 65 per cent in the units undertaken towards the course for the degree of Bachelor of Medicine and Bachelor of Surgery of this University. and
(c) has a proposed project which is longitudinal in nature and would suit research over a three year period.

Submission of Research Proposal

11.1.55.4 No later than one month before the date of first enrolment in the combined course a student must submit a research proposal through the appropriate head of school and supervisor(s) to the Associate Dean (Research) for consideration.

Course Structure

11.1.55.5 The course consists of units to a total value of 320 points comprising a Bachelor of Medical Science component to the value of 48 points and a Bachelor of Medicine and Bachelor of Surgery component to the value of 272 points, at least 48 points of which are comprised of units completed within the single degree course for the Bachelor of Medicine and Bachelor of Surgery. These totals include all units completed in the single degree course for the MB BS prior to enrolment in the combined course.

Bachelor of Medical Science Component

11.1.55.6 The Bachelor of Medical Science component consists of units to a total value of 48 points comprising all units in Table 11.1.55a (Combined Course Bachelor of Medical Science Core Units).

Award of Bachelor of Medical Science Degree

11.1.55.7 The Bachelor of Medical Science degree is awarded with honours of the appropriate class.

Bachelor of Medicine and Bachelor of Surgery Component

11.1.55.8

(1) The Bachelor of Medicine and Bachelor of Surgery component consists of units to a total value of 272 points comprising -

(a) the units in Table 8.2.2a (Bachelor of Medicine and Bachelor of Surgery Core Units) with the exception of the following:

IMED4501 Research and Discovery Part 1 (2 points)
IMED4502 Research and Discovery Part 2 (2 points)

and

(b) one Level 1 unit chosen with the approval of the Faculty from among the Level 1 units offered with the University with the proviso that students who, in the opinion of the Faculty, do not have adequate knowledge of physics must complete PHYS1131 Introductory Physics - (6 points)

(2) All units completed by a student towards the Bachelor of Medicine and Bachelor of Surgery single degree course prior to enrolment in the combined course are credited towards the combined course.
Award of Bachelor of Medicine and Bachelor of Surgery with Honours

11.1.55.9 The degree of Bachelor of Medicine and Bachelor of Surgery is awarded with honours to students who, in the opinion of the Board of Examiners in Medicine, achieve an appropriately high standard of work in each of the sets of units required at Levels 1 to 6 respectively for the Bachelor of Medicine and Bachelor of Surgery component of the course.

Table 11.1.55a—Combined Course Bachelor of Medical Science Core Units

All units have a value of six points unless otherwise stated.

**Level Two**
- IMED7296  Honours Thesis - Research
- IMED7297  Honours Thesis - Research (Vacation) (12 points)

**Level Three**
- IMED7396  Honours Thesis - Research
- IMED7397  Honours Thesis - Research (Vacation) (12 points)

**Level Four**
- IMED7490  Honours Thesis - Research (Vacation) (12 points)
Every member of our staff is available to supervise a BMedSc project. Each academic has projects for students to consider, however if students wish to nominate and pursue topics of their own choice, the School is very happy to consider this option. Students interested in undertaking a BMedSc should, in the first instance, discuss this with an academic working in the area of research which interests them. This research year is run in parallel with the Honours programme in the School.

Much of the learning emphasis in the BMedSc year is on completing an original research project under the supervision of School staff who are internationally recognised in their specific field/s of research. Although you will receive many benefits from your year with us, you will also experience the following:

- introduction into the challenging world of full-time research
- investigating a biological problem at a professional level
- introduction to the vast information related to your topic stored in scientific journals, the internet, and in the minds of your colleagues
- exposed to challenges, frustration, routine and inspirational times of research
- stimulation by contributing to the knowledge/technical background of the problem area you have selected
- appreciate the value and cooperation of working with academic and technical colleagues
- develop the technical, writing and verbal skills required in successful research
- mature as a person by close contact with the like-minded peer group and professional university staff
- test your abilities and resolve about your future directions

The School’s major research areas are:

- Cell and Developmental Biology
- Endocrine and Reproductive
- Human Biology
- Morphology
- Neuroscience
- Education and Information Technology

Research can be undertaken in many areas, such as:

- Ecology
- Education
- Evolutionary Biology
- Functional And Clinical Anatomy
- Human Biology
- Information Technology
- Muscle Regeneration
- Neuroscience
- Reproductive Biology
- Sleep Science


Specific projects already designed for BMedSc or Science Honours research programmes follow, but can also be accessed at http://www.anhb.uwa.edu.au/about/research/SRP:
Bone in Health and Disease

Dr Luis Filgueira  6488 3907  Email: luis.filgueira@uwa.edu.au

Bone is an important structural and functional part of the human body. Consequently, bone diseases, such as osteosclerotic (too much bone) and osteoporotic (not enough bone) conditions, are relevant to human health, quality of life and longevity.

Bone is a very dynamic tissue, continuously adapting to changing biomechanical conditions throughout the whole life. This adaptation is called bone remodelling.

Bone remodelling consists of two major parts, namely, bone formation and bone resorption. Bone resorption is performed by osteoclasts, a specialised macrophage population, derived from haematopoietic bone marrow precursor cells.

Bone formation is achieved by osteoblasts. Osteoblasts are recruited from stromal stem cells. They develop through an osteoprogenitor stage and reach their final developmental stage as osteocytes, embedded into the newly formed bone.

More research has to be done to understand the complex and finetuned process of bone remodelling, bone formation and bone healing. Cellular and molecular questions can be addressed.

Methods and Techniques:
Cell culture
Light microscopy
Electron microscopy
Confocal microscopy
Immunostaining
Western blot
Real time reverse transcription polymerase chain reaction (RT-PCR)
ELISA
Functional assays: proliferation, cell death, bone matrix formation, enzyme activity.

Metals in Medicine

Dr Luis Filgueira  6488 3907  Email: luis.filgueira@uwa.edu.au

Humans are exposed to metals on a daily base due to anthropogenic activities or in their metals-containing natural environment. Excessive exposure to metals might happen through occupational activities in smelters or mining, through hazardous waste or through contaminated water or air. Most important, as metals are used for production of daily used commodities, potentially everybody is exposed to metals in the western societies. Usually, metals enter the human body through the digestive and the respiratory system or through the skin. More recently, metals are also used for implanted biomedical devices, including joint replacements and dental castings, resulting in a close contact of diverse organs, tissues and cells to pure metals or metal alloys. Little is known, how cells and tissue process and react to pure metals and metal ions. Consequently, more research in this area is very much needed.

For Honours and BMedSc students, there is the possibility of doing projects in the research areas mentioned above, and the following methods can be learnt and applied to corresponding research projects.

Methods and Techniques:
Cell culture
Light microscopy
Electron microscopy
Confocal microscopy
Immunostaining
Western blot
Real time reverse transcription polymerase chain reaction (RT-PCR)
Functional assays: proliferation, cell death, bone matrix formation, enzyme activity.
A number of projects are available and they may involve comparative studies of life histories of mammals using databases of species characteristics and statistical modeling. Areas of special interest include the evolution of cooperative breeding, the role of environmental uncertainty in the reproductive strategies in Australian fauna, and primate socioecology and life history. The focus of this research is on the evolution of prolonged adult lifespans and associated patterns of reproduction and intergenerational transfers of resources.

1. Project on intergenerational relationships in terms of help provided to adult offspring by mothers and fathers.
2. There is potential for projects on intergenerational relations in conjunction with ICHR or WAHD.
5. Behavioural studies of sex differences in humans.
6. Potential for field studies of family well-being in East Timor for selected and highly motivated students.

Development of computer Aided education

This project would involve the examination of current teaching methods in neuroanatomy and first year medicine. It could involve the analysis of examination results for statistical correlations with examination methods, the development of new teaching material and the adaptation and assessment of new teaching methods in human anatomy.

Evolutionary Biology

Professor Chisholm uses the principles of evolutionary ecology and life history theory to generate hypotheses about the development of alternative reproductive strategies in humans. Current projects focus on the role of early stress on age at menarche, adult attachment and sexual/romantic behaviour, teen pregnancy, theory of mind, time preference, empathy, and social exchange.

The Genetic Consequences of Isolation in Kimberley, Pilbara and Abrolhos Islands.

Many vertebrates occur on the numerous offshore islands of Western Australia. These islands have been separated from the mainland for up to 12,000 years. Isolated populations are at high risk of extinction due to specialized adaptations and loss of genetic variability, which limit a population’s ability to evolve in response to environmental change. Apart from isolation, there are concerns about the impact of grazing, tourism, fire and the mining industry, all of which have an inimical effect on population size and distribution. Examining the genetic diversity of vertebrates using mtDNA and microsatellite markers provides an insight into the population structure and the effects and risks of adverse impacts. Of course this study has significance for human evolution - early human populations were also very fragmented and experienced ecological change so in observing the impact of fragmentation on other vertebrates we may be able to clarify this and other impacts on our own history.
Functional and Clinical Anatomy

Functional Anatomy

**Associate Professor Nick Milne**  6488 8644  
Email: nick.milne@uwa.edu.au

Functional anatomy research involves understanding the meaning of shape variation in biology. The reason for the variation might be function, phylogeny/inheritance, environment, disease or just something that changes shape over time (like during growth or locomotion). The biological object is frequently a bone, but can be soft tissues (like faces, or feet!). Data can be collected from bone collections, or CT scans, photographs or living people. The questions that can be asked using these techniques have relevance to anatomy, biomechanics, development, evolution, forensics, medicine, physical anthropology, and palaeontology.

Examples of two projects are:

1. An examination of variation in quokka crania. Quokkas live on Rottnest Island but also in south west Australia and on some other off-shore islands. We could discover whether there is island dwarfism in quokkas, whether they are subject to Bergmann's rule and how much quokkas from different parts of Rottnest interbreed.

2. The skulls in the Anatomy and Human Biology teaching collection are thought to have all come from South Asia. Data has already been collected on cranial collections from other parts of the world. This honours project could digitise the School's crania collection and analyse their variation in relation to known samples.

There are numerous other projects that could be negotiated...

Information Technology

Development of Medical Diagnostic Software

**Professor Stuart Bunt**  6488 2983  
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This can involve work with a number of diseases from ophthalmology to back injury. The research would involve reading the relevant literature, doing a meta-analysis of the data then entering it into a software program (no computer expertise required). You would then have to test the software's accuracy with medics on the wards or in GP's office to estimate its accuracy, false positives and negatives etc. I am also involved with research into using heart rate to diagnose psychological state such as depression, anxiety etc. A project could involve working with researchers in Fremantle hospital and Sir Charles Gardener Hospital using portable heart rate and movement monitors.

Muscle Regeneration

The research of the Grounds & Shavlakadze Muscle Group is focussed on skeletal muscle research. 4 areas are outlined here, but many projects can be developed with the student.

Our background papers to all of this work can be found as PDFs.

**http://school.anhb.uwa.edu.au/personalpages/grounds/**

Age-related loss of skeletal muscle mass and function

**Professor Miranda Grounds**  6488 3486  
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**Key personnel:** this is collaborative research between A&HB and BBCS, involving Prof. Miranda Grounds, Dr Thea Shavlakadze, Prof. John McGeachie, Dr Peter Arthur, Dr Ahmed Elshafey and PhD students Jessica Terrill, Ruth (Jinfen) Chai, Pearl Tan, Hatice Tohma.

**Background.** Skeletal muscles constitute approximately 40% of the mass of the human body and are essential for all aspects of movement such as breathing, eating, posture, walking and reflexes as well as heat generation and metabolism. A loss of muscle mass, known as atrophy or wasting, has major consequences for strength and muscle function. Muscle wasting can result from disuse (e.g. bed rest or space travel), injury, starvation, diseases such as cancer, sepsis, neuromuscular disorders, and also ageing. Different factors contribute to muscle wasting in the various conditions. The progressive loss of muscle mass associated with ageing is known as sarcopenia and is the focus of this research. Sarcopenia results from a decrease in myofibre size, combined with a loss of myofibres and changes in myofibre types. Between the ages of 50 and 80 in humans, muscle mass is reduced by about one-third; this is a major contributing factor to increased falls and fractures, with impaired physical function (frailty) resulting in dependency and sometimes death.

Development of new targeted interventions to reduce sarcopenia and frailty would have a major impact on reducing health system costs, as well as improving the quality of life for the growing population of older individuals. In order to develop appropriate interventions to reduce muscle-wasting we need to understand the key factors responsible for sarcopenia. This is the focus of our current research.
Projects. We have many current projects related to muscles in very old (geriatric) mice aged up to 30 months of age and the development of potential therapies. These include transgenic mice and other interventions related to insulin-like growth factor-1 (IGF-1) combined with exercise, the pro-inflammatory cytokine Tumour Necrosis Factor (TNF) and oxidative stress (e.g. using over-expression of catalase). We are examining not only skeletal muscles but the hearts, brains and neuronal systems of these ageing mouse models.

Techniques used range from microscopy and immunostaining, histological and morphometric analyses of tissues, many molecular techniques including qPCR and phosphoprotein signalling, tissue culture studies and various measurements of oxidative stress.

We also collaborate with the physiologists Drs Gavin Pinniger and Anthony Bakker to study functional properties of muscles (in vivo and ex vivo) with respect to the above interventions. In addition we have new projects to examine the capacity of geriatric muscles to regenerate after injury and form new muscles – reflecting the muscle precursor (stem) cell capacity of old skeletal muscles. In discussion with the student we can select projects to best suit their interests.

Muscle metabolism and dietary interventions: impact on muscular dystrophy

Professor Miranda Grounds 6488 3486  Email: miranda.grounds@uwa.edu.au

Key personnel. Prof. Miranda Grounds, Dr Thea Shavlakadze and PhD student Hannah Radley

Background. Our research on metabolism in skeletal muscle has implications for diabetes and the metabolic syndrome. Studies this year (by Hannah Radley & Dr Marta Fiorotto a colleague in the USA) have intensively analysed energy status, metabolic profiles and protein turnover in dystrophic mdx mice that are a model for the lethal human muscle disease Duchenne Muscular Dystrophy (DMD), as well as assessing the impact of different diets on a range of muscle parameters. These data are currently being assessed by Hannah Radley (as part of her PhD) and new directions and projects will emerge from this work.

Project. High fat or high protein diets and other additives influence the body composition, metabolism and energy balance. This is of key interest to the metabolic syndrome related to the increasing incidence of obesity and type 2 diabetes, especially in the ageing population. There is also evidence that such dietary interventions have a profound effect on the pathology of muscular dystrophy: we will investigate this latter aspect using dystrophic mdx mice. This is a new project being initiated within our group. The dietary interventions to be investigated for Honours projects could be one of many but are likely to include: (i) Taurine (an amino acid) or (ii) BBIC (Bowman Birk Inhibitor,a protease inhibitor:a component of soy). Mice would be placed on these diets for varying lengths of time e.g. 6 weeks, and weighed and monitored carefully. Mice would then be killed, sampled and analysed as follows: (most of these techniques are well established in our lab)

- Measure body weight. Measure fat deposition
- Quantitate histologically the extent of muscle necrosis in young (3 weeks) and in adult (6 week) mdx mice subjected to voluntary exercise (wheel running).
- Measure blood creatine kinase levels and various cytokines
- Analyse the metabolism of the mdx vs normal control mice and also do in mdx (and control) mice treated with antibodies to TNF-alpha (use the mouse antibody cVIq). e.g. Protein synthesis and degradation (using stable radioisotopes proline and leucine) Various signalling pathways. Insulin resistance, glucose uptake, FFA, adipogenesis.

The Extracellular Matrix: differences between muscles, the impact of age and interventions to reduce fibrosis.

Professor Miranda Grounds 6488 3486  Email: miranda.grounds@uwa.edu.au

Key personnel. Prof. Miranda Grounds in collaboration with Prof. Deirdre Coombe and Dr Danielle Day (both at Curtin University)

Background. There is great interest in why different muscles are affected with various degrees of severity by a range of genetic muscle diseases. One possibility is that the anatomically different muscles with very different developmental pathways and function (e.g extraocular, facial, diaphragm and fast and slow limb muscles) have post-natal differences in their extracellular matrix (ECM) composition. The ECM plays a key role in the maintenance and function of mature skeletal muscle and all aspects of skeletal muscle regeneration [1]: thus defining differences in ECM composition between such muscles is of interest.

With age there are changes in many ECM components with increasing fibrosis (deposition of collagen) and increasing glycation and cross-linking of collagens (also seen in diabetes) that has adverse effects on muscle function and repair: thus understanding changes in ECM with age is of interest.

In diseased muscles where muscle necrosis occurs, such as in the lethal human Duchenne Muscular Dystrophy (and mdx mouse model of this disease), there is increased inflammation and one adverse effect of inflammation is increased fibrosis. Fibrosis is a new therapeutic focus on the laboratory. In project 4 (below) anti-fibrotic drugs will be trialled in combination with other proven anti-inflammatory drugs to reduce the severity of muscular dystrophy.
Combined Therapies for Muscular Dystrophy

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**Key personnel.** Prof. Miranda Grounds and **PhD student** Hannah Radley

We have applied several clinically proven drugs that block TNF-alpha in the mdx mouse model of muscular dystrophy which result in a marked reduction in muscle necrosis. (Remicade and cV1q are antibodies and Enbrel is soluble receptors to TNF-alpha). This strategy reduces the necrosis of dystrophic muscle (the ideal approach to reduce the severity of the dystrophopathy) but probably does not prevent all damage. Where necrosis occurs, the associated inflammation leads to progressive fibrosis and this becomes an increasing problem as the disease progresses over time. Anti-fibrotic drugs are attracting much interest to reduce the deposition of excessive collagen and reduce fibrosis in older dystrophic muscles. We will combine our well establish anti-TNF therapy (using the antibody cV1q) with anti-fibrotic drugs, to assess if this has a cumulative benefit to reduce the dystrophopathy in mdx mice.

**Neuroscience**

**Cell and Tissue Transplantation, Gene Therapy and The Repair Of Central Nervous Tissue Damaged After Injury.**

**Professor Alan Harvey** 6488 3294  
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The research by the neuroscience groups in Anatomy and Human Biology has a particular emphasis on cell and tissue transplantation, gene therapy and the repair of central nervous tissue damaged after injury. Ways are being tested for preventing nerve cells from dying after injury and promoting the regenerative growth of damaged axons. The specificity of axon/target cell reconnection after injury is of particular interest. The potential for replacing compromised cells with new healthy cells, including stem cells, is also under investigation. Studies are mostly carried out in the visual system and in the spinal cord.

**Fetal Origins of Adult Health and Disease**

**Professor Brendan Waddell** 6488 3297  
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Our major interests centre on the role of glucocorticoids on the development of the brain and long term neuroendocrine stress regulation.

Adolescent brain development represents the last phase of brain development aimed at establishing optimal functional neural pathways in the central nervous system. This type of maturation of brain function is based on selective synapse elimination or pruning to optimize cortico-limbic neural networks underling cognition and behaviour. It is hypothesized that long-term effects of early life stress on adolescent regulation of stress perturb these neurodevelopmental processes during adolescence.

To study the neurobiological mechanisms by which changes in adolescent basal hypothalamic-pituitary-adrenal (HPA) activity and stress responsiveness (as a result of early life stress exposure) may induce alterations in brain morphology and function during adolescent neurodevelopment, a mouse model is proposed.

This Honours project encompasses the research required to generate and validate this mouse model, in which pre and/or postnatal stress is anticipated to induce dysfunction of the adolescent HPA-axis. We aim to study stress responsiveness as well as molecular, biochemical and neuromorphological changes in stress-sensitive brain regions in cohorts of adolescent C57Bl/6J mice exposed to controlled incidental or trajectories of early life stress.

**Reproductive Biology**

**The Influence of Age and Reproductive Status on Stress Perception and Responsivity**

**Dr Kathy Sanders** 6488 1527  
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There is a growing body of evidence supporting an association between higher levels of stress and reproductive failure. However, the association is weaker in women of advanced reproductive age (>35 years) compared to younger women. This is consistent with the reproductive suppression model which posits reproduction should not be suppressed when the costs of delay in terms of lost reproductive opportunities outweigh the benefits of suppression. But what are the mechanisms? This project will examine the influence of age and different reproductive states (eg. nulliparous, multiparous) on women's perception of stress and their physiological reactivity to a variety of stressors.
Attitudes to Release of Information in Open-Identity Donor Programs

Dr Kathy Sanders  6488 1527  Email: kathy.sanders@uwa.edu.au

Historically sperm donation and conception have remained secretive. The donor was anonymous and only limited, non-identifying information (eg. hair and eye colour, education and interests) was made available to recipients. Few donor conceived children were told of the manner of their conception. Oocyte recipients were also unlikely to disclose to their offspring despite being more likely to know their donor (e.g. a friend or relative).

However, social attitudes to the use of donor gametes/embryos have changed. Accordingly an increasing number of countries/states (Sweden, Netherlands, UK, States of Victoria and Western Australia) have legislated for open-identity donor systems where children born of gamete or embryo donation can access identifying information about their donor on reaching maturity. This project addresses issues surrounding the release of identifying information in a donor gamete/embryo program from the perspectives of the donor, the recipient and the offspring. Some questions include:

- What factors motivate individuals to donate gametes/embryos in an open-identity system?
- Is the extent and availability of biographical information about the donor important in recipients’ decisions to (or not to) disclose?
- How do donor conceived offspring perceive their donor, and what information about the donor do they desire?

Developmental Origins of Health and Disease

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and Dr Peter Mark  6488 2609  Email: peter.mark@uwa.edu.au

Our major interests centre on the role of glucocorticoids and dietary omega-3 fatty acids on pregnancy. This includes their effects on placental function, fetal growth and programming the phenotype of adult offspring.

Studies under this project title focus on the effects of excess fetal glucocorticoid exposure on the adult phenotype, particularly in relation to programming of the metabolic syndrome. The interactive effects of variations in postnatal diet, particularly in relation to possible protective effects of dietary fish oil, are the current focus in this work.

Oxidative Stress and Placental Function

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Our major interests centre on the role of glucocorticoids and dietary omega-3 fatty acids on pregnancy. This includes their effects on placental function, fetal growth and programming the phenotype of adult offspring.

Oxidative stress results from the accumulation of reactive oxygen species (ROS) within cells and is thought to underlie a range of disease states. The detrimental effects of oxidative stress are mediated via damaging effects of ROS on cellular protein, DNA and lipids. Placental oxidative stress is thought to play a key role in several pregnancy disorders such as miscarriage, intrauterine growth retardation and preeclampsia. This project is designed to investigate whether dietary omega-3 fatty acids (derived mostly from fish oil) can protect the placenta from the deleterious effects of oxidative stress.

Sleep Science

Obstructive Sleep Apnoea

Associate Professor Peter Eastwood  9346 1706  Email: peter.eastwood@health.wa.gov.au

Obstructive sleep apnoea is a common condition, affecting as many as 2–4% of middle-aged adults, and is accompanied by heavy snoring. It is characterised by repetitive partial or complete collapse of the upper airway (throat) during sleep. These episodes, which can occur hundreds of times during a single night, are accompanied by a momentary fall in blood oxygen levels, an increase in blood pressure and arousal. These disruptions result in excessive daytime tiredness and lethargy.

Sleep researchers at the School of Anatomy & Human Biology (The University of Western Australia) and the West Australian Sleep Disorders Research Institute (Sir Charles Gairdner Hospital) have an active interest in understanding the role of pharyngeal anatomy, body posture, head and neck posture and body fat distribution in predisposing individuals to obstructive sleep apnoea. Projects can be undertaken in waking and/or sleeping individuals with and without sleep disorders.

Projects can be undertaken at the new Sleep Research and Teaching Facility on the UWA campus or at The West Australian Sleep Disorders Research Institute at Sir Charles Gairdner Hospital. Large numbers of patients are seen at the hospital clinic each year, most of whom are suitable for participation in these types of studies. A variety of research projects are available at the Honours, Masters or PhD levels.
In 2012 Physiology will be joining with Anatomy and Human Biology in a new combined school

**Physiology**

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**Skeletal Muscle Damage & Disease**

Skeletal muscle function can be severely compromised by injury and disease, leading to loss of mobility and decreased quality of life. In the case of inherited muscle wasting diseases such as the muscular dystrophies, damage to respiratory muscles (diaphragm) can lead to death of patients in their early twenties.

Injuries have a direct impact on skeletal muscle function due to acute damage to the muscle structure. However, it is now apparent that the inflammatory response involved in the healing process can also have deleterious effects on muscle performance. This is due to the release from inflammatory cells of inflammatory mediators such as cytokines, which alter skeletal muscle contractile output and protein turnover through increases in intracellular levels of reactive oxygen species, Ca\(^{2+}\), phospholipase A2 and other factors. Many muscle diseases (e.g. muscular dystrophies) have a significant inflammatory component, and many non-muscle diseases such as cancer and chronic heart failure lead to loss of muscle performance due to the effects on muscle of increased circulating inflammatory cytokine levels.

In this laboratory, we are interested in determining the role of inflammation in skeletal muscle damage after injury or disease, and uncovering novel strategies to inhibit these pathways in order to provide therapies for affected patients.

**PROJECTS**

1. **The Role of Protease-Activated Receptors (PARs) in Muscle Injury**  
   **Supervisors:** Dr Tony Bakker, Dr Gavin Pinniger

2. **The mechanism responsible for the severe long term loss of skeletal muscle function after burn injury.**  
   **Supervisors:** Dr Tony Bakker, Dr Gavin Pinniger & Professor Fiona Wood (Director of Burn Service of Western Australia, Royal Perth Hospital and Princess Margaret Hospital for Children)

3. **Investigating the mechanisms responsible for the high rate of respiratory failure in premature babies, using an animal model.**  
   **Supervisors:** Assoc. Prof. Tony Bakker, Dr Gavin Pinniger (Physiology, School of Biomedical, Biomolecular & Chemical Sciences), Prof. Jane Pillow (School of Women’s and Infants’ Health).

4. **The role of reactive oxygen species (free radicals) on skeletal muscle fatigue**  
   **Supervisors:** Assoc. Prof. Tony Bakker, Dr Gavin Pinniger & Assoc. Prof Peter Arthur (Physiology, School of Biomedical, Biomolecular & Chemical Sciences).

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**Associate Professor Livia Hool**  
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**Project outline:** Currently, cardiovascular disease accounts for 41% of all deaths in Australia. This is a staggering proportion when compared with the 22% from all cancers and 4% from road deaths. A number of the deaths in the cardiovascular group are due to arrhythmia or disturbances in the electrical activity in the heart. Certain pathophysiological conditions contribute to arrhythmias such as hypoxia and oxidative stress. Under these conditions there is a reduction in blood flow to the muscle in the heart resulting in a reduction in available oxygen and reactive oxygen species production. This is then followed by an increase in generation of reactive oxygen species. There is increased sympathetic drive and the heart has a greater vulnerability to sudden cardiac death. Associated with the increase in reactive oxygen species is the development of cardiac hypertrophy (enlarged heart) and cardiac failure. We have good evidence that an early mechanism involves increased calcium influx through the L-type calcium channel. The laboratory uses a number of techniques from expression and purification of ion channel protein, biochemical techniques for assay of generation of reactive oxygen species, ex vivo ischemia reperfusion models through to transgenic animal models and human tissue. The method that will be used to study membrane currents is the patch-clamp technique. We collaborate with local, national and international research groups. A number of projects are on offer.
Comparative Physiology of Adaptation

Our group is interested in the physiological mechanisms whereby animal species (including humans) adapt to environmental stressors. We mainly focus on thermal and osmotic stress, but exercise, inanition (starvation), and infection are also studied. Most experimental work is on systems level adaptations, but organ level adaptations are also studied. Our long-term aim is to identify specific adaptations that allow animals to survive and reproduce in challenging environments, and to identify how “homeostasis” handles the trade-offs when simultaneous challenges are presented to an organism, (such as combined thermal and osmotic stress, or combined inanition [starvation] and infection stress). Prospective Honours students with a background in General Systems Physiology, Exercise Physiology, Applied Animal Physiology, or Comparative Physiology are encouraged to apply. Depending on the project chosen a background in Cell Physiology could be an advantage.

Students will be exposed to a range of approaches and techniques including (in non-human animals) recovery anesthesia and surgery, implantation of physiological recording equipment, blood sampling for hormone measurement, and husbandry techniques for various species. In human research we use state of the art equipment to record physiological parameters in ambulatory subjects, including core and skin temperature transmitters, ambulatory blood pressure recording equipment, laser Doppler skin blood flow techniques, and infra-red thermography for surface temperature measurement.

PROJECTS

1. Is a Large Brown Fat Depot Protective Against Diet Induced Weight Gain?  
   With Prof. Phil Withers (Animal Biology)

2. Undernutrition and the defence of body temperature in the cold.

3. Does extracranial cooling really reduce brain temperature independently of arterial blood temperature?

4. Feeding, inflammation, and the circadian rhythm of body temperature.

5. Can we use vibration to enhance cooling from hyperthermia?

Respiratory Physiology Group

The respiratory group in Physiology has had a long-standing interest in the control and function of conducting bronchi. The trachea, bronchi and other airways conduct air into and out of the lung. During an asthma attack contraction of airway smooth muscle (ASM) narrows the conducting bronchi and obstructs airflow. Airway obstruction also occurs in several other respiratory disease including Chronic Obstructive Pulmonary Disease (COPD), chronic bronchitis and emphysema. The focus of our research has been in understanding the detailed mechanisms involved in the control of airway diameter and airway obstruction.

PROJECTS

1. Airway wall isotropy: is a push the same as a pull?
   Airway narrowing, bronchoconstriction, is a key feature of several respiratory diseases including asthma. Our developing understanding of bronchoconstriction now suggest that narrowing is depends on the interactions of airways smooth muscle contraction with the loads placed on the airway and the modulating actions of breathing movements such as deep breaths. Currently models of airway function assume that the airway is isotropic and behaves the same way to forces pulling on the outside as to a pressure in the lumen pushing from the inside. This project aims to directly test that assumption using Anatomical Optical Coherence Tomography (AOCT) in isolate pig airways. These experiment use state of the art imaging techniques being developed at UWA’s school of electronic and electrical engineering to map the inside of individual bronchi with LASER probes. The question is how does the lumen move in response to an inflation by positive pressure in the lumen compared to negative pressure on the serosal surface and what change does that produce during airway contraction and in simulated breathing movements. This project uses isolated lung tissue from pigs.
2. Breathing pattern in obstructive airway disease.
Over the last decade a surprising finding in asthma research is that breathing is a bronchodilator in healthy subjects but not in asthmatics or COPD (chronic obstructive pulmonary disease) patients. In a healthy person taking a deep breath greatly reduces bronchoconstriction and relaxes airway smooth muscle. However few studies have examined pattern of breathing differences between healthy and diseased subjects. This project aims to measure the frequency and pattern of spontaneous deep breath (i.e. sighs) in healthy subjects and patients with respiratory disease such as asthma. A collaborative project involving Physiology at UWA and Respiratory Medicine at QEII that will use respiratory monitors to measure normal breathing pattern in human volunteers.
With Alan James, Medicine (School of Medicine and Pharmacology)

3. Force adaptation.
Over the last decade work with isolated airway smooth muscle (ASM) has shown that ASM has a plastic length-tension curve, that is given time the muscle will adapt to make its current length the optimum operating length. Two recent reports in the literature suggest a similar phenomenon can happen to muscle force production, where ASM is left partially contracted for some time the maximum force that can be generated is increased. This project will attempt to prove the phenomena of force adaptation and test is continuous partial contraction can make isolated bronchi asthma like in there response to bronchoconstrictors. This project will use isolate pig bronchi and explant culture.

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Muscle Physiology Group
Skeletal muscles serve numerous functions that are essential for life. Not only do they provide the power required for movement and locomotion, but they also have vital roles in respiration, thermoregulation and metabolism. Not surprisingly, the loss of muscle mass and/or muscle function can be life threatening. Skeletal muscles of pre-term babies, elderly people and of people suffering from muscle diseases such as the debilitating Duchenne muscular dystrophy are highly vulnerable to injury and are inherently weaker than healthy muscle. The goal of our research group is to understand the mechanisms of muscle damage and contractile dysfunction associated with ageing and disease and to evaluate potential therapeutic treatments to alleviate the severity of symptoms and improve the quality of life of these individuals.

Using a range of experimental models from in vitro single cell recordings to in vivo experiments on whole animals can investigate the molecular processes regulating muscle contraction and the mechanisms of contractile dysfunction from a cellular and systems approach. Students will be exposed to experimental techniques including recovery anesthesia and surgery, non-recovery anesthesia and microdissection of whole muscle and single muscle fibres, cell-culture and calcium imaging. We have several multi-disciplinary collaborations with local researches and are particularly interested in: i) the molecular processes underlying exercise-induced muscle damage; ii) the effectiveness of anti-oxidant and anti-inflammatory treatments in reducing injury related muscle weakness; iii) gene therapy treatments for Duchenne muscular dystrophy, and iv) the impact of exposure to clinically relevant treatments on diaphragm dysfunction in pre-term infants. Specific details of these projects are listed below. Although the majority of this work is based on widely accepted and well established animal models of muscle disorders, there is also the possibility of projects working on skeletal muscle function in humans as well.

PROJECTS
1. Molecular Mechanism of Stretch-Induced Force Enhancement
With Dr Tony Bakker

2. The ability of antisense oigonucleotides to improve the function of dystrophic skeletal muscle
In collaboration with Dr Tony Bakker and Prof Steve Wilton & Dr Sue Fletcher, Australian Neuromuscular Research Institute.

3. The role of inflammation and reactive oxygen species in skeletal muscle weakness in Duchenne Muscular Dystrophy (DMD)
With Dr Peter Arthur (Biochemistry) and Prof. Miranda Grounds (Anatomy and Human Biology)

4. Ventilation induced diaphragmatic dysfunction in an ovine model of pre-term infants
With Dr Tony Bakker & A/Prof Jane Pillow (School of Women’s and Infants’ Health)
The Auditory Laboratory

Deafness and other hearing disorders such as tinnitus are among the most common forms of sensory impairment with profound consequences for the individual and society. Normal hearing depends on the proper function of the many component parts of the inner ear and the brain pathways to which it is connected. Our laboratory seeks an integrated understanding of the normal operation of this sense organ and its associated neural pathways and to describe the mechanisms underlying various hearing pathologies.

PROJECTS

1. **Does loud sound exposure result in altered calcium regulation in the brain?**
   **Supervisors:** Professor Don Robertson, Dr Tony Bakker

Loud sound exposure results in a complex series of maladaptive changes in the brain that can lead to abnormal conditions such as hypersensitivity to sound and tinnitus—so-called “ringing in the ears”. These changes in auditory system function can severely affect quality of life and in extreme cases can lead to suicide. The cellular basis of these changes in nerve cell function is the subject of intense investigation but little attention has been paid to possible changes in calcium dynamics in neurons in the auditory pathway. We have developed a method for studying calcium influx in neurons of the auditory midbrain of experimental animals. The project will investigate the calcium dynamics in the midbrain of normal animals and those exposed to loud sound known to cause abnormal neural behaviour. If changes in calcium dynamics are found in sound-exposed animals this could lead to new therapeutic approaches to auditory hypersensitivity and tinnitus. In this project the student will acquire skills in small animal handling and anaesthesia, brain slice preparation and fluorescence measurement of intracellular calcium.

2. **Investigation of a possible drug treatment for neural hyperactivity and tinnitus**
   **Supervisors:** Research Associate Professor Helmy Mulders and Professor Don Robertson

Tinnitus is an increasing problem in modern society, but there is no reliable drug therapy for this condition. We have shown in an animal model that loud sound exposure leads to the development of excessive neural activity in the central auditory pathways as well as behavioural signs of tinnitus. We have also shown that the neural hyperactivity can be immediately reduced by acute treatments that reduce the spontaneous firing of primary sensory neurons in the cochlea. The loop diuretic furosemide is a drug with potential for use in humans that is known to reduce spontaneous firing of auditory nerve fibres. The project will use our animal model to test the ability of furosemide to reduce central neural activity and the behavioral signs of tinnitus. In this project the student will learn techniques for small animal handling and anaesthesia, behavioural testing and single neuron recording.
Mammalian histidine kinases catalyse the phosphorylation of histidine residues in substrate proteins. This is a little understood form of phosphorylation in mammalian cells and its biological roles are not yet clear, although we have established a link between enhanced histone H4 histidine kinase activity and hepatocellular carcinoma in human liver and shown it to be a possible oncodevelopmental marker of hepatocellular carcinoma. This discovery offers a potential target for treatment or diagnosis of liver cancer. However, we really need to know more about the cellular role of histidine phosphorylation in general and particularly in histone H4. One of the difficulties in the investigation of histidine phosphorylation is the detection of proteins containing phosphohistidine in cells and tissues, partly due to the lability of the P-N bond and also because there are two isomers of phosphohistidine N1 and N3 (see below). To address this problem I am currently collaborating with Dr. Matthew Piggott in Chemistry to develop pan-phosphohistidine antibodies for the detection of histidine-phosphorylated proteins, by synthesizing and using non-hydrolysable analogues of phosphohistidine as immunogenic haptons (see triazole analogues below). Components of the project could include some purification and characterization of histidine kinases. And anti-phosphohistidine antibody production.

Our group is interested in the transcriptional regulation of gene expression. We are also interested in the effects of genetic polymorphism (SNPs) on the expression of genes, particularly promoter and other regulatory variants. The focus is on genes that are involved in regulating inflammatory responses and understanding how genetically determined differences in expression contribute to diseases such as autoimmune disease, cancer and cardiovascular disease.

The Transcriptional control of the CD30 Gene in Anaplastic Large Cell Lymphoma

Anaplastic large cell lymphoma (ALCL) is a variant of immunoblastic lymphoma and tends to be clinically aggressive, resulting in the destruction of the involved lymph node structure, the infiltration of the lymph node sinuses by large transformed neoplastic cells with prominent nucleoli. The major diagnostic marker of ALCL is strong overexpression of the CD30 gene thought to result from a transforming event that leads to neoplasia. Fundamental to our understanding of the causes and treatment of ALCL is an understanding of the mechanism of overexpression of CD30. The CD30 gene promoter, including an ALCL-specific hypersensitive site we have discovered in the 1st intron, will be characterised with respect to transcriptional control elements by EMSAs, CD30 reporter gene analysis and CHART (chromatin accessibility by real-time PCR). The transcription factors binding to the promoter and the 1st intron will be identified by use of a 2-dimensional proteomics technique developed in our group. Once cloned, the identified proteins will be tested for the ability to repress endogenous expression and reporter constructs by overexpression in cell lines and by RNAi approaches. Chromatin immunoprecipitation (ChIP) assays will also be carried out to establish the in vivo relationship between the various cis-elements and trans-acting factors, including sites of histone modification. The long-term aim is to develop therapeutic strategies that interfere with the transcriptional regulation of CD30 and so block the deleterious effects resulting from overexpression of CD30.

Characterisation of functional variants of Vanin 1, a QTL controlling HDL-C Levels

This collaborative project with the Texas Biomedical Research Institute, USA involves the characterisation of the Vanin 1 gene, which has been shown to be genetically associated with low levels of High Density Lipoprotein-cholesterol (“good” cholesterol) levels in the blood. Low HDL levels are a strong risk factor for cardiovascular diseases such as artherosclerosis and heart attack. Twelve non-coding variants in the Vanin 1 gene were found that fall into 4 isocorrelated redundant variant sets (IRVS) show significant correlations with HDL-C as well as Vanin 1 mRNA expression levels. The most likely functional promoter variant at -137 exhibits a strong association with HDL-C levels (p = 0.002). The project aims to characterise transcription factors that differentially bind to the IRVS variants using EMSA followed by peptide mass fingerprinting and also to determine the effects of the candidate functional SNPs on transcriptional activity using reporter gene analysis. A further aim is to identify modulators of VNN1 expression & determine their effects on allele-specific transcription of VNN1 using mRNA expression profiling. An understanding of how the gene is controlled will inform the development of therapeutic strategies and/or drugs to modulate the activity of the Vanin 1 gene with the objective of raising HDL-cholesterol levels in individuals at risk.
Mechanism of Action of Newly Synthesised Thalidomide Derivatives.
Thalidomide is a synthetic glutamic acid derivative used in the 1950’s as a treatment for insomnia and as an antiemetic agent. Later investigations found that thalidomide had teratogenic properties. In a collaborative project with Dr Scott Stewart (Chemistry), newly synthesised and potentially safe thalidomide-based drugs will be screened for novel biological activities using TNF reporter gene assays. For those students interested in the functional aspects of thalidomide and the newly synthesised derivatives, transcriptional profiling will be carried out, using Affymetrix microarrays to define novel cellular activities, with a focus on therapeutic application. The project also involves the identification of the cellular targets of thalidomide which will be informative in a more rational drug design. Photoactivatable biotin-derivatized thalidomide will be used to treat cells, followed by UV-catalysed cross-linking. Proteins will be isolated and identified by biotin-streptavidin affinity chromatography and mass spectrometry. The proteins identified will be validated with respect to their interaction with thalidomide and by assessing functional aspects of the candidate proteins. Interactions will also be validated using confocal cell imaging.

Identification of Genetic Variation in Preeclampsia by Whole-Genome Exome Sequencing
The genetic analysis of preeclampsia continues to be one of the most critically important and unresolved areas of obstetric medicine. There is currently no known cure for preeclampsia other than delivery of the baby. Like many other common human diseases there is a large genetic component underlying susceptibility to developing preeclampsia but the genetics are complex and not yet fully understood. This project is a collaboration with W/Prof Eric Moses and involves the identification of functional genetic variants associated with preeclampsia. The emphasis is on whole-genome exome sequencing in families and represents the current state-of-the-science for genetic dissection of complex traits. The goal is to identify the specific genetic polymorphisms responsible for susceptibility to preeclampsia with the view to informing the development of much-needed diagnostic reagents and therapeutic strategies. This approach has been made possible by recent technological advances and efficiencies in high-throughput next generation DNA sequencing. This project involves a multidisciplinary team of investigators who have led the field in the recruitment and genetic analysis of preeclampsia and cardiovascular disease in families. The collection of 72 preeclampsia families from Australia/New Zealand, Finland, Iceland and Norway are the best available worldwide, making this a time of unprecedented opportunity for finding the most likely functional variants influencing susceptibility to preeclampsia.

Dr Peter Arthur 6488 1750 Email: peter.arthur@uwa.edu.au
Oxidative Stress in health and disease
Oxidative stress is caused by reactive oxygen species (ROS), also known as free radicals, and is considered to be harmful to human health. Research suggests that ROS exacerbates pathology associated with many chronic diseases and conditions. Examples include Alzheimer’s disease, atherosclerosis, diabetes, heart disease, HIV/AIDS, kidney disease, liver disease, muscular dystrophy, Parkinson’s disease, Rheumatoid arthritis and aging.

Although oxidative stress is well recognised as harmful to human health, effective treatments remain elusive. One challenge has been the lack of understanding of the various molecular mechanisms by which ROS cause pathology. Our work into how ROS affect cell signalling pathways will offer new opportunities to treat oxidative stress prior to the development of cellular damage.

Current projects examine the role of ROS in diabetes, and muscle wasting caused by dystrophy or aging. Experimental models include cells in culture as well as transgenic mouse models. Techniques include proteomic technologies (HPLC, 2D gel electrophoresis) and protein identification techniques (mass spectrometry). Additional techniques may include immunohistochemistry, western blotting, quantitative PCR and EMSA.
Structure of the paraspeckle interactome

**co-supervisors: Dr Archa Fox and Dr Sven Hennig (WAIMR)**

An emerging and exciting research area is the role of noncoding RNAs in controlling gene expression. 'Noncoding' RNAs are molecules that are functional as RNAs, and do not encode for proteins. Paraspeckles are the first sub-nuclear structure known to form around a long noncoding RNA (lncRNA), making them an important model system within lncRNA research. This is particularly relevant when it comes to cancer, as several lncRNA have been shown to act as molecular scaffolds, recruiting proteins to form oncogenic complexes that drastically alter gene expression leading to metastasis and ultimately poorer outcome for patients.

Paraspeckles contain a number of different proteins that are either (1) responsible for paraspeckle formation (2) required for paraspeckle function, or (3) are regulated by sequestration within paraspeckles. The Bond lab has recently solved the 3D structure of a number of homo- and heterodimers of paraspeckle proteins (see figure 2). In an effort to determine the roles of the other known paraspeckle proteins in paraspeckle formation and function, we are undertaking a large-scale interactome analysis of paraspeckle components.

This project involves investigating interactions of key paraspeckle proteins PSP2 and Matrin3 with other paraspeckle proteins. It will involve mapping the domains in each protein responsible for protein:protein interactions. A number of techniques will be applied, including molecular biology, yeast-two-hybrid assays, protein expression in bacteria, purification and *in vitro* interaction assays. The ultimate goal is to crystallise and solve the structure of protein complexes. The project will provide important building blocks for understanding how nuclear proteins together build up a lncRNA-structure, and how their sequestration affects function.

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**Professor Peter E Hartmann** 6488 3327  
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Almost all mothers know that breastfeeding is best for their babies but many mothers do not achieve a successful lactation. Therefore, a fundamental understanding of the physiology and biochemistry of milk synthesis and secretion, milk ejection, the mechanics of breastfeeding and infant appetite are required so that appropriate clinical assistance can be given to mothers so they can successfully breastfeed. These studies are particularly relevant to mothers who have delivered prematurely because the improved outcomes for premature babies who receive breastmilk.

BMedSci candidates may participate in a variety of projects that will result in developing clinically relevant evidence based procedures that will directly impact on the care and health outcomes of both pre-term and term infants. Topics include: 1) Ultraviolet irradiation pasteurization of human milk, 2) Exploring the peptidome/metabolome of human milk. 3) Investigation of persistent pain during breastfeeding. 4) Wound care during breastfeeding.

**Dr Robert C Tuckey** 6488 3040  
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**Cytochrome P-450 and Steroid Hormone Synthesis**

Steroid hormone synthesis is dependent upon cytochrome P-450scc which catalyses the three hydroxylation reactions involved in the conversion of cholesterol into pregnenolone, the precursor of all steroid hormones. We have purified and characterised the human form of this enzyme from placenta. To facilitate the study of the human enzyme we have isolated the cDNA encoding the protein and have expressed the cytochrome in bacteria. The bacterially expressed enzyme displays similar properties to the enzyme purified from the placenta and provides a more convenient source of the enzyme for catalytic studies. To elucidate how cytochrome P-450scc catalyses the hydroxylation of cholesterol we will make changes to the primary amino acid sequence of the enzyme by the technique of site-directed mutagenesis. This will enable us to test the role of individual amino acids in the catalytic conversion of cholesterol to pregnenolone. Regulation of progesterone synthesis by the placenta is also being investigated. We are testing the hypothesis that electron supply to cytochrome P-450 scc is the rate-determining step of the progesterone biosynthetic pathway.

References:


Dr Daniela Ulgiati 6488 4423 Email: daniela.ulgiati@uwa.edu.au

My research interest is in the role of complement in health and disease. My ambition is to clarify the roles of complement and B cell biology in autoimmune disease, using Systemic Lupus Erythematosus (SLE) as a model for this and other autoimmune diseases. Specifically, my research focuses on the control of complement receptor in health and disease. Students with a background in Molecular Biology, Biochemistry, Genetics or Immunology are able to apply. Students will be exposed to a range of techniques including Genotyping, Chomatin Assays, ChIP assays, DNA sequencing and cloning, cell culture, stable and transient transfection assays, PCR, DNA binding assays, proteomic analysis, and FACS analysis.

Projects

1. Isolation of Transcription Factors Involved in Regulating Human Complement Receptor 2 (CR2/CD21) during B Cell Development.

2. The role of CR2 promoter polymorphisms in Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA).

3. Understanding the Role of Notch Signalling and associated Transcription Factors in Lineage Commitment.

4. Characterisation of the Upstream Repressor Element in the Complement C4 Gene and its control by Lupus-associated Factors. (Co-supervised with Prof Lawrie Abraham)

Professor James Whelan 6488 1749 Email: jim.whelan@uwa.edu.au

Organelle Biogenesis

Mitochondria in all eukaryotic organisms are the source of energy (ATP) which is synthesised during oxidative phosphorylation. The respiratory chain, which is composed of several multisubunit complexes, is derived from two separate genetic systems; that of the nucleus and the mitochondrion. The nucleus is present in a single copy per cell and typically nuclear encoded mitochondrial proteins are encoded in small gene families. In contrast cells contain from 10's to several 100 mitochondria, each with multiple copies of the mitochondrial genome. Therefore the cell must co-ordinate the expression of these two distinct genomes to synthesise functional mitochondria. Additionally the cytosolically synthesised proteins must be transported specifically into the mitochondrion. Research in the laboratory carries out studies on the co-ordination of gene expression between the nucleus and the mitochondrion and how cytoplasmically synthesised proteins are imported into the mitochondrion.

As pointed out above the mitochondrion is the site of oxidative phosphorylation. Although the basic components of the respiratory chain are well conserved between organisms, some species contain additional components in the respiratory chain. These components are puzzling in that their activity often by-passes the energy harvesting complexes of the respiratory chain. However these novel proteins are expressed in a gene and tissue specific manner suggesting that their activity is highly regulated. Research focuses on the characterisation of the role of these additional protein activities of the respiratory chain.

In the last ten years the role of mitochondrial mutations in disease has emerged as a new area in medicine. Mitochondrial mutations are not inherited in a mendelian manner, accumulate with age and can display a mosaic effect in different tissues. Mitochondrial mutations have been shown to be responsible for a number of syndromes in humans and have also been implicated in age related degenerative diseases such as Alzheimer’s and Parkinson’s. Research in the laboratory is attempting to determine the biochemical effects of mitochondrial mutations and ways of overcoming these biochemical lesions.
Biology and Bioinformatics of Poly-Amino Acid Stutters

Poly-amino-acid stutters are largely a eukaryote innovation, being largely absent in prokaryotes, particularly those that parasitize other prokaryotes (such as bacteriophages) (Wise 2001). These stutters have been thought to arise due to Slip Strand Mispairing (Levinson and Gutman, 1987), in which a bulge appears during DNA replication, but replication is able to continue because it able to continue with exactly the same sequence repeated a little further downstream. This would suggest that stutter codons should (at least initially) be identical. They may then diverge due to mutation. On the other hand, if the codons remain identical, the stutters may lengthen (which has been used to explain the range of poly-glutamine repeat lengths in the Huntington protein. (Poly-Gln repeat above a certain critical length are associated with Huntington's Disease.

There is also a disease associated with poly-alanine repeats: Oculopharyngeal Muscular Dystrophy. While research by other authors has targeted specifically the poly-Gln repeats, in this project you will take a broad view, starting with the following questions:

1. Are there diseases associated with other poly-amino-acid stutters?
2. Are the codons associated with poly-amino-acid stutters largely uniform or non-uniform?
3. How are the distributed by length?
4. Do the codons used in repeats reflect the Codon Adaptation Index for that organism (Sharp and Li, 1987)

Viral Codons

You are no doubt aware that the "Universal" codon translation table in fact only applies to eukaryote genomes, and even then not to all of them; slime mold has a different table. The set of different tables can be found at: http://www.ncbi.nlm.nih.gov/Taxonomy/Utils/wprintgc.cgi?mode=c If you look at that site you will notice that there is no mention of viruses. One may assume, however, that because viruses are dependent on the replication machinery of their hosts that their genes will be encoded like their hosts, i.e: use the same codon translation tables. So, for example, MUMPS will use the Universal table, while lambda phage will use a bacterial table.

The Codon Adaptation Index was developed some years ago and reflects the observation that some codons are far more used than other codons for a given amino acid, arguably reflecting greater numbers of the corresponding anti-codons (Sharp and Li, 1987). The authors also observed that highly expressed genes tend to use the most abundant codons. The Codon Adaptation Index was developed to reflect these observations.

The project is to examine viral genes in terms of their Codon Adaptation Index to gauge the extent to which the codon usage biases of a virus mirror that of its host. Is it possible to see significant differences between codon usage in the different isolates of the same virus which target different species, eg: influenza virus affecting humans and birds.

Winthrop Professor George Yeoh

Our research group focuses on the biology of the liver progenitor cell (LPC) called an “oval cell” which describes its shape. This has enormous potential as the vehicle for cell and gene therapy to treat liver disease. Liver disease has become a significant health issue because its causes which are mainly lifestyle related – alcohol, viral infection (HBV and HCV) and obesity are increasing at an alarming rate. All lead to chronic liver disease and liver cancer (HCC) is a common final outcome. Liver transplantation is the only option currently available for treating end-stage liver disease. This option is severely limited by the availability of livers for organ transplant, hence we are exploring the potential of the LPC for use in cell therapy.

Cell Therapy Project: Towards the generation of an artificial liver: optimising culture conditions which allow the differentiation of LPCs into functional hepatocytes.

Cancer Projects:
1. Identifying cellular and molecular changes which accompany LPC transformation in vivo and in vitro; which are causal in relation to HCC?
2. Metabolic changes accompanying transformation of LPCs: is the Warburg effect in cancer cells due to loss of P53 expression activity?
The School of Medicine and Pharmacology is located across four sites in the metropolitan Perth/Fremantle area: Fremantle Hospital, QEII Medical Centre, Royal Perth Hospital, and Sir Charles Gairdner Hospital. Academic staff at each site offer stimulating projects across a broad range of science and clinical topics. The School maintains research partnerships and joint supervision opportunities with the Western Australian Institute of Medical Research, the Centre for Neurological and Neuromuscular Research, and the Lung Institute of Western Australia Medicine.

**CARDIOLOGY/CARDIOVASCULAR MEDICINE**

**Associate Professor Doug J McKitrick (RPH)**  9224 8065  email: doug.mckitrick@uwa.edu.au

1. Mechanisms of thirst and vasopressin secretion in left ventricular dysfunction. Includes studies on the regulation of vasopressin secretion and the mechanisms of disordered thirst in humans after myocardial infarction and in an animal model of heart failure.
2. The role of coronary artery baroreceptors in cardiopulmonary reflexes. Includes anatomical and physiological studies to establish the existence and significance of coronary artery baroreceptors in cardiovascular regulation.
3. Brainstem and spinal cord neurotransmitter systems involved in cardiovascular control. Includes studies of the cellular mechanisms of neurotransmitter activation of neurons in cardiovascular regulatory sites in the central nervous system.
4. Pharmacological and electrophysiological characteristics of vascular mechanoreceptors. Includes studies to describe the characteristics of stretch-activated ion channels in mammalian blood vessels and to define their role in cardiovascular control.

**Winthrop Professor J Hung (QEII)**  9346 2677/3483  email: joe.hung@uwa.edu.au

1. Inflammation, genes, and other novel risk factors for atherosclerosis and coronary heart disease.
4. Determinants of coronary artery disease with focus on the role of obesity, metabolic risk factors, and diabetes.

**DISORDERS OF THE LIVER AND BILIARY TRACT**

**Winthrop Professor G P Jeffrey (QEII)**  9346 3292  email: gary.jeffrey@uwa.edu.au

1. Studies of the immune effector mechanisms and the role of cytokines in production of liver cell damage in acute and chronic hepatitis and in liver transplant rejection.
2. Study of the molecular mechanisms of iron induced oxidative stress in overload disorders.
3. Study of immunopathogenesis of Hepatitis C.
4. Clinical Trials in liver disease.

**Associate Professor Leon Adams (QEII)**  9346 3228  email: leon.adams@uwa.edu.au

A range of resources including clinical cohorts, data-bases and biological specimen banks allow a wide-range of clinical research projects to be successfully undertaken in the time-frame required.
1. Pathophysiology, epidemiology and clinical features of nonalcoholic fatty liver disease.
2. The clinical and pathological significance of diabetes and obesity in chronic liver disease and liver transplantation.
3. Serum markers of hepatic fibrosis.
4. Clinical trials in liver disease.
5. Genetics and chronic liver disease.

**GERIATRIC MEDICINE**

**Winthrop Professor D G Bruce (FH) and Assistant Professor Janet Mace (FH)***  9431 3774  email: david.bruce@uwa.edu.au  9431 3648  email: janet.mace@uwa.edu.au

1. Health of the older person
2. Impact of diabetes on physical and cognitive function in the elderly
3. Clinical neuroscience in older persons
Many of the current research projects are performed in collaboration with the School of Psychiatry and Clinical Neurosciences, Stroke Unit, Neuroradiologists or interstate and remote colleagues. Several areas are suitable for one year of research training:

1. Systematic review of osteoporosis and dementia therapies.
2. Epidemiology, aetiology and treatment of osteoporosis, cognitive impairment, falls and dementia.
5. Neuro imaging in patients with cognitive impairment and stroke.

ENDOCRINOLOGY

Effects of genes, hormones and lifestyle on bone and the cardiovascular system

Our group has been researching bone and endocrine disorders for 20 years resulting in many ground breaking publications in the top literature. Projects are available to students with the aim of giving them a broad understanding of research methodology in the area of clinical research, laboratory research and genetic research with emphasis on good research practice including record keeping, data management and statistical analysis. The successful candidate will be encouraged to present their data at a national or international meeting. Specific projects include gene discovery for bone and cardiovascular disease, new methods of bone structural assessment and nutritional effects on bone and cardiovascular disease.

Vascular complications of type 2 diabetes including diastolic dysfunction, endothelial dysfunction and arterial stiffness.

Project titles:

1. Defining role of SLIRP and other novel nuclear hormone receptor coregulators in cancer and metabolism (with Dr Shane Colley).

Hormones, acting through nuclear receptors (NRs), play critical roles in the development of human cancer and the control of body homeostasis and metabolism. The discovery of nuclear NRs that selectively modify NR activity has transformed our understanding of hormone action. We have recently identified several novel NR coregulators that regulate a range of NR signaling pathways. These molecules include SLIRP, a NR repressor of estrogen action in breast cancer. SLIRP also represses PPAR signaling, and its expression in fat and muscle suggests an important role in energy and metabolism.

We have generated a SLIRP knock out mouse which is providing added resources for interesting projects. There are many exciting questions regarding the function of these proteins in cancer, as well as fat and muscle cells. Available projects involve studies on the biology of SLIRP as a regulator of hormone signaling in cancer, muscle, fat and the pancreas, and its functional role as a regulator of body homeostasis and metabolism (diabetes). Additional projects include understanding the functional biology of some of the other coregulators in the metabolism of microRNA processing, regulators of hormone action, and investigating the intersection between miRNA biology and NR signaling.
2. The functional role of miRNAs in human disease (with Dr Keith Giles)

The identification of small RNAs (RNAi, microRNAs (miRs)) is transforming our understanding of the regulation of gene expression. In particular, miRNAs have been shown to be aberrantly expressed in a range of human diseases, including cancer. Furthermore, altering the level of a miRNA within a cell is a powerful way to regulate gene expression of target proteins. We have recently identified miRNAs that target key growth factor receptors that are responsible for the proliferation of several different human cancers. Transfection of cells with the miRNAs dramatically reduces the growth factor receptor expression and can lead to cell cycle arrest and cell death. Moreover, the miRNA may coordinately regulate several other genes with the same miRNA target sequence, suggesting a very well orchestrated system in which the miRNA targets downstream members of the same signaling pathway. We now are addressing the role of these miRNAs in a range of human cancers (lung, breast, glioma, head and neck, prostate, pancreas), and in normal tissues in which they are highly expressed. Available projects involve studies to understand how these miRNAs function, identification of other targets in cells within cancer and endocrine paradigms and studies to examine the therapeutic potential of these miRNAs.

General Background:

Each of these projects has a background of signaling in cancer and normal tissues, and involves a large number of molecular and cellular biological techniques, including functional analyses with siRNA and DNA, as well as miRNA microarrays, next generation sequencing and ChIP-seq. The laboratory also has components focussing on a translational focus using human tissue microarrays to provide direct clinical relevance to specific aspects of the work. The laboratory has excellent infrastructure and several senior scientists, PhD students and research assistants who provide help and guidance in all aspects of the work.

Professor Bu Yeap (FH) 9431 2276  email: bu.yeap@uwa.edu.au
Expression, activation and function of nuclear transcription factors in the contexts of diabetes/atherogenesis and hormone-dependent cancer.

HYPERTENSION AND CARDIOVASCULAR DISEASE

Winthrop Professor Lawrie J Beilin (RPH) 9224 0258  email: lawrie.beilin@uwa.edu.au
1. Studies of childhood origins of adult cardiovascular disease, obesity and diabetes; genetic and environmental effects and interactions.
3. Alcohol and cardiovascular disease.
4. Dietary antioxidants and blood pressure risk.

Research Professor Anne Barden (RPH) 9224 0272  email: anne.barden@uwa.edu.au
2. Studies of genetic and environmental factors relating to obesity, the metabolic syndrome and cardiovascular risk.
3. Pregnancy diabetes and pre-eclampsia.
4. Alcohol and cardiovascular disease.
5. Cytochrome P450 arachidonic acid metabolism.

Research Professor Trevor Mori (RPH) 9224 0273  email: trevor.mori@uwa.edu.au
2. The role of omega-3 fatty acids in cardiovascular disease and other chronic diseases.
3. Studies of genetic and environmental factors relating to obesity, the metabolic syndrome and cardiovascular risk precursors in children.
4. Alcohol and cardiovascular disease.

Research Professor Trevor Mori (RPH) 9224 0273  email: trevor.mori@uwa.edu.au
Research Professor Anne Barden (RPH) 9224 0272  email: anne.barden@uwa.edu.au
Professor Kevin D Croft (RPH) 9224 0275  email: kevin.croft@uwa.edu.au
1. Markers of oxidative stress in disease
2. Lipid / protein oxidation and cardiovascular disease

Professor Kevin D Croft (RPH) and 9224 0275  email: kevin.croft@uwa.edu.au
Winthrop Professor Lawrie J Beilin (RPH) 9224 0258  email: lawrie.beilin@uwa.edu.au
1. Atherogenic components of oxidised low density lipoproteins.
2. Dietary antioxidants and atherogenesis.
3. Cytochrome P450 arachidonic acid metabolism: Role in vascular function.
4. Absorption and metabolism of dietary polyphenols.
Patients with diabetes, obesity and the metabolic syndrome are at increased risk of heart disease. Studies of lipid and lipoprotein metabolism help identify abnormal pathways of lipid metabolism. We employ stable isotopes, GCMS methods and mathematical modeling to quantitate lipoprotein metabolic pathways and determine rates of lipoprotein production and catabolism. The research focus is on understanding how interventions, lifestyle and pharmacological, reduce cardiovascular disease risk.

1. Studies of postprandial lipoproteins
2. Studies of HDL metabolism

Development of mechanistic (mathematical) models using tracer kinetics or pharmacokinetic, pharmacodynamic data. Models of *in vitro* and *in vivo* systems can be developed to provide quantitative information about the system under investigation.

Winthrop Professor G F Watts (RPH) 9224 0248  email: gerald.watts@uwa.edu.au

1. Use of stable isotopes/mass spectrometry to study the physiology and pathophysiology of lipoprotein transport in human subjects. Includes studies of the role of lipid substrates in the regulation of the hepatic secretion of apolipoproteins B-100 and A-I in normolipidaemic subjects, subjects with primary and secondary hyperlipidaemias and, obese subjects.

**IMMUNOLOGY AND CANCER**

Winthrop Professor B W S Robinson (QEII) 9346 3129  email: bruce.robinson@uwa.edu.au
Dr D Nelson (QEII) 9346 4967  email: delian@cyllene.uwa.edu.au
Adj/Professor R Lake (QEII) 9346 3127  email: rlake@cyllene.uwa.edu.au

1. Studies of human immunological anti-cancer defence processes. These studies range from laboratory experiments to clinical trials utilising biological response modifiers and/or lymphocytes.
2. Use of gene transfer techniques and gene therapy in cancer.
3. Evaluation of immunological processes in the normal and diseased human lung using cellular and molecular immunological techniques, including transgenic animals.
4. Discovery of cancer genes.
5. Investigation of biomarkers for early mesothelioma detection

**IRON METABOLISM AND DISEASE**

Professor Ian Lawrance (FH) 9431 3647  email: ian.lawrance@uwa.edu.au
Dr Angela Chew (FH) 9431 3223  email: angela.chew@uwa.edu.au

The research work in this unit encompasses basic science, clinical research and clinical trials. The basic science research focuses on the chronic inflammation-induced intestinal changes that occur in Inflammatory Bowel Diseases (IBD) and the subsequent complications of fibrosis and carcinogenesis. Investigation has been undertaken in both the human and animal models. The aims are to understand the extracellular matrix changes that underlie fibrosis, to identify the regulating factors mediating these alternations and to determine ways to modify these factors so as to alter the clinical patterns of ulcerative colitis (UC) and Crohn¹s disease (CD).

Present investigations include an animal model of chronic inflammation-induces intestinal fibrosis and primary cell culture, which are investigated by gene expressions studies. Other work examines the development of tumors in a mouse model of inflammation-induce colonic carcinogenesis. The inflammatory aspects, roles of Secreted protein acidic and rich in cysteine (SPARC), systemic and oral iron levels, and genetic alterations in the intestinal mucosa are being investigated.

Clinical research investigates the efficacy and tolerability of novel medications in CD. Other clinically based research that has been or is being undertaken includes the cancer risk of small colonic polyps, skin cancer risk in IBD patients on azathioprine, sperm DNA fragmentation and nutritional levels in IBD patients, markers of colon cancer, and the efficacy of rectal tacrolimus in resistant proctitis.
Characterisation of novel genes in Tfr2-associated haemochromatosis – Project aims: We have recently identified a number of novel genes which are associated with type 3 haemochromatosis. This project will involve the characterisation of one of these genes. Changes in gene expression will be confirmed by real-time polymerase chain reaction (PCR) and Western blotting. Additionally, the gene will be cloned into an expression vector and transfected into an appropriate cell line. The subcellular location of the protein will be determined using fluorescence microscopy. Uptake of iron bound to transferrin and citrate will be measured and compared to the gene expression.

Hereditary Haemochromatosis – Project aims: HFE is hypothesized to be a sensor of body iron levels which signals to a regulatory molecule hepcidin to control iron absorption and liver iron metabolism. In this project we will use a Hfe knockout mouse model of haemochromatosis type 1 to measure expression of iron transporters and regulators to identify the role of HFE in sensing body iron levels and the regulation of liver iron metabolism and determine how the absence of HFE causes liver iron overload.

Gastroenterology

MEDICAL ONCOLOGY

CANCER TREATMENTS

PALLIATIVE CARE

RENAL MEDICINE

1. Immune effects of chemotherapy and combination chemoimmunotherapy in animal models
2. Psycho-oncology and patterns of care studies in patients with brain tumors
3. Imaging and clinical trials of new therapies in malignant mesothelioma

3. Prediction of response and toxicity to cancer treatments.
4. Apoptosis and cancer

Palliative care is a relatively young discipline, still building its research capacity and infrastructure. It is developing an evidence base that will directly improve practice and policy in providing care for a growing number of the Australian population afflicted by a life-limiting illness. Broad opportunities exist in a range of areas including symptom assessment and management in the clinical practice of palliative care, families and caregiver support, psychosocial support, which may include bereavement and/or spiritual aspects, and models of care in palliation. In Australia research and evidence are urgently needed to guide clinical practice, to develop national and local health policy, and to identify effective methods of service delivery.

There is Government, health consumer and health provider recognition of the importance of palliative care as an integral component of our health systems and individual clinical practices in maximising quality of life for patients suffering incurable life-limiting illnesses, both malignant and non-malignant.

Please contact David Thorne to discuss a range of potential research projects in Palliative Care.

1. Long-term medical and psychosocial outcomes following living kidney donation.
2. Factors affecting progression of chronic kidney disease. Including co-morbid diseases seen in chronic kidney disease, eg. Hypertension
4. Dialysis adequacy. Including bioimpedence volume assessment tools and sodium removal with dialysis
5. Haemoglobin variability with chronic kidney disease
RESPIRATORY MEDICINE

Winthrop Professor Philip J Thompson (QEII)  9346 3822/9346 3198  email: philip.thompson@uwa.edu.au

A broad range of respiratory research is undertaken within the Centre for Asthma, Allergy and Respiratory Research and in the Lung Institute of Western Australia. This includes: genetics of airway diseases, development of gene therapies, micro RNA studies, investigation of chronic airway inflammation, stem cell biology and immunology, lung injury and repair – lung fibrosis, clinical trials, cystic fibrosis and bronchiectasis, physiotherapy and lung vascular diseases and lung transplantation. Our basic laboratory work involves using the following techniques: flow cytometry; confocal microscopy, eosinophil and neutrophil separation; cell culture; pharmacology; molecular biology and cell biology techniques. We also have staff skilled in clinical trial design and application. Some of our current research areas are:

1. Assessment of regulatory systems relating to the airway epithelium
3. Lung cancer and mesothelioma cell biology
4. Airway inflammation including the role of prostanoids, leukotrienes, kinins and their biochemistry
5. Eosinophils, neutrophils and their relevant mediators and regulation
6. Pharmacogenetics of asthma and COPD
7. Clinical drug trials and their design
8. Role of RAGE in chronic lung diseases
9. Aspirin sensitive asthma
10. The role of exercise training in chronic lung disease
11. Epidemiology and management of pulmonary hypertension.
12. Stem cells and cystic fibrosis.

Professor Grant Waterer (RPH)  9224 0245/9224 0337  email: grant.waterer@uwa.edu.au

1. Genetic Susceptibility to Pulmonary Infections. Investigation and gene polymorphisms within cytokines are related proton genes that influence the susceptibility to or outcome of pulmonary infectious diseases.
2. Microbiological Diagnostic Techniques in Pneumonia. Particularly the application of real-time PCR in patients with community-acquired pneumonia.

PLEURAL DISEASE RESEARCH

Winthrop Professor Y C Gary Lee (QEII)  9346 4968  email: gary.lee@uwa.edu.au

Pleural diseases affect 3000 patient / million population each year, with pleural infection (pleurisy) and malignant pleural effusion being the most common. Breathlessness is the most common symptom and can be debilitating in many patients.

Our group has a variety of projects focusing on better diagnosis and management of pleural diseases, all of which employ a translational approach involving clinical and laboratory techniques.

i) Mechanism of malignant pleural effusion formation.
   About 1 in every 3 patient with breast cancer, every 4 with lung cancer and 95% of patients with mesothelioma suffer from a pleural effusion. Using a variety of in vitro and in vivo techniques, we aim to identify key molecules that govern the formation of pleural effusions in patients with cancer.

ii) Predictors and mechanism of breathlessness in pleural effusions.
   We are establishing a database capturing patients with malignant pleural effusions in Western Australia. Analysing the physiological (esp the diaphragmatic movement) and biochemical characteristics of the pleural effusion, we aim to identify predictors of symptomatic benefits of drainage of fluid and thus need of intervention.

iii) Mechanism of pleural infection.
   Pleural infection affects 65000 patients in the US and UK each year, and many more in developing countries. Using a new animal model and in vitro techniques, we investigate the pathophysiological effects of common bacteria on the pleura and aim to identify factors governing the migration of bacteria through the mesothelial cell layers.
Tumour Immunology Group of NCARD
The National Centre for Asbestos Related Diseases (NCARD) is a research centre funded by the federal government as part of the Governments Strengthening Cancer Care package with measures aimed at prevention, treatment and support for cancer patients and their families. NCARD is a collaboration of researchers who have a national and strategic focus for research into asbestos related diseases and cancers. The National Centre for Asbestos Related Diseases provides a platform to build on Australia’s existing research expertise and encourages strong organisational linkages to ensure our research is systematic and complementary to existing research efforts in the area of asbestos related diseases.

Asbestos-induced cancers such as mesothelioma kill more than 20,000 people worldwide a year and 500 a year in Australia. There is typically a long latency between asbestos exposure and disease diagnosis that makes identification and prognosis difficult.

The Tumour Immunology Group is an exciting collaboration of 25 scientists (including 7 postdoctoral scientists), clinicians, and students with a broad range of expertise that is recognised as being at the forefront of asbestos-related diseases research.

The group is based on the 4th Floor of G block at Sir Charles Gairdner Hospital and conducts weekly educational meetings, has opportunity for conference travel, hosts international visiting scientists, and holds regular scientific symposia.

Research projects offered by the group include projects in the field of the following NCARD grants:

- The development of sensitive serum markers for improved diagnosis, monitoring and screening for early detection of cancer.
- An investigation of the importance of specific genes in asbestos-related disorders and their relationship to environmental factors.
- The development of a national resource for mouse models, to help understand the disease in humans and provide essential data for clinical trials.
- An investigation of mechanisms to inhibit the body’s collagen production to slow growth in malignant mesothelioma tumours.
- A combination of conventional therapies with immuno/gene therapies that encourage the body’s own anti-cancer immune responses to attack cancer.
- An investigation of ways to improve the ability to measure patient responses to chemotherapy treatment.
- An examination of chromosomal changes in cancer cells to help improve early cancer detection.

For information on the projects
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Professor Anna Nowak (QEII) 9345 2432 email: anna.nowak@uwa.edu.au

Novel imaging paradigms in malignant pleural mesothelioma
The overall aim of the project is to improve the validity and reliability of anatomical imaging as an endpoint for assessment of patient benefit in clinical trials of malignant pleural mesothelioma.

Background:
Whilst research on the molecular basis of mesothelioma, potential therapeutic targets, and novel early phase clinical trials has proliferated, little academic attention has been given to the foundations on which all clinical advances are built: the ability to reliably predict successful therapies using validated biomarkers. The key biomarker on which academic and commercial clinical trial decisions are made is objective tumour response on CT imaging. Even endpoints such as 6 month progression-free survival and time to progression rely on a. accrual of patients with measurable disease into clinical trials b. reliable and validated imaging assessment of progression and c. endpoints that can be considered congruent across clinical trials.

Assessment of response and progression is uniquely challenging in MPM due to the circumferential rind-like growth pattern most commonly associated with this tumour. Other difficulties include acknowledged interobserver variability, the presence of pleural effusion and atelectasis, and the large total bulk of tumour that can be present even with thin, ostensibly ‘non-measurable’ circumferential disease.

Our research re-evaluates these foundations using radiological and nuclear medicine imaging in conjunction with a comprehensive clinical database.
Professor Anna Nowak and Dr Roslyn Francis have internationally recognised expertise in this area, and collaborate with other researchers in Milan and Chicago. A large patient image and clinical database is available. Projects are available within this field that include systematic reviews of assessment of response and progression in clinical trials of mesothelioma, determination of inter- and intra-observer variability in response studies, incorporating tumour bulk measurement into staging, and correlating patient-related outcomes such as quality of life and lung function tests with imaging.

**Chemo-immunotherapy, biomarkers and immune response**

Malignant mesothelioma originates in mesothelial cells lining the pleura, peritoneum or pericardium, and is predominantly caused by asbestos exposure. Most patients receive palliative chemotherapy only, with a median survival for patients treated with cisplatin and pemetrexed of around 12 months. Treatment advances are needed. This project will trial the use of standard chemotherapy of cisplatin and pemetrexed with an adjuvant immunotherapy protocol, following our observations *in vivo* that pemetrexed alone or in combination is immunostimulatory and synergizes with immunotherapy. The trial will test the efficacy of using CD40 activation by the novel agent CP-870,893 to mimic CD4+ T cell help. CD40 is a member of the TNF super-receptor family. CD40–CD40 ligand interactions mediate T cell help for cytotoxic T lymphocyte (CTL) priming. The CD40–CD40L interaction may determine whether CTLs become primed or tolerized. When the CD40 molecule on the antigen-presenting cell (APC) interacts with its ligand on the CD4+ T cell, APC activation occurs, with cytokine production and up-regulation of other co-stimulatory molecules, leading to a priming interaction with the CD8+ T cell.

The clinical component of this phase Ib trial is funded, however, a PhD student can address further important questions, including:

- What immunological biomarkers correlate with anti-tumour activity?
- What changes will be observed in the dendritic cell and CD8+ T cell compartments?
- Will anti-tumour antibody responses become evident during or after treatment?

**NK cells as the missing link between anti-cancer chemotherapy and CD8 T cell responses**

Chemotherapy is the most common treatment for cancer. By itself, it is not usually curative, but we and others have shown that some drugs can synergise with particular immunotherapies. Many cytotoxic agents target cellular division and so cause DNA damage and in this project, we propose to explore the immunological consequences of this damage in a mouse model of human cancer. Cells react to DNA damage by the upregulation of several so-called stress-ligands, including molecules such as *H-60, RAE-1, MIC-A*, and *MIC-B* that bind to the activating NKG2D receptor. This receptor is expressed (amongst others) on NK cells. Activated NK cells can stimulate dendritic cells and CD8 T cells, promoting an adaptive anti-tumour immune response. We hypothesize that NK cells are a limiting factor in the development of this response and therefore that NK-targeted therapeutic intervention will enhance the adaptive anti-tumour immune response. We have already been able to show that NKG2D recognition plays an important role in the development of post-chemotherapy T cell responses and that NK cells are an essential component. Therefore, the project will explore the link between this pathway and DNA damaging chemotherapy. Briefly, the plan is to investigate the *in vitro* and *in vivo* expression patterns of NKG2D ligands after chemotherapy. Then, to study how activated NK cells help the CD8 T cell response and ultimately test two therapeutic options, one aimed at increasing NKG2D ligand expression, and the second designed to increase the number of cells responding to DNA damage.

**Immunotherapy Plus Chemotherapy Boosts Mesothelioma Treatment Effectiveness**

A combination of immunotherapy and traditional chemotherapy may be more effective than either treatment alone against mesothelioma, according to a recent analysis published in the journal, *Tissue Antigens*. Mesothelioma is one of the most difficult cancers to treat, and the prognosis is often poor. Surgery and chemotherapy are the standard mesothelioma treatments, but even with these therapies many patients do not live more than a year after their diagnosis. A newer treatment option is immunotherapy, which enhances the immune system response to help the body attack cancer cells. Because mesothelioma engages the immune system, immunotherapy would appear to be a promising treatment strategy for this cancer. However, studies conducted so far on immunotherapy for mesothelioma have yielded disappointing results. Combining immunotherapy with chemotherapy might be the key to improving its effectiveness, according to Richard Lake, PhD, Adjunct Professor at the National Centre for Asbestos Related Diseases and School of Medicine and Pharmacology at the University of Western Australia. In the past, chemotherapy and immunotherapy were considered to be antagonistic treatments, but according to Professor Lake, chemotherapy may actually enhance the effects of immunotherapy. Chemotherapy destroys cancer cells and shrinks tumours, making them smaller and easier for immunotherapy to destroy. Some chemotherapy drugs also appear to stimulate the immune system to recognize and attack tumours.
Animal studies have already indicated that chemotherapy and immunotherapy might have a synergistic effect on cancer cells. However, selecting the right drugs will be critical to treatment effectiveness, because different drug combinations may have different effects on the immune response, according to the report. The researchers have already begun to pinpoint a few chemotherapy drugs that might work well in combination with immunotherapy. “Our studies have focused on gemcitabine, and it seems to have many of the characteristics that we were looking for,” Dr. Lake says. “Others have cited doxorubicin as a drug with the capacity to generate immune responses.” For the immunotherapy part of the treatment, Dr. Lake says that a cancer vaccine or monoclonal antibodies (antibodies produced in a lab that stimulate the immune system) might be the best option.

Professor Lake and his colleagues are currently launching clinical trials to study various chemotherapy-immunotherapy drug combinations. Although he does not know what effect these drug cocktails will ultimately have on mesothelioma treatment, Professor Lake is optimistic. “This disease is at the most difficult-to-treat end of the spectrum, so survival is likely to increase incrementally as treatments improve,” he says.


**Adj/Professor Jenette Creaney (QEII) 9346 3510 email: [jenette.creaney@uwa.edu.au](mailto:jenette.creaney@uwa.edu.au)**

Professor Creaney is the Head of the Biomarkers and Discovery unit of NCARD. The group is investigating biomarkers for improved diagnosis and monitoring of patients with mesothelioma and also examining the use of biomarkers for screening asbestos-exposed individuals for early detection of mesothelioma.

Jenette received her PhD in 1995 from La Trobe University (Melbourne, Australia), and has worked in the cancer and immunology fields as a molecular biologist and protein chemist since. Jenette returned to Australia from the US in 1999 to work with Winthrop Professor Bruce Robinson and Adjunct Professor Richard Lake in Perth, on principally the marker discovery projects. The work from the group includes the seminal work on the biomarker mesothelin for use in patients with mesothelioma this work was published in the journal, Lancet.

Jenette has received several prestigious awards for her work in Science including the Howard Hughes Medical Institute Postdoctoral Fellowship and a Young Investigator Award.

**Mesothelin – a tumour associated antigen for mesothelioma**

**Background:**

Malignant mesothelioma (MM) is an aggressive asbestos-induced tumour. Once considered rare, mesothelioma is now more, or as, common a cause of death in Australia as cancers of the bone, liver, cervix, bladder and ovary. There are estimated to be around 15-20,000 deaths per annum from this disease worldwide. Left untreated the life expectancy of patients is between 7 and 12 months. In general MM is largely resistant to surgery, chemotherapy and radiotherapy. An improvement in treatment options may follow on from an improved understanding of the biology of MM.

Mesothelin is a mesothelial differentiation antigen identified in 1992. Mesothelin is ~40kDa glycosylated protein predominately anchored to the cell surface of normal mesothelial cells by a glycosylphosphatidyl inositol (GPI) sequence. There are at least 4 members of the mesothelin family of proteins; megakaryocyte potentiating factor (MPF), mesothelin variant 1, mesothelin variant 2, and serum mesothelin related protein (SMRP). Little is understood about the function or regulation of these proteins in normal or malignant mesothelial cells. The Robinson group have been intensively investigating mesothelin in MM patients and shown that approximately 50 % of patients have elevated mesothelin in their serum at diagnosis.

Recently it was shown that mesothelin binds to CA125 and there has been intense speculation in the literature as to whether the binding of mesothelin to CA125 plays a role in the invasiveness and metastatic spread of MM and also of ovarian cancer. Ovarian cancer is another tumour that expresses both mesothelin and CA125. CA125 is a very high molecular weight transmembrane mucin and a well characterised tumour marker which is elevated in approximately 50% of MM patients. Of particular interest was that it was not the same patient population that had elevated mesothelin and CA125 in their serum. One potential explanation for this is that the two glycoproteins are binding together in the serum and preventing an accurate measure of either being made. It would be of interest to determine if this were the case.

Given the limited treatment options for patients with MM and its universal fatal outcome little work has been done to divide MM patients into different sub-classifications, beyond what is determined by gross tumour histology. Approximately 10% of MM are classified as being sarcomatoid in nature and the remainder are either of epithelial or mixed histology’s. Though there is a very wide range in observed disease progression and responses to treatment in the MM cohort as a whole. The current proposed project aims to investigate the role, if any, of mesothelin and CA125 in MM invasion and metastatic spread.

This project will investigate the nature of the mesothelin CA125 binding using a modification of the ELISA techniques routinely used to measure each biomarker independently. Also the invasiveness and metastatic potential of MM cell lines will be determined in vitro. And in parallel patients survival and progression will be monitored in relation to the mesothelin and CA125 characteristics of their tumour.
Biomarkers for determination of drug sensitivity in mesothelioma
Chemotherapy is offered to patients with mesothelioma. Using a combined pemetrexed and cisplatin regime improvement in survival have been seen in approximately 40% of patients. This means the majority of patients are enduring this debilitating treatment for little benefit during the final period of their lives.

In efforts to understand the pathogenesis of mesothelioma and to test therapeutic agents we have developed a number of human in vitro cultured cell lines. In preliminary work we have found that expression of the enzyme ribonucleotide reductase (RR) correlates with in vitro sensitivity to gemcitabine. The chemotherapeutic agent of choice used before pemetrexed became the standard of care. RR converts ribonucleotides to their corresponding deoxyribonucleotides. This is the rate-limiting step in DNA synthesis and repair. In proliferating cells, like tumours, RR levels are high, and gemcitabine, in addition to its actions as a nucleoside analogue, directly inhibits the RR enzyme.

In this current project we plan to define the molecular pathways responsible for resistance to pemetrexed in firstly in vitro cell lines systems, and secondly in tumour samples from patients undergoing pemetrexed based therapies. The aim of this study is ultimately to identify those patients most likely to respond to a specific chemotherapy agent so that their treatment regimes can be best targeted.

Identification of a microRNA signature for malignant mesothelioma diagnosis
Malignant mesothelioma is an asbestos-induced cancer with very poor prognosis. Diagnosis of this cancer can often be difficult and time-consuming. We have an integrated team of scientists working on improving methods for mesothelioma diagnosis, which would not only allow patients to begin appropriate treatment at an earlier stage of disease but would also reduce costs to the health care system.

Micro RNAs (miRNAs) are short, single-stranded RNAs that negatively regulate gene expression by modulating the translational efficiency of target mRNAs. miRNAs are involved in many cell processes including development, differentiation, proliferation, apoptosis and response to stress. Aberrant expression of miRNAs have been described in several types of cancers, including breast, lung and colon, where they may function in either an oncogenic or tumour suppressing manner.

In this project we plan to identify the signature of miRNA expression differentiating between malignant mesothelioma and (1) benign disease and (2) lung adenocarcinoma. This may provide new biomarkers to assist with the diagnosis of this cancer, and also lead to improved understanding of the genes and pathways deregulated during the mesothelioma transformation process.

Developing biomarkers for the early detection of malignant mesothelioma
Malignant mesothelioma (MM) is an asbestos-induced, aggressive tumour that almost invariably results in death within 12 months. An inability to diagnose the disease at an early stage means that treatment is not effective. An earlier diagnosis than is presently possible and prior to the patient presenting with clinical symptoms may result in more effective therapy and allow for better management of the disease and increased survival times.

We are currently searching for biomarkers that are present in blood, urine or pleural effusions in patients with MM, which enables the detection of the disease at a considerably earlier time than currently available clinical and biomarker techniques allow. An approach that we have adopted is the detection of antibodies to proteins that may be over-expressed, or that are mutated, in MM patients. Using protein microarray technology we have identified a number of promising candidate proteins for which immune responses are observed in MM patients. This project will involve developing biological assays of high sensitivity and specificity to these candidate proteins and to use these assays to develop a testing strategy to efficiently detect MM with a high sensitivity and specificity. This project will involve producing and purifying proteins using cloning vectors and affinity chromatography, the development of ELISA assays, the use of these assays to detect antibodies in patient samples, and the analyses of the resulting data for determining specificity and sensitivity of the assays for detecting MM.

Research Assistant Professor Amanda Cleaver (QEII) 9346 7275 email: amanda.cleaver@uwa.edu.au

Determining the phenotype and function of suppressive CD4 T cells that limit the efficacy of immunotherapy in the treatment of cancer
Mesothelioma is an aggressive and terminal form of cancer that forms in the serosal cavities after exposure to asbestos. Current therapies (including chemotherapy and debulking surgery) only extend life for a matter of months. New approaches to treatment include the use of immunotherapies, but clinical trials thus far have shown only limited patient responses. The discovery of regulatory T cells and suppressive molecules expressed in the tumour environment may explain these poor responses, and has opened up new avenues for the development of targeted immunotherapies.

Tumours have evolved multiple mechanisms to evade immune destruction. One of these is the expression of T cell inhibitory ligands such as PD-L1 (B7-H1). Clinical trials are already underway to block PD-L1 expression in patients with cancer. However, our studies indicate that CD4 T cell responses are enhanced after PD-L1 blockade but seem to have an overall pro-tumour role by suppressing CD8 T cell activation. Thus, PD-L1 has the potential to
control both anti-tumour and pro-tumour (immunosuppressive) T cell responses. The main focus of this project will be to identify and characterise this potentially novel CD4 suppressor cell population. Upon determining the specific phenotype and function of PD-L1 induced suppressor CD4 T cells, we will be able to specifically target these cells and improve anti-PD-L1 immunotherapy. This combined strategy has the potential to boost clinical responses to other CD8 T cell dependent immunotherapies currently under development and may be beneficial for treatment of a wide range of cancer types.

**Optimisation of adjuvant therapies when combined with tumour debulking surgery to eradicate residual or metastatic cancer**

Surgery is the principal mode of therapy for many solid human tumours including the lung malignancies malignant mesothelioma (MM) and lung cancer (LC). However, surgery alone is often not curative, with patients subsequently dying because of local recurrence of unresectable tumour, or from distant metastases that were undetectable at the time of operation. Adjuvant chemotherapy is sometimes used to eradicate sub-clinical distant metastases or residual local disease, and radiotherapy also sometimes has a role. These adjuvant modalities can deliver some survival benefits but because recurrences still occur post-adjuvant therapy, better treatments are needed.

Post-surgery immunotherapy, aimed at destroying residual tumour, has always been an attractive proposition but has had few successes clinically. There is renewed interest now in the use of this approach with the development of new immunotherapy modalities. However, the science underlying immunotherapy in the respected patient and the factors that determine success or failure remain obscure. It is therefore difficult for surgeons to decide how or when to apply immunotherapy in the setting of clinical trials. To shed light on these issues, this project will focus on lung malignancies and use relevant animal models to determine the optimal timing, dosing and route of chemotherapy/immunotherapy administration to eradicate residual or metastatic tumour after debulking surgery.

**Development of Prime-Boost anti-cancer vaccines.**

This project aims to develop an anti-tumour prime-boost vaccination strategy. This vaccine is designed in two stages, such that the priming dose breaks immunological tolerance against tumour-associated antigens and the boosting dose expands the primed response. Our understanding in the fields of CD8 T cell regulation and immunological tolerance has progressed enormously during the last decade, and has now reached the point that these insights can be translated into rational vaccine design and product development. This project proposes to insert tumour antigens into DNA plasmid and modified vaccinia virus Ankara (MVA) vectors, using the DNA-TA vector to prime the response and rMVA-TA vaccine to expand the tumour specific CD8 T cell population. To realise the goal of producing a tolerance-breaking prime-boost vaccination strategy, the following Specific Aims will be pursued:

1. To construct DNA and MVA recombinants expressing known tumour antigens.
2. To assess TA-specific CD8 T cell responses after immunization.
3. To assess prophylactic and therapeutic anti-tumour efficacy of prime-boost vaccination.
4. To evaluate anti-tumour efficacy under immuno-compromised conditions.

**Combining Prime-Boost vaccination with debulking surgery for the treatment of Malignant Mesothelioma; investigating efficacy and the impact of vaccine timing (with Dr Amanda Cleaver)**

Many malignant mesothelioma (MM) patients undergo tumour debulking surgery. However, surgical debulking alone is seldom curative and adjuvant therapies such as chemotherapy or radiotherapy do not significantly improve patient survival. While vaccination against known tumour antigens presents an appealing therapeutic option, most anti-cancer vaccines have had limited success. The inability of these vaccines to elicit strong immune responses to tumour antigens is thought to be related to their inability to break tolerance and overcome immunodominance in the context of a generally immunosuppressive tumour environment. Previous work in our laboratory has shown that debulking surgery can reduce the level tumour driven immunosuppression, resulting in improved treatment outcomes when used in combination with adjuvant immunotherapies. Furthermore, recent advances in vaccine design have led to novel prime-boost vaccination strategies that have the ability to overcome issues relating to tolerance and immunodominance. However, the timing of vaccine delivery is of critical importance. In this proposal, we will use our well established murine model of MM to investigate the importance of timing and the overall efficacy of our novel anti-tumour heterologous prime-boost vaccine strategy in combination with partial debulking surgery. This combined strategy has the potential to enhance anti-tumour immune responses and completely eradicate residual tumour after debulking surgery.

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SPECIFIC AIMS

Aim 1: To optimise timing of anti-tumour prime-boost vaccine administration when used in combination with partial surgical resection to boost anti-tumour immune responses.

Aim 2: To determine the mechanism of action by which anti-tumour vaccination combined with debulking surgery enhances therapeutic outcome.

Aim 2A: Determine immunological cell types critical to anti-tumour protection.

Aim 2B: Determine if combination therapy can induce protective immunological memory.

Evaluation of the efficiency of tumour antigen cross-presentation in vivo

We are currently investigating several important questions relating to the efficiency and mechanisms of tumour antigen cross-presentation and how this may affect vaccine efficacy and design. Cross-presentation refers to a process whereby exogenous proteins are taken up by antigen presenting cells (APCs) then processed and presented on the surface of that APC by MHC class I molecules to CD8 T cells. Understanding how cellular location influences the level of antigen cross-presentation is critical for developing the types of immunotherapies that have the capacity to generate highly effective CD8+ T cells required for effective cancer treatment.

We will use our newly developed cross-presentation tumour model to focus on investigating how cellular location of tumour antigen influences the efficiency of tumour antigen cross-presentation.

Specific Aim 1: Assess the level of cross-presentation of tumour antigens from different cellular locations.

To investigate TA cross-presentation, Balb/c x C57Bl/6 F1 mice will be subcutaneously inoculated with different C57Bl/6 (H-2Kb) derived tumour cell lines that express the Balb/c (H-2Kd) restricted influenza HA-CL4 epitope fused to a GFP reporter molecule in either the membrane (mCL4), cytoplasmic (cCL4), secretory (sCL4) or nuclear (nCL4) compartments. Direct presentation of Balb/c (H-2Kd) restricted epitopes by these cell lines to C57Bl/6 (H-2Kb) restricted CD8 T cells is prevented in H-2Kb (C57Bl/6) or H-2Kb/d (C57Bl/6 x Balb/c F1 mice) due to MHC incompatibility. This ensures that the CL4 epitopes can only be cross-presented via APC to Balb/c (H-2Kd) restricted CD8 T cells. “Lyons Parish” and in vivo CTL assays will then be used to measure antigen presentation and to detect the presence and functionality of antigen specific CD8+ CTL mediated anti-tumour immune responses respectively.

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Developing biomarkers for the early detection of malignant mesothelioma

Malignant mesothelioma (MM) is an asbestos-induced, aggressive tumour that almost invariably results in death within 12 months. An inability to diagnose the disease at an early stage means that treatment is not effective. An earlier diagnosis than is presently possible and prior to the patient presenting with clinical symptoms may result in more effective therapy and allow for better management of the disease and increased survival times.

We are currently searching for biomarkers that are present in blood, urine or pleural effusions in patients with MM, which enable the detection of the disease at a considerably earlier time than currently available clinical and biomarker techniques allow. An approach that we have adopted is the detection of antibodies to proteins that may be over-expressed, or that are mutated, in MM patients. Using protein microarray technology we have identified a number of promising candidate proteins for which immune responses are observed in MM patients. This project will involve developing biological assays of high sensitivity and specificity to these candidate proteins and to use these assays to develop a testing strategy to efficiently detect MM with a high sensitivity and specificity. This project will involve producing and purifying proteins using cloning vectors and affinity chromatography, the development of ELISA assays, the use of these assays to detect antibodies in patient samples, and the analyses of the resulting data for determining specificity and sensitivity of the assays for detecting MM.
Chemoprevention of Mesothelioma

Mesotheliomas typically occur many years after exposure to asbestos. This long latency offers an opportunity for chemoprevention. In the 1990s the Wittenoom workforce cohort was invited to participate in a program of vitamin A (β-carotene or retinol), assistance to quit smoking, and dietary advice. The rate of mesothelioma between groups was not statistically different overall, but the study showed the potential for intervention.

The aim of this project is to screen the Clinical Compound Library (JHCCL, Version 1) consisting of 1514 approved drugs available as 37 x 96-well plates each for activity against a number of established mesothelioma cell lines. We plan to select candidate drugs for preclinical verification in the MexTAg transgenic mesothelioma model. In these mice SV40 (Simian Virus 40) large T antigen (TAG) is expressed by the mesothelium. After exposure to asbestos, mesothelioma develops in all MexTAg mice compared to 20-30% of wild type mice. After intraperitoneal asbestos injection, the mice predictably develop mesothelioma (mostly sarcomatoid) with median survival of 24 weeks, compared with 56 weeks for asbestos injected wild-type mice. Plasma levels of drug or intermediate metabolite will be measured in tail vein blood at suitable intervals to assess adequacy of administration and dosing. Initially, each of four candidate drugs will be administered to thirty-two MexTAg mice and placebo to a control group of thirty-two MexTAg mice. Two outcome measures are of interest 1) difference in mesothelioma rates over the follow-up period between asbestos injected control MexTAg animals and asbestos injected MexTAg animals treated with a chemopreventive candidate, and 2) differences in median survival time between these two experimental arms.

Investigating Tolerance Using a SV40 Large T Antigen Transgenic Mouse Model of Mesothelioma

Cancer develops from host cells and is therefore immunologically likely to be mostly self. Self-reactivity is controlled by several mechanisms which result in immunological tolerance; essentially the ability of the immune system to discriminate appropriately and minimize autoimmunity. The degree of tolerance to an antigen is affected by both its anatomical location and the amount of antigen expressed. So to develop a cancer vaccine a suitable target must be found that is predominantly expressed on cancerous cells with limited or weak expression by normal tissues. Such a vaccine could prevent disease from developing in susceptible people and may have therapeutic value. A unique opportunity is available to investigate immunological tolerance in SV40 large T antigen transgenic mice that are susceptible to mesothelioma; the MexTAg model.

The project will investigate immunological tolerance to SV40 TAG in MexTAg mouse strains. By investigating the ability of cancer cell lines expressing different levels of TAG, to grow in the four different MexTAg mouse lines, tolerance can be assessed. A high copy tumour cell line (299h) does not grow in a wild type mouse because the TAG makes the cells an immunological target. A single TAG copy mice (266s) grows, but appears much later and grows slower than non TAG tumours. With four lines of mice that express between 1 and 100 copies of TAG we can map vaccine efficacy to the degree of tolerance.

RHEUMATOLOGY

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1. Structure pain associations in joint diseases
2. Clinical management paradigms in rheumatic diseases
3. Outcome assessment
4. Musculoskeletal Ultrasonography

TROPICAL AND INFECTIOUS DISEASES

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Epidemiological studies of diabetes in the local community. Drug treatment of malaria.

Assistant Professor Jane E Allan (FH) 9431 2641 email: jane.allan@uwa.edu.au

Pathogenesis of intracellular infections and the development of host responses. Development of vaccines and immunotherapeutic strategies to control or prevent disease. Cytomegalovirus and hepatitis C virus are major infections that are the focus of pre-clinical models and tissue culture based studies.

PHARMACOLOGY AND ANAESTHESIOLOGY

Head of Discipline:
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RESPIRATORY PHARMACOLOGY

Professor Peter J Henry (QEII) 9346 3123 email: peter.henry@uwa.edu.au
Associate Professor Lynette B Fernandes (QEII) 9346 4517 email: lynette.fernandes@uwa.edu.au

The group is currently interested in novel drug targets for bronchial asthma, with particular reference to protease-activated receptors and rho kinase. Techniques include cell culture, immunohistochemistry and confocal microscopy, radioligand binding and quantitative autoradiography, together with airway function studies in vitro and in vivo. The effect of important asthma triggers, including respiratory tract viruses and allergens on receptor function and density in the airways and the identification of key cellular pathways in airway neurons is also under investigation.

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Winthrop Professor TME Davis (FH) 9431 3229 email: tim.davis@uwa.edu.au

Pharmacokinetics and pharmacodynamics of antimalarial drugs

Our group is able to offer a project associated with research into the clinical pharmacology of antimalarial drugs. During 2005 we will have ongoing NH&MRC funded clinical studies in Madang, PNG and anticipate that there will be an opportunity for associated laboratory-based studies. The drugs of interest are mainly artesunate and piperazine. The technology used is based around high performance liquid chromatography ± mass spectrometry to quantify drug concentrations in plasma, and to relate the resulting pharmacokinetic profiles to the antiparasitic (pharmacodynamic) actions in humans. We are also intending to carry out some in vitro and in vivo studies on the metabolite profile of piperazine in humans.

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The laboratory's research centres on the areas of:

- Signalling for activation and survival in macrophage cells, which is relevant to those cells' functions in inflammatory diseases and cancer;
- Adaptation of signalling to redox, hypoxic, hyperoxic and nutritional conditions in inflammatory cell environment;
- Mitochondrial uncoupling as a response to oxygen radical stress

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Psychoneuropharmacology

This group is primarily, but not exclusively, interested in schizophrenia and drug addiction. Research is conducted on biological and pharmacological aspects of both schizophrenia and drug addiction in both preclinical and clinical measures. That is, an animal preclinical lab is operated from QEII and a human clinical lab is based at Graylands Hospital. Electromyographic measures of specific biological reflexes that are influenced by schizophrenia and/or chronic cannabis use are the areas of most interest. However, new research lines are opening up in the novel psychiatric treatment with Transmagnetic stimulation of the cerebral cortex in patients. In addition, there is substantial interest in cannabinoid-glucocorticoid interactions in the aetiology of schizophrenia.

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Anaesthesiology and Pain Medicine

The interests of this clinical research group lie in the areas of anaesthesiology, perioperative care and acute and chronic pain medicine with some focus on pharmacological aspects.

In anaesthesiology, areas currently investigated include among others various aspects of monitoring and the effect of medications and anaesthetic techniques on parameters of perioperative outcome including morbidity and mortality. Other areas of interest include the medical management of patients before and after surgery and at King Edward Memorial hospital clinical and pharmacological research related to obstetric anaesthesia; pain management during labour and after caesarean section; postoperative pain control (especially new analgesics, novel drug delivery systems and neuraxial drugs); and in collaboration with Emeritus Professor Ilett, drug pharmacology during lactation.

In pain medicine, studies are focussing on the treatment of neuropathic pain, the development of new routes of analgesic administration and pharmacokinetic studies. Furthermore, the psychological aspects of chronic pain, its development out of acute pain states and approaches of clinical psychology to its treatment are studied. Other potential topics for research include the interaction between neuro-endocrine and acute stress responses to trauma, post-traumatic stress disorder and chronic pain development.

The research takes place in Royal Perth Hospital and King Edward Memorial Hospital and involves primarily the conduct of clinical trials. Students interested in clinical research in these areas of medicine can be involved into the ongoing research program and focus on an area or trials of their specific interest.
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The main focus in paediatric anaesthesia is the research into the prediction and prevention of respiratory complication in paediatric anaesthesia and lung function changes in the perioperative period. Respiratory complications are the most common cause for critical incidents in children undergoing anaesthesia. Other areas of interest include the evaluation of different airway devices as well as the impact of anaesthesia on the developing brain.

Associate Professor Fiona Pixley (QEII)  9346 4047
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Macrophages and their role in promoting tumour invasion and inflammation.
Macrophages have been shown to promote disease progression in tumour dissemination and in chronic inflammatory disorders. Studies in the laboratory are aimed at delineating the molecular mechanisms regulating macrophage motility in order to develop therapies to inhibit macrophage infiltration of disease sites. Techniques used in the laboratory include cell culture, microscopy and protein biochemistry.

Professor Phil Burcham (QEII)  9346 2986
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Molecular Toxicology Group
This laboratory is interested in the molecular and chemical events underlying the toxicity of reactive aldehydes formed during the process of lipid peroxidation. The process accompanies the production of reactive oxygen species within cells and tissues on account of the susceptibility of polyunsaturated lipids to attack by free radicals. Our main interest at present is the toxicology of acrolein, a highly reactive species formed during membrane peroxidation and also during the combustion of organic matter. Due to its presence in smoke, our Group is presently exploring the contribution of acrolein to smoke-induced lung cell injury. Techniques used in the laboratory include cell culture, protein electrophoresis and immunological analysis of protein modifications, proteomic identification of protein targets and microarray analysis of transcriptional responses to acrolein.

Professor Vimal Kapoor (QEII)  9346 2506
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The main focus of the laboratory is the study of the "Kynurenine Pathway" of tryptophan metabolism. This pathway is critical for the de novo synthesis of NAD (nicotinamide adenine dinucleotide), which is critical for not just energy metabolism, but also many intracellular signalling, protein modification and gene expression pathways. Some of the areas of interest in my laboratory include:

Schizophrenia. Recent work in our laboratory has shown that Kynurenic Acid (a kynurenine pathway intermediate that acts as a glutamate receptor antagonist) synthesis is higher in post-mortem brain tissue from Schizophrenic patients, which may explain why schizophrenic patients appear to have a reduced sensitivity to glutamate as a neurotransmitter. This project will examine the expression of splice variants of enzymes involved in the response of glutamate in human brain tissue to try and identify these mechanisms, and try and develop new drug targets for the treatment of schizophrenia.

Inflammation, senescence, ageing and age-related diseases. The recent identification of the critical involvement of SirT1 (Silent Information Regulator T1), a protein, NAD dependent, (Lys) deacetylase (leading to protein in/activation and gene silencing) in Alzheimer’s disease, cancer, inflammation and in calorie-restriction induced extension of lifespan has generated a lot of excitement. This project will examine factors which may modulated the de novo synthesis of NAD in specific cells and how this can be manipulated to enhance (or reduce) functional survival of cells when challenges with free radicals and other toxins, delaying senescence (cell death) and the ageing process as well as ageing related diseases.
My research interests are in the area of natural product and medicinal chemistry and focus on the isolation and identification of bioactive compounds from a variety of natural sources, in particular from traditional Australian and Asian medicinal plants. I am also interested in new approaches to the synthesis of isoquinoline alkaloids by exploring benzotriazole-mediated cyclisation reactions.

Students are encouraged to discuss any research topic in the area of natural product chemistry they might have an interest in. Examples of Honours projects offered in 2012 (others can also be negotiated):

1. Chemical and antimicrobial analysis of some *Eucalyptus* kinos, which have been used extensively by Australia's indigenous people as well as early European settlers for their antimicrobial and general astringent properties. The project will focus on the isolation and chemical identification of tannin- and non-tannin based bioactive constituents using column chromatography, HPLC and preparative HPLC. Their contribution to the overall antimicrobial effect will be examined, in particular the role played by hydrolysable and condensed tannins.

2. Another possible Honours project has a stronger organic chemistry focus, exploring different synthetic strategies in the (stereoselective) preparation of 1-substituted tetrahydroisoquinolines using benzotriazole methodology.

**Application of nanotechnology to optimise drug delivery**

**Winthrop Professor Lee Yong Lim (UWA)** 6488 4413 email: lee.lim@uwa.edu.au  
Room 2.06, Pharmacy Building,

**Laboratory for Drug Delivery**

Our research focuses on understanding the mechanisms and constraints of drug delivery across biological barriers, and applying nanotechnology to overcome these barriers. Delivery platforms based on polymer nanoparticles, liposomes and plant viral protein cages have been developed for drugs and genes, and targeting ligands, such as plant lectins and folic acid, are used to enhance the accumulation of drugs in tumours.

**Projects:**

1. Highly potent anticancer drugs are often associated with high morbidity and mortality due to their inability to differentiate cancer cells from normal cells. The aim of this project is to develop a delivery platform that will direct anticancer drugs specifically to cancer cells, thereby minimizing the indiscriminate drug deposition that results in adverse drug reactions. The nanoparticle formulations will be characterized using a range of analytical tools available at UWA, and the optimized formulations evaluated for efficacy using in vitro cancer cell models.

2. Curcumin, the active component of turmeric, a common household spice, has been shown to possess a range of useful pharmacological activities. Its progression into clinical use is, however, hampered by a low peroral bioavailability caused by a combination of factors, including an extremely low aqueous solubility, poor intestinal permeability and rapid degradation. The aim of this project is to determine whether curcumin formulated as nanoparticle formulations is able to overcome its low aqueous solubility, rapid metabolism and uptake into absorptive cells. The project will involve the synthesis and characterization of curcumin nanoparticle formulations and their evaluation in in vitro cell culture models.

3. Tea tree oil (TTO) is known for its antibacterial and antifungal activities. Recent studies have shown TTO to be a potential anticancer agent against skin lesions, but its efficacy is hindered by poor intrinsic transdermal permeability. The purpose of this project is to formulate TTO nanoparticle formulations using appropriate FDA-approved excipients that may facilitate the permeability of TTO through the skin.
Acute viral lower respiratory tract infections (AVRI) in children are a major health issue and a leading cause of death in children worldwide. This project investigates mechanisms involved in AVRI in young children using assessments of viral infection, bacteriology, immunology, genetics and physiology in children presenting with acute asthma. We have recruited 200 children who have presented to the Princess Margaret Hospital Emergency Department with an AVRI and plan to recruit at least 200 more for ongoing studies. The children are followed up both when they present acutely and on recovery. We will also study community control groups of children to determine how commonly HRV and HRVC are found and the role of HRVC in mild to moderately severe acute asthma. These studies are most important to establish the basic information on pathogenicity of HRV and HRVC that is urgently needed. We are particularly interested in discovering why certain viruses cause particular clinical problems. For example, we have recently discovered that human rhinovirus (HRV) is much more common than expected as a cause of both AVRI and acute asthma and over 85% of children with acute wheeze or acute asthma are infected with this virus. Even more exciting, we have also recently discovered that a newly-identified HRV group, HRV group C, is responsible for the majority of these cases. Hence, HRVC is the most common cause of the most common diagnosis in children admitted to hospital in the developed world, but almost all the basic information central to our understanding of this remains to be discovered. Such opportunities to work at the basic level in an important new area with such broad implications to common diseases are very rare in research these days. Our work has raised many crucial questions about AVRI, acute asthma and HRVC. Aspects of this work that have strong potential as BMedSc projects include:

(i) The effect of AVRI on the respiratory microbiome (RMB) - "The pace of technical advancement in microbial genomics has been breathtaking" (Relman et al. New England Journal of Medicine 2011;365:347-57). Hence, the opportunity has arisen to add an exciting new component to the MAVRIC study - the respiratory microbiome. In brief, a healthy microbiome (includes the microbiota - the totality of microbes) in an organ is now seen as essential for its health. Thus, interest in the RMB is increasing exponentially. Surprisingly, there has been almost no research in this area of medicine and the simple question "How does an acute respiratory viral infection affect the airway bacteria?” has not been addressed. Professors Peter Le Souëf, UWA and Bill Cookson, Imperial College London, have both recognized the importance of this question and the strong likelihood that AVRI in infants have a major effect on the RMB. Since the MAVRIC protocol is also ideal for assessing the RMB, Prof Cookson has offered to assess the RMB bacteria fully in all subjects and controls in the MAVRIC study. His group’s methodology (high throughput pyrosequencing of the bacterial 16S rRNA gene) detects and quantifies all bacteria independently of culture, can detect previously unknown microorganisms, and is highly specialized. Hence, we now include a new addition to the MAVRIC study: Aim: To evaluate the influence of AVRI on the RMB. Hypothesis: AVRI, especially HRVC, will induce a disordered RMB and eventually lead to chronic respiratory disorders including asthma. Given the intense current focus on the RMB, this addition should attract strong international interest and provide major insight into the role of both AVRI and the RMB in the acquisition of asthma.

(ii) Studies of AVRI (including HRV and HRVC) in Africa – We have recently established major new collaborations with a Spanish group working on AVRI in Manhica, Mozambique and Rabat, Morocco and a South African group studying AVRI in Pretoria. We plan to determine the role of HRV and HRVC in AVRI in young children in the developing world. This research is important to assist in determining which viruses are important in causing the high morbidity and mortality in developing countries and the mechanisms by which they do this. We will also be studying the effect of AVRI on the respiratory microbiome in these sites. The project is expected to require travel to Africa and collection of specimens there as well as laboratory work back in Perth to analyse the specimens.
Studies of genetic and immunological factors that contribute to susceptibility to HRV and HRVC infection and acute asthma.

There are several questions of major importance that relate to this. Understanding why some children have the genetic susceptibility to AVRI or develop acute asthma in response to respiratory viral infections is crucial to our understanding of viral respiratory infections and asthma at all ages. Just as important are the immunological responses to respiratory virus infection and why these allow acute asthma to develop in only some children.

We have the resources to investigate each of these important aspects of AVRI in detail and each would make an excellent BMedSc project.

**Evolution of the human immune system and genetic diversity of human populations**

**Professor Peter LeSouef**  
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Global study with 12 collaborative groups (ARC grant). We have hypothesized that human populations living in the tropics would have evolved a vigorous Th2 immune response to protect from parasite infections common to this environment, as compared with populations living in temperate or arctic environments. We have a collected numerous indigenous populations from tropical, temperate and arctic regions around the world and have investigated several genotypes in Th2 genes with the data obtained so far supporting our general hypothesis. There are numerous sub-projects available within this project and these could involve travel to one or more of our many collaborative centres in Africa, North America (including Greenland), South America, Asia (including Siberia), Europe and Australia. Our further analyses will assess relationships between ancestral location, Th1, Th2 and innate immune response genotypes and markers of ancestry and genetic differentiation using Y-chromosome and mitochondrial DNA markers.

**24 yr assessment of Perth Infant Asthma Follow-up (PIAF) cohort**

**Professor Peter LeSouef**  
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This is the latest follow-up of a population of 253 subjects who were recruited at birth and have been followed up on previous occasions at 1 month, 6, 11 and 18 years of age. This internationally-recognized NHMRC funded project has produced over 63 publications in high ranking international medical journals and now aims to examine clinical, physiological, immunological, genetic and environmental factors associated with respiratory disease in children and how this affects respiratory status in young adults.

**Immunogenetics of malaria infection in early life**

**Professor Peter LeSouef**  
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Collaborative study with Barcelona research group of population in Mozambique (EU/NHMRC project). We have been working on the immunogenetics of malaria infection in south-east Africa with our Spanish colleagues for the last six years. This ongoing project addresses the immunogenetic factors associated with early malaria infection in young children in Mozambique and how these interact with developmental aspects of the immune system development.

**Adolescent Medicine**

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Short and long term consequences of prolonged school non-attendance among adolescents  
Transition from paediatric to adult care for patients with chronic illness  
Clinical service delivery for adolescent and young adults  
Improving the provision of mental health services for adolescents and young adults

**Developmental origins of childhood asthma**

**Professor Lou Landau**  
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**Medical aspects of adolescent eating disorders**

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Professor Susan Prescott  Phone: 9340 8171  Email: susan.prescott@uwa.edu.au

Primary prevention of allergy in children
Early immune development in fetal and early postnatal life
The effects of diet (vitamin D, folate, probiotics, fatty acids, antioxidants and early dietary allergen exposure) on immune function
Paediatric allergy, asthma and immunology
For further information: Prof Prescott: susan.prescott@uwa.edu.au

Professor Stephen Stick  Phone: 9340 8830  Email: stephen.stick@health.wa.gov.au
Paediatric Respiratory and Sleep Physiology
Epithelial Cell Biology
Paediatric Respiratory Diseases
Cystic Fibrosis

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Paediatric Respiratory and Sleep Physiology
Epithelial Cell Biology
Paediatric Respiratory Diseases
Cystic Fibrosis

Dr Anthony Kikic  Phone: 9340 8140  Email: anthonyk@ichr.uwa.edu.au
Epithelial Cell Biology

Epithelial Cell Biology
Dr Anthony Kikic  Phone: 9340 8140  Email: anthonyk@ichr.uwa.edu.au

1. Assessment of the dynamics of normal and asthmatic airway epithelial repair.
Project outline: Asthma is the most common chronic respiratory disorder in children. Recent evidence indicates that the airway epithelium plays an important role in the pathogenesis of asthma. Under normal circumstances damage and desquamation of epithelial cells is followed by repair of the denuded luminal surface by the adjacent epithelium. The airway epithelial cells surrounding the injury are triggered to synthesize and deposit extracellular matrix (ECM) on the exposed basement membrane to promote adhesion and migration of adjacent epithelial cells into the injury site. These proteins profoundly influence the survival, proliferation and differentiation of the airway epithelial cells suggesting it is an important target in epithelial wound repair. This project aims to deduce the initiating and subsequent cascade of events that occurs in normal and asthmatic airway epithelial repair focusing on the proliferative and migratory components. Overall, this project will directly assess the wound healing capacity of pediatric asthmatic airway epithelium and our findings aim to confirm that compromised repair processes are a feature of asthmatic epithelium and that these changes occur early in disease progression.

2. Assessment of aerosolized fibronectin to treat abnormal epithelial repair in asthma
Project outline: Fibronectin (FN) from lining cells of the airways, i.e., the epithelium, is essential for airway repair. Repair is dysregulated in asthmatic epithelium due to low fibronectin and its addition to primary cultures of asthmatic cells that have been damaged restores their reparative capacity. This project will test (1) the restorative capacity of synthetic fibronectin in wounded, cultured cells, and (2) the safety of inhaled synthetic fibronectin in a mouse model of asthma, and (3) whether synthetic fibronectin can be effectively delivered by aerosol to humans. The project will employ a well-characterized in vitro human primary airway model, a mouse model of allergic sensitization and established cellular and molecular techniques to examine epithelial repair.

3. Identification and investigation of community strains of Rhinovirus on airway epithelial cells
Project outline: Epithelial cells of the lung airways function as a barrier that prevents injurious particles, toxins and infectious agents from entering the body. Respiratory viral infections play a role as the most common cause of childhood wheezing. Particular attention has been focused on human rhinovirus (RV) as its infection during infancy is a significant risk factor for development of wheezing and asthma in later life. It has also been suggested that RV plays a role in serious respiratory diseases leading to increased morbidity and mortality. This project will aim to (i) identify and culture community strains of RV with the purpose of establishing a RV repository, (ii) investigate the propensity of epithelial cells to cause inflammation in response to respiratory viruses and compare responses in cells from children with respiratory diseases from healthy children and (iii) compare newly identified community strains of RV with currently utilized laboratory strains of RV to determine whether inflammatory responses are non-specific or dependent upon the type of virus. The generation of a repository of community isolates of RV will facilitate many investigations that will be beneficial for patients, hospital and the community at large.
4. Investigation on the restoration of apoptosis in paediatric cystic fibrosis airway epithelium post viral infection

**Project outline:** Cystic fibrosis (CF) is a genetically inherited disease affecting mostly the Caucasian population. There are over 300 individual with CF in WA and 12-15 newborns are diagnosed each year following newborn screening. As part of the Australian Respiratory Early Surveillance Team for CF, we have demonstrated that early lung damage present early in life and that the lungs of children with CF are prone to inflammation from birth. The Airways in the lungs are lined with specific type of cells, the epithelial cells, whose roles are to provide barrier to the external environment and as such are continually exposed to pollutants, allergens and pathogens. In CF, this epithelial function is defective, and one of the earliest trigger for inflammation is viral infection, which are common in young children. Recently, we have published data demonstrating the abnormal responses of CF cells to viral infection compared to healthy cells. This study aims to investigate the potential of adding protein or using antibiotic treatment, azithromycin to ameliorate these responses. Outcomes from this study would help us to better understand the mechanism(s) involve in innate immune response to viral infection and to provide an avenue for better patient management.

**Paediatric Infectious Diseases and Microbiology**

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The epidemiology, diagnosis, treatment and prevention of upper and lower respiratory infections  
Respiratory infections including emerging bacterial, viral and fungal pathogens  
The epidemiology, diagnosis and management of severe sepsis  
Invasive infections in high risk neonates and immunocompromised children  
Antimicrobial stewardship in paediatric hospitals

**Association between cytochrome genotypes, Glutathione-S-transferase (GST) genotypes and biomarker concentrations in urine samples from the Perth Infant Asthma Cohort 18 year follow-up.**  
A/Prof. Sunalene Devadason and Dr. Catherine Hayden.  
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Email: catherine.hayden@uwa.edu.au

Inhaled pollutants are detoxified by enzymes in the lung. This project aims to identify associations between the genotypes of cytochromes (Phase I enzymes), GSTs (Phase II enzymes), markers of pollutant exposure in urine and lung health outcomes. Genotyping of cytochrome genes will be done by PCR and restriction fragment length polymorphism analysis. Quantification of biomarkers of pollutant exposure in urine will be done using established HPLC methods. Enzyme activities will be determined with assays developed in our lab. Results will enhance the understanding of gene/environment interactions in respiratory disease.

**Does a potentially deleterious Single Nucleotide Polymorphism (SNP) in the gene coding for GSTP1, a detoxification enzyme, cause compensatory up-regulation of protein expression?**  
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GSTP1 is a Phase II detoxification enzyme expressed in the lung. Gene polymorphism may alter specific activities of the enzyme. This project aims to assay the protein levels and specific activity of GSTP1 enzyme in blood samples from subjects of known and different GSTP1 genotypes. High levels of gene expression will be shown by higher concentrations of the protein to compensate for lower activity. Enzyme activity will be measured by an activity assay using a substrate specific for GSTP1. Protein levels will be measured by GSTP1-specific ELISA developed as part of the project. Results will increase knowledge about compensatory mechanisms of gene expression after environmental exposure to pollutants.
Determination of levels of salbutamol in urine following inhalation of aerosol-borne drug, and relevance as a proxy for lung deposition.
A/Prof. Sunalene Devadason
Phone: 9340 8985 Email: sunalene.devadason@uwa.edu.au

Measuring lung deposition of inhaled medication in vivo requires subjects to inhale a low dose of radioactive aerosol, and the ultimate destination of the drug can be assessed by gamma scintigraphy. To assist in the development of an alternative method, this project aims to confirm the hypothesis that the levels of salbutamol in urine directly after inhalation of an aerosol correlate with total levels of drug inhaled. Breathing traces will be recorded during drug administration and a urine sample collected after a short time. The recorded trace will be replayed using a flow-volume simulator, in an ex-vivo setup, to measure total drug output from the test device under realistic simulated breathing conditions, as an indication of the total drug inhaled by subject. Urine will be assayed for salbutamol levels by an HPLC method optimised during the project. Confirmation that levels of salbutamol in urine are a good proxy for efficiency of drug delivery by aerosol will present the possibility of removing the need for radioactive deposition studies in the future.

Analysis of the levels of biomarkers of cigarette exposure in urine from a cohort from remote Greenland and associations with GST genotype and lung health.
A/Prof. Sunalene Devadason and Dr. Catherine Hayden
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In Greenland, a large study of subjects with different lifestyles has been ongoing for several years. The overall aim of the study is to examine the effects of lifestyle, such as diet or smoking, on lung health. To add to the study, this project will examine the role of polymorphisms in the glutathione-S-transferase (GST) detoxification gene on these health outcomes, and on levels of biomarkers of exposure in the rural population included in this large cohort, and compare the results with those already obtained from an urban population. Genotyping of GST genes will be done with PCR and restriction fragment length polymorphism analysis, and HPLC used to quantify biomarkers of pollutant exposure in urine.

A/Prof. Sunalene Devadason and Dr. Catherine Hayden
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In asthmatic children, antioxidants such as the glutathione redox system play a crucial role in defence against both respiratory infections and pollutants, so any factors that alter the antioxidant balance may contribute to more severe asthma in susceptible children. Using a previously optimised assay to measure total, oxidised and reduced glutathione levels in samples collected from acute asthmatic children, this project aims to assess the effect on glutathione levels, of variations in enzyme activity resulting from genetic polymorphisms in glutathione pathway genes, to clarify any associations with the severity of acute asthma episodes and determine how cigarette smoke exposure affects these relationships. Genotyping of glutathione pathway genes will be done by PCR and restriction enzyme digestion of DNA samples from the cohort, and cigarette smoke exposure will be assessed by measuring cotinine in urine. The results will shed light on the role of genetic variations in the glutathione pathway on glutathione levels as well as acute asthma severity. Importantly, it will help to determine how exposure to respiratory viruses and cigarette smoke affect acute asthma severity.

Environmental exposures, foetal growth and child health
Dr Peter Franklin Phone: 9340 8176 Email: peter.franklin@uwa.edu.au

Developmental origins of health and disease is an area of growing interest. Environmental exposures during early, including foetal, life may affect disease outcomes in both childhood and adulthood. A large pregnancy/birth cohort study is currently being conducted in the Peel region. About 500 pregnant women have been recruited and recruitment should continue until the end of 2012. Data is being collected on foetal growth, birth outcomes and early childhood development. Measures of indoor air pollution, metals, allergens, endotoxin and persistent toxic substances are being collected during pregnancy. There are opportunities to be involved in studies of the impacts of these environmental exposures on foetal and childhood outcomes.
Gene by environment interaction on asthma and allergy in children
Dr Guicheng Zhang  
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Asthma and atopy are "complex" heritable conditions. However, these conditions may never develop without exposure to environmental stimuli that interact with their corresponding pathway genes. This project will investigate the important interactions between variations of asthma susceptibility genes and prenatal and early exposure to environmental risk factors such as endotoxin, HDM allergens and ETS with respect to the pathogenesis of allergic diseases. The goal of the study is therefore to understand the interactions of these asthma genes with pre-natal and early life exposure to environmental stimuli on the development of allergic diseases, and in turn identify preventive measures.

Paediatric Endocrinology and Diabetes
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Research interests include investigation of paediatric endocrine conditions including:
Disorders of sexual differentiation,  
Growth and pubertal disorders  
Thyroid disease  
Endocrine late effects of childhood cancer and treatment

Early life events and markers of adolescent neurocognitive functioning and mental health
Clinical Research Professor Jonathan Foster  
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The research (conducted in collaboration with Drs Anke van Eekelen, Dr Eugen Mattes, Dr Jianghong Li, Dr Andrew Whitehouse and others based at the Telethon Institute for Child Health Research and other UWA researchers - including Prof Karen Simmer and Prof Susan Prescott) aims to study pre- and post-natal childhood factors and examine the association of these factors with neurocognitive capacity, mental health and key brain biomarkers during childhood, adolescence and adulthood. Relevant variables include trajectories of stressful life events, family context and mental health status during childhood, in addition to the intrauterine environment, immune functioning and postnatal growth patterns. We also investigate neurocognitive ability and evaluate brain activity while participants are performing specific cognitive tasks and/or at rest, using non-invasive techniques including functional magnetic resonance imaging (fMRI). Students working on this research (which has been funded by the NHMRC) would interact with internationally outstanding clinical scientists in Australia, USA and Europe and likely produce several high profile publications from their research in leading peer-reviewed medical journals. The outcomes of this research will help us to identify at risk children who would potentially benefit from psychosocial and public health interventions.

Contribution of glutathione (GSH) pathway gene variants to the variability in lung GSH levels and disease severity in children with cystic fibrosis (CF).
Dr Ingrid Laing  
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Dr Anthony Kicic  
Phone: 9340-8140  Email: anthonyk@ichr.uwa.edu.au

Cystic fibrosis (CF) is a genetic disorder that leads to premature death in early adulthood, predominantly as a result of chronic bacterial infection and progressive lung damage. Yet, how the gene defect is involved in initiating lung disease in early life is still unclear. CF is caused by the inheritance of two mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene that results in the failure of the encoded ion channel to be expressed or function on the surface of airway epithelial cells. CFTR is an anion transport glycoprotein responsible for cellular chloride and sodium homeostasis and the main route of transport for glutathione out of epithelial cells and into airways. Glutathione in the reduced form, GSH, is the most significant component of the lung’s anti-oxidate defence mechanism, acts as a mucolytic and a regulator of inflammation, immune response and cell viability. This project aims to determine the role of GSH pathway gene polymorphisms on GSH levels in children with CF and investigate their effect on lung inflammation, infection and damage in early life.

Children with CF attending clinics at Princess Margaret Hospital, Perth and The Royal Children’s Hospital, Melbourne are part of the AREST CF (www.arestcf.org) surveillance program where lung fluids (bronchoalveolar lavage (BAL) are collected for assessments of pulmonary inflammation and infection at 3 mths of age and then annually until age 6 yrs, together with measures of lung function and structure. GSH and glutathione by-products in: (A) BAL and (B) extra- and intra-cellular samples from primary airway epithelial cell cultures from children with and without CF, will be measured by our collaborators in New Zealand. This project would most likely include: DNA extraction, measurements or airway inflammation in BAL (% neutrophils, neutrophil elastase activity, IL-1β, IL-12, IL-6, IL-8, IL-10 and TNF levels), collection of epithelial cells, assessment of GSH pathway gene polymorphisms and analysis of their impact on GSH levels and disease outcomes.
Viral burden in infants with Cystic Fibrosis (CF)
Dr Ingrid Laing  Email: ingrid@ichr.uwa.edu.au
Dr Anthony Kicic  Phone: 9340-8140  Email anthonyk@ichr.uwa.edu.au
Prof Steve Stick, Dept of Respiratory Medicine, Princess Margaret Hospital

Cystic fibrosis is a genetic disorder that leads to premature death in early adulthood, predominantly caused by chronic bacterial infection and lung damage. Yet, how the gene defect leads to lung disease is still unclear.

All children suffer acute respiratory infections in early life. Respiratory viruses initially infect the upper airway and may progress to infection of the lower airway. Recent data suggests that the spread of common respiratory viruses to the lung is responsible for the majority of acute exacerbations of asthma and other respiratory disease including CF and COPD.

We know lung disease begins early in infants with CF, as bacterial infections and excessive pulmonary inflammation are often detected in lungs fluid samples collected when the infants are well, during annual bronchoalveolar lavage (BAL). However, the role of viral upper respiratory infections and viral spread to the lower airway in initiating or perpetuating pulmonary inflammation in young children with CF is unknown.

The project involves viral surveillance of infants and young children with CF over 1-2 years in Perth, Melbourne and Brisbane. Parents will collect a nasal swab once a fortnight and also when their infant is sick, and record clinical symptoms (such as the presence of a runny nose, fever or cough) using a daily diary card. In addition, the infants in Perth & Melbourne are part of the AREST CF (www.arestcf.org) surveillance program that involves BAL for assessment of pulmonary inflammation and infection at 3, 12 and 24 months of age.

The viral surveillance program mirrors a similar program to be conducted in Brisbane in a cohort of healthy infants. This will allow a direct comparison between healthy children and those with CF. The swabs will be processed in Brisbane by our collaborators for the presence of common respiratory viruses including: human rhinoviruses, respiratory syncytial virus, influenzas, parainfluenzaes, adenovirus and human metapneumovirus. This project will determine whether viral respiratory infections play a role in initiating respiratory symptoms and pulmonary inflammation in infants with CF.

Gene/environment interactions in the glutathione antioxidant defence system in acute asthmatic children
Dr Catherine Hayden  Phone: 9340 8740  Email: catherine.hayden@uwa.edu.au
A/Prof. Sunalene Devadason Phone: 9340 8985 Email: sunalene.devadason@uwa.edu.au

Major research themes: Asthma, allergy and respiratory disease

Project outline: Background: In asthmatic children, acute asthma attacks are often precipitated by infections with respiratory viruses, particularly rhinoviruses. Other important environmental factors that contribute to acute attacks include exposure to pollutants, especially cigarette smoke. Antioxidants play a crucial role in defence against both respiratory infections and pollutants, so any factors that alter the antioxidant balance may contribute to more severe asthma in susceptible children. The glutathione redox system is the most important antioxidant defence system in the lungs and genetic variations in many glutathione pathway genes have been reported and shown to affect the encoded proteins.

Aim: To assess the effect of genetic variations in glutathione pathway genes on the severity of acute asthma episodes and glutathione levels, and to determine how cigarette smoke exposure affects these relationships.

Methodology: The project will involve measuring total, as well as oxidised and reduced glutathione levels in samples collected from acute asthmatic children using a previously optimised assay. Genotyping of glutathione pathway genes will be done by PCR and restriction enzyme digestion of DNA samples and cigarette smoke exposure will be assessed by measuring cotinine, a breakdown product of nicotine. The cotinine assay has been optimised in the lab and DNA is available for the study cohort.

Analysis: The results of the lab experiments will be analysed using basic statistical methods to determine if there are relationships between genetic variations and total, oxidised and reduced glutathione levels and if these relationships are associated with the severity of acute asthma attacks in the study children. Furthermore, the effect of cigarette smoke exposure will be assessed by comparing results of analyses in children exposed compared to those unexposed. Relevance: This project will shed light on the role of genetic variations in the glutathione pathway on glutathione levels as well acute asthma severity. Importantly, it will help to determine how exposure to respiratory viruses and cigarette smoke affect acute asthma severity.
At the Telethon Institute for Child Health Research our focus is on the whole child, from pre-conception through the teenage years.

The Institute’s unique, multidisciplinary approach means we tackle these issues from a range of angles. Our world class teams include geneticists, molecular and cell biologists, bioinformaticians, biostatisticians, epidemiologists, psychologists, public health researchers, clinicians and social scientists.

We have eight overarching research streams:
- Aboriginal child health
- Asthma, allergy and respiratory disease
- Cancer and leukaemia
- Healthy Development
- Infectious disease
- Social and emotional wellbeing
- The early years
- Understanding disability

Our priority in every area is on prevention - of disease, disability and disadvantage. We are also investigating better treatments, therapies and intervention strategies.

The Telethon Institute for Child Health Research is a Centre of UWA located within the Faculty of Medicine, Dentistry and Health Sciences. The 2012 Telethon Institute for Child Health Research Honours Student project booklet outlines 37 potential student projects. The listed projects are a guide only and not a definitive list. If you are interested in any of the projects, we suggest you contact the relevant researcher indicated in the booklet. Please visit:


Students can enrol for their degree through any UWA school and undertake their research at the Institute under the supervision of an Institute researcher. Eligibility and conditions for completion of the degree are the same as for any UWA enrolled student. Enrolment through a UWA school can be accomplished by either contacting a potential supervisor at the Institute or by contacting a course supervisor at UWA. Most university schools welcome supervision at research institutes.

**Predicting the safety of air travel in ex-premature infants**

School of Paediatrics and Child Health/Telethon Institute for Child Health Research

Chief Supervisor: A/Prof Graham Hall (TICHR)

Other Supervisors: Maureen Verheggen (SPACH)

Contact: A/Prof Graham Hall  Email: grahamh@ichr.uwa.edu.au

Infants with a history of premature birth may develop respiratory distress during air travel. A hypoxia test is used to test safety to fly. Those failing the test either delay travel, or are provided with supplemental oxygen during the flight. The hypoxia test has been validated in older children and adults; conversely work from our group suggests the test is not suitable in very young infants. This project aims to validate the hypoxia test in older infants by performing hypoxia tests and monitoring in-flight oxygen saturation in infants with a history of premature birth.

The objectives of the project are to investigate the ability of the hypoxia test to predict the response of infants to air travel.
Assessment of respiratory function in children with Neuromuscular disease
School of Paediatrics and Child Health/Telethon Institute for Child Health Research
Chief Supervisor:  A/Prof Graham Hall (TICHR)
Other Supervisors: Dr Andrew Wilson (PMH, SPACH)
Contact:  A/Prof Graham Hall  Email: grahamh@ichr.uwa.edu.au

Neuromuscular disease leads to progressive respiratory decline and eventually respiratory failure. Conventional lung function testing (such as spirometry) is poorly sensitive to disease progression, while other tests such as respiratory muscle strength can be difficult for younger children to complete. There have been several newer tests that may provide additional information in individuals with NMD and assist in the clinical management of these patients.

This project will examine the feasibility of these newer tests to be used in this patient group and assess the role of these tests in identifying disease progression.

SCHOOL OF DENTISTRY

Head of School:  
Winthrop Professor Andrew Smith  9346 7636  email: andrew.smith@uwa.edu.au

The staff in the School of Dentistry has interests in laboratory, clinical and epidemiological research. There are a range of project areas that would be suitable for a one year project including:
Smoking  
Oral cancer  
Oral pathology  
Work life balance  
Quality of life in cancer

Associate Professor Linda Slack-Smith  9346 7874  email: Linda.Slack-Smith@uwa.edu.au

A/Prof Slack-Smith is an epidemiologist with particular interests in child health, oral health and groups that are disadvantaged in terms of health. She has extensive experience in qualitative and quantitative approaches to research.

SCHOOL OF PATHOLOGY AND LABORATORY MEDICINE

Head of School:  
Winthrop Professor Wendy Erber  9346 2739  email: wendy.erber@uwa.edu.au

Adjunct Associate Professor Jacky Bentel  9224 3123  email: jacky.bentel@health.wa.gov.au
Adjunct Senior Lecturer Marc Thomas  9224 1190  email: marc.thomas@health.wa.gov.au

Characterisation of Hormone Dependent Cancers
The androgen receptor (AR) is expressed in both prostate and breast cancers and its function is regulated by the expression and activity of other signalling pathways and transcriptional co-regulators. Our laboratory is investigating effects on the AR of the transcription factor and AR binding partner, ETS1, which is frequently overexpressed in human prostate and breast cancers. Both AR and ETS1 function are modified by ERK/MAPK signalling activity, which is also upregulated in prostate and breast cancers. These studies will help to determine mechanisms of sensitivity and resistance to breast and prostate cancer treatments that target these pathways. This is a molecular/cell biology laboratory and techniques used in the projects include cell culture, transfection of cells, luciferase assays, protein extraction, immunoprecipitation, western blotting and immunohistochemistry.

Current Projects: (others are available)
1. Characterisation of ETS factor function in prostate cancer cells
2. Investigation of cell signalling pathways in hormone dependent cancers
3. Interactions between ETS factor and androgen receptor signalling in prostate and breast cancer
4. Androgen action in breast cancer cells
Immunological Aspects of HIV

With over 40 million people now infected with HIV, the United Nations has now accepted that anti-retroviral therapy must be made available to all patients wherever they live. Hence many people will be very immunodeficient when they begin therapy and little is known about how their immune systems will recover and whether any improvement will be stable. This group is addressing this issue in patients who were immunodeficient when they began therapy. Factors affecting the recovery of CD4 T-cell numbers and function, as well as clinical outcomes, are assessed. This includes studies of regulatory T-cells and cytokines, antibodies, dendritic cells, monocytes and natural killer cells. Samples are available from immunodeficient HIV patients beginning ART in studies that we have established in Jakarta. These include many patients co-infected with hepatitis C virus or tuberculosis and HIV, so a focus of our work is to understand protective and pathological immune responses to these pathogens in the context of HIV disease and ART. Students will learn cell culture, flow cytometry, quantitative RT-PCR and ELISpot techniques and will be engaged with an active and very productive research team. Some projects will involve travel.

Pulmonary Disease associated with non-tuberculous mycobacteria (NTM)

NTM are ubiquitous environmental organisms to which we are exposed on a daily basis. NTM typically cause lung disease in immunocompromised individuals or those with underlying lung conditions. However, a large number of individuals with NTM lung disease do not have any identifiable risk factors. Unfortunately for these patients, NTM lung infections are notoriously difficult to treat – antibiotics are expensive and poorly tolerated, treatment success rates are poor (approximately 50%) and relapse is common. Our research aims to identify whether defects exist in patients’ immune responses against mycobacteria, and also to develop assays that can be used as prognostic tools in monitoring treatment efficacy and/or to predict treatment outcome.

(Project A) Assessment of host innate immunity in NTM lung disease.

Innate immune cells such as dendritic cells (DC) mediate the initial inflammatory response against microorganisms. NTM are capable of colonising host airways but do not normally cause disease. Poor innate immunity may facilitate invasion of lung tissue by NTM leading to disease. This project will characterise the inflammatory responses of myeloid DC and plasmacytoid DC (and possibly neutrophils) following stimulation with NTM antigens.

(Project B) The role of antibodies to cytokines in NTM lung disease

We have established that NTM patients are not deficient on the production of interferon-g. autoantibodies against cytokines represent a novel mechanism by which the immune system may be compromised facilitating infection.

Immunology: Natural Killer Cell Genetics

This group’s interest focuses on the biological and clinical relevance of genetic polymorphism of natural killer cell receptor genes as they affect bone marrow transplantation, allergy, malaria and pregnancy.

Projects:
1. Investigation of effects of genetic polymorphism in the NK cell receptor KIR2DL4 on function
2. Using genetic polymorphism in natural killer cell receptors to fight leukemia
3. Influence of genetic polymorphism of the NK cell KIR receptors on NK cell responses to malaria
4. Influence of genetic polymorphism of the NK cell receptor KIR2DL4 on predisposition to asthma

Cutaneous Malignant Melanoma

This research group performs experiments to isolate and characterise circulating melanoma cells from the peripheral blood of Cutaneous Malignant Melanoma patients. Australia has the highest incidence of melanoma in the world and melanoma is now the most common cancer in people aged 15-39. The specific outcome of this research is to identify markers of circulating melanoma cells associated with tumour progression. A blood test able to identify such markers would make a significant contribution to melanoma treatment. To achieve this aim we will use cell sorting (FACS), immunomagnetic bead technology, quantitative real time RT-PCR and microarray analysis. This project is performed in collaboration with scientists at Boston University, USA, Cambridge University, UK and a Biotech Company in Germany.
Molecular Biology and Pathogenesis of Bone Diseases

Major research interests are in molecular biology and pathogenesis of bone diseases. Common bone diseases such as osteoporosis occur because the cells that normally change the shape of bones during life, called osteoclasts, break the bone down more than they should. Understanding some of the reasons why osteoclasts may be overactive and present in excessive numbers has been the research objective. Specific aims include the identification and characterization of gene products that control osteoclast formation and activity. To achieve these goals, we have employed microarray and subtractive hybridization of cDNA to identify novel genes of interest that are regulated during osteoclast formation and activation. We have then used a wide range of molecular tools to understand the function of these genes including the yeast two hybrid system for protein interaction; site directed mutagenesis for the mapping of function domains; RNA silencing for gene knockdown; osteoclastogenesis and bone resorption assays; reporter gene assays; Western blot; and confocal microscopy for the examination of function and signalling pathways. In addition, gene knockout and transgenic mouse models are also employed. Understanding the influences that drive osteoporosis will eventually uncover opportunities for treating the osteolytic condition.

Specific areas of investigation include:
- The role of V-ATPase in osteoclast function
- RANKL signalling and osteoclastogenesis
- Screening of natural compound inhibitors for osteolysis
- Osteoclast and osteoblast intercellular communication
- Structural and functional analysis of RANKL mutants
- Screening of bone phenotypes from genetic mutant mice
**Professor Niyi Awofeso** (6488 1282)

**International Public Health, Policy Studies, Tropical Infectious Diseases, Vulnerable Population Groups**

Professor Awofeso worked in Africa as an infectious diseases’ physician for eight years prior to developing research interests in international public health (e.g. MDG implementation and managing health workers’ migration), translating health policy into practice (e.g. implementing influenza and alcohol policies), and improving health care access for vulnerable groups (e.g. implementing hepatitis B vaccination and smoking cessation programs in prison settings).

**Assistant Professor Alexandra Bremner** (6488 3386)

**Statistical Methods in Medical and Epidemiological Research; Busselton Health Studies**

Dr Bremner is a Lecturer in Biostatistics. Her research interests include: statistical methods in epidemiology, analysis of longitudinal data and repeated measures and statistical consulting.

**Research Associate Professor Tom Briffa** (6488 1292)

**Secondary Prevention and Translational Cardiovascular Disease Research**

Dr Briffa leads the School’s Cardiovascular Disease Research Group. He is an allied health graduate with postgraduate qualifications in cardiovascular secondary prevention and is currently researching trends and models of care in cardiovascular disease treatment and management. His main interests are improved secondary prevention services across practice settings, absolute cardiovascular risk assessment, and the prevention and treatment of cardiovascular disease and related risk factors.

**Dr Angus Cook** (6488 7804)

**Environmental Epidemiology; Air Pollution, Water Borne Disease from Pathogens and Pollutants; Vector-borne Disease; Medical Geology**

Dr Cook is an Associate Professor and Director of the School’s Ecology and Health group. He is a medical graduate with postgraduate qualifications in environmental epidemiology and biostatistics, and is currently coordinating research into the safety of disinfection products in drinking water, air pollutants, the relationships between land use and health outcomes, and role of environmental change in emerging infectious diseases.
Dr Hayley Christian (6488 1267)

Environmental and Individual Determinants of Physical Activity and Obesity; Children’s Physical Activity & Play; Dog Walking Behaviour; Health Research Translation

Dr Christian is a research fellow on the Centre for the Built Environment and Health NHMRC funded capacity building grant. Hayley was awarded a PhD with distinction for her thesis titled “The Relationship between Dog Ownership and Physical Activity”. She is presently working on the RESIDE project. Hayley’s research interests incorporate the relationship between the physical and social environment (including dog ownership) and physical activity and obesity. She is also interested in children’s physical activity, play and weight status and the translation of health research findings into policy and practice.

Mr Brian Devine (6488 8667)

Environmental Health; Water Quality; Recycled Water and Recreational Water Management.

Mr Devine is a Senior Research Fellow in the Schools Ecology and Health group. He has extensive experience in the field of environmental health. His current areas of interest relate to health risk assessment in regard to water quality, recycled water and recreational waters.

Dr Kristjana Einarsdóttir (6488 1298)

Health service delivery in older people with chronic diseases
a) Maternal and infant’s health outcomes and health service provision
b) Clinical outcomes from coronary revascularisation procedures and health service provision
c) Patterns of care in adolescents and young adults with cancer

Dr Einarsdottir is a Research Associate in the Centre for Health Services Research

Associate Professor Colleen Fisher (6488 2193)

Family and Domestic Violence, Health Promotion, Qualitative Research Methods; Women’s Health

Dr Fisher is an Associate Professor in Health Promotion and Qualitative Research Methods. Her major research interest is in family and domestic violence including cross-cultural experiences and understandings; and prevention and early intervention. Colleen has been involved in a number of local and international research projects examining this issue and in the evaluation of local initiatives. Colleen also has expertise in qualitative research methodology which she has used extensively in her research.

Professor Elizabeth Geelhoed (6488 7129)

Health Economics; Economic Evaluation; Resource Allocation; Burden of Disease; Quality of Life; Cost Analysis

Professor Geelhoed’s major interests are in Economic Evaluation, Resource Allocation and Burden of Disease. Current research projects include economic aspects of critical care, childhood obesity, aged care and interventions to reduce hospital admissions.
Professor Bilie Giles-Corti (6488 1257)

Environmental and Individual Determinants of Health Behaviours; Health Promotion Intervention Research and Evaluation

Professor Giles-Corti is Director of the Built Environment and Health. She leads a team of investigators and students examining the impact of urban design on a range of health behaviours and health outcomes, including physical inactivity, walking, cycling, sense of community, mental health and social capital. She lectures in health promotion and research methods. She has a strong interest in combining the behavioural and social sciences and the use of qualitative and quantitative methods to explore research hypotheses. She has extensive experience in the design and evaluation of health promotion programs, including evaluations of state and nationally-based service programs. Nevertheless, the major focus of her research at present, is understanding the impact of the built environment on health behaviour and health.

Associate Professor Jane Heyworth (6488 7370)

Environmental Epidemiology, especially Food and Water Quality; Environmental Causes of Cancer

Dr Heyworth is an environmental epidemiologist and her current research interests relate to, environmental causes of breast cancer, assessing environmental exposures, air and noise pollution and health; and community perceptions of risk.

Assessment of Community Noise Concerns in Suburbs of Perth

Supervisor(s) and Research Group: Dr Jane Heyworth and Dr Alison Reid, OEE

Background:
Noise is a health issue that is increasingly becoming one of community concern. Unwanted noise impacts on quality of life by disrupting individual activities including concentration, relaxation and sleep. However there are limited recent data on the extent to which people are concerned about noise and whether this varies by source.

Outline:
This project will include a review of the health effects of noise and also collation of existing data on noise levels across Perth (from DEC) and noise annoyance in Australia (ABS data). In addition, a noise questionnaire will be developed and used to survey residents in selected suburbs across Perth. The survey will address main sources of noise in the community and the extent to which these impact on annoyance, quality of life or self-reported health effects.

Assessment of Impact of Industrial Expansion on Health in the Collie region of WA

Supervisor(s) and Research Group: Dr Peter Franklin (ORE), Dr Jane Heyworth (ORE), Dr Andrea Hinwood, ECU

The South West region of Western Australia has gold mines, nickel and iron ore mines, coal mines and power stations, in close proximity to both bauxite mining and alumina production. The region is predominantly rural with land used for a range of agricultural purposes.

The air shed in specific South west locations such as Collie has received little attention over the past few years despite the presence of power stations and an alumina refinery, mining operations and small to medium industrial enterprises. Monitoring in the Collie area for air pollutants takes place at the Worsley refinery and at two locations offsite, to the south east and east-north-east of the refinery. Other monitoring sites are located at the various power stations. These sites monitor NO₂, NOx, SO₂ and particulate matter (PM 10 and 2.5). Localized exceedences of NEPM standards have been reported resulting from coal fires power stations MUJA A, B, C and D and also from bushfires in the region. The measured air quality in the town of Collie is usually well below NEPM standards.

Future significant development in this region will however significantly increase the quantity of pollutants emitted to atmosphere and is predicted to result in an increase in the concentration of pollutants that may impact on both human health and the environment. Recent environmental review documents for a variety of power proposals indicate both air quality in the township of Collie will deteriorate, and there may also be cumulative impacts from increases in noise levels. This is due to bauxite mining, road and rail transport, refinery operations and power station operations.

The South West region provides a setting to undertake investigations of health and environment as the region will have a predicted increase in pollution (both air and noise) in a relatively short time period.
Outline:

This project will involve collating existing air pollution data from monitoring and modelling in the region and undertaking a baseline study of respiratory health among residents of Collie. These data will provide baseline data on health and well being prior to industrial expansion.

**Assistant Professor Siobhan Hickling** (6488 7369)

Dr Hickling is an Accredited Practising Dietitian working in public health nutrition research, practice and teaching. She is a member of the School's Cardiovascular Disease Research Group and her primary research involves the investigation of dietary and associated risk factors and the impact of these on cardiovascular disease.

**Professor D'Arcy Holman** (6488 1251)

Health Services and Population Health Research, and especially Evaluations of Preventive or Treatment Services That Make Use of Innovative Research Methods, including Randomised Trials, Quasi-Experimental Designs, Case-Crossover and other Non-Experimental Design with or without the use of Data Linkage.

Professor Holman is a leading researcher in the Centre for Health Services Research and has considerable experience in research programs designed to evaluate the effectiveness, efficiency and equity of preventive and treatment services. He is especially interested in the application of innovative research methods that combine epidemiological, economic, behavioural and social science perspectives, as a means to evaluate health services utilisation and the outcomes of health interventions.

**Assistant Professor Helena Iredell** (6488 1274)

Social Aspects of Ageing, Loneliness and Social Isolation in Later Life; Health Promotion

Assistant Professor Iredell has a background in population health and health promotion. Her current research interests lie in health-related issues associated with positive ageing, including loneliness, social isolation and living alone, social support, social participation, and its relationship to health. She has also been involved in research dealing with road safety and older people and exploring social capital in physical activity.

**Winthrop Professor Matthew Knuiman** (6488 1250)

Busselton Health Studies; Epidemiology of Chronic Diseases; Statistical Methods in Medical and Epidemiological Research

Professor Knuiman, Head of School, is custodian of the Busselton Health Studies database and has been conducting epidemiological research with the Busselton Health Studies research group for over 15 years on topics in cardiovascular and respiratory diseases, cancer and diabetes. He is also interested in the application of statistical methods in medical and epidemiology research.
**Associate Professor David Preen** (6488 1307)

**Health Services Research; research involving Health Record Linkage, Type II Diabetes, Obesity, Health Outcomes associated with Bariatric Surgery; Pharmacoepidemiology and the Appropriate Use of Medicines**

Dr Preen is Director of the Centre for Health Services Research at the School of Population Health. His current research interests include the impact of co-morbidity and 'burden of disease' on health outcomes, as well as novel methodological research design using population-based medical record linkage. Further, Dr Preen is currently investigating health outcomes, service utilization and chronic disease management in the WA diabetic community as well as conducting projects in the areas of adverse drug reactions in older Australians, psychostimulant prescribing patterns for the treatment of ADHD in children and health outcomes following bariatric surgery.

**Assistant Professor Frank Sanfilippo** (6488 8181)

**Clinical Epidemiology, Pharmacoepidemiology, Health Services Research, Analysis of Linked Data**

Dr Sanfilippo is a Research Fellow in the Cardiovascular Research Group. He is also a senior pharmacist at Royal Perth Hospital and works at the hospital one day per week. His previous work at the School was on the WA Audit of Surgical Mortality (WAASM) through the Centre for Health Services Research. Currently, he is working in cardiovascular epidemiology with projects on acute coronary heart disease and outcomes of drug eluting stents. His main interests are in clinical epidemiology and pharmacoepidemiology, and he is involved in other projects on medication safety, chronic diseases and treatment of ADHD.

**Assistant Professor Lisa Wood** (6488 7809)

**Health Promotion Intervention Research and Evaluation; Social Capital and Sense of Community; Built Environment and Health; Social Determinants of Health; Tobacco**

Dr Wood is a postdoctoral fellow on a NHMRC funded capacity building grant. Her PhD research examined the relationship between neighbourhood environments, social capital and health. Current research interests include: social capital and sense of community; urban design/built environment and health; social determinants of health; healthy communities; tobacco; life-course approaches to health; indigenous health; and the translation of research into policy and practice. She also is involved in some projects that seek to apply public health models to the issues of domestic violence and child abuse prevention.

**Research Associate Professor Min Zhang** (6488 8175)

Director of Lu Cha (Green Tea) Sino-Australian Research Collaboration (LCSARC)

LCSARC were established in 2004 by Prof Holman, Research A/Prof Zhang, and Prof Xie (Zhejiang University Women's Hospital), Prof Zhao (Zhejiang University) joined in 2005 with respect to leukaemia research, and Prof Liu (China Medical University) and Prof Chen (Dalian Medical University) joined in 2006 to extend its research base in north-eastern China.

The Collaboration focuses on:
- identifying risk factors and conducting intervention in diet, nutrition, green tea, and modifiable lifestyle factors for primary prevention and early control of cancers;
- developing new research methods.

LCSARC aims to find sufficient evidence for large-scale primary cancer preventions in complementary medicine.

Research

i) Green tea polyphenols and cancer prevention: use of biomarkers and population controls to elicit causal pathways (NHMRC project grant 2009-2011)

ii) Green tea polyphenols and serum hormone level and mammographic density: a pilot study of placebo-controlled RCT in healthy women (UWA RDA/Endeavour Award)

iii) A lab-based study of green tea polyphenols and breast cancer as an adjunct to the trial (supported by funds from a private benefactor).
Head of School: Professor Jon Emery 9449 5150 Email: jon.emery@uwa.edu.au

SPARHC collectively contributes to quality primary health care outcomes for the Western Australian community with particular emphasis on rural and Indigenous health. The School has a role in facilitating and developing strategies for collaboration within the School and its key stakeholders to maximise the benefits that flow from such collaborations. Research activities in SPARHC are carried out by groups of academic and research staff. For more detailed information about possible BMedSci research projects in the School, students are encouraged to talk to the individual supervisors listed below. Information on current projects is on the School's website at: http://www.sparhc.uwa.edu.au/research

GENERAL PRACTICE RESEARCH PROJECTS
General Practice carries out extensive research into a variety of areas of primary care, community health and general practice education. There are opportunities for Bachelor of Medical Science students to participate in primary health care research. The following research projects are currently underway and you may be able to undertake your BMedSci project in one of these areas:

Title: Improving Rural Cancer Outcomes Project
Supervisor/s: Winthrop Professor Jon Emery
Contact details: jon.emery@uwa.edu.au 9346 7508
Project outline: A range of exciting opportunities exist with the Improving Rural Cancer Outcomes (IRCO) Project. The IRCO Project is a research project that is investigating why people, with cancer, from regional and rural areas experience poorer health outcomes than metropolitan patients. Using a 2x2 factorial randomised control trial design, a series of community and GP interventions will be delivered and evaluated to try and improve the situation. If successful the interventions are likely to be taken up as part of normal service delivery.

Title: The FAST study: family history screening for chronic disease prevention in primary care
Supervisor/s: Winthrop Professor Jon Emery, Ms Gabrielle Reid
Contact details: jon.emery@uwa.edu.au 9346 7508
Project outline: This international collaborative study is developing and validating a new brief screening tool for use in primary care to identify people with a significant family history of a common chronic disease such as certain cancers, ischaemic heard disease, Type 2 diabetes..

Title: Prescribing Issues in General Practice
Supervisor/s: Associate Professor Brett Montgomery
Contact details: brett.montgomery@uwa.edu.au 9346 2369
Project outline: Dr Montgomery’s research interests include prescribing issues in general practice, especially regarding medicines for the reduction of cardiovascular risk (including antihypertensives and statins). He has also been involved in research on the effect of pharmaceutical promotion on doctors’ prescribing.
Chronic disease management programs in WA

**Supervisor/s:** Professor Alistair Vickery, Associate Professor David Whyatt and Winthrop Professor Jon Emery

**Contact details:** alistair.vickery@uwa.edu.au 9346 1908

**Project outline:**
This study is evaluating the effectiveness of chronic disease management programs that are intended to reduce the impact of chronic disease on healthcare demand. Both the true impact of such programs on patient outcomes and subsequent costs to WA Health are being determined by collection of biometric, hospitalisation and socioeconomic data. We anticipate that this analysis will identify those patients who would most benefit from participation in the CDMP and will support the establishment of continued monitoring and expanded implementation of such program in an effective manner.

Multidisciplinary models of health care delivery

**Supervisor/s:** Associate Professor David Whyatt

**Contact details:** david.whyatt@uwa.edu.au 9346 7326

**Project outline:**
In addition to the chronic disease management study outlined above, Associate Professor Whyatt’s research interests include multidisciplinary models of health care delivery, social determinants of health, implementation of evidence-based best practice and models of capacity development in primary health care research and evaluation. Students are encouraged to discuss possible projects with A/Prof Whyatt directly.

Emergency Medicine Research Projects

Emergency Medicine has a growing research infrastructure, particularly in epidemiological linked database studies examining health care outcomes for emergency patients including those attending hospital by ambulance, critical illness research including anaphylaxis, sepsis and trauma, poisons information and toxicology, and in evaluation of teaching and learning in emergency medicine. The following research projects are currently underway and you may be able to undertake your BMedSci project in one of these areas:

The Cardiac Arrest Registry

**Supervisor/s:** Winthrop Professor Ian Jacobs

**Contact details:** Ian.Jacobs@uwa.edu.au 9346 4354

**Project outline:**
The Cardiac Arrest Registry, currently funded through the WA Ambulance Service and Laerdal, aims to further understand the epidemiology of cardiac arrest through ongoing population-based surveillance of patients suffering a heart attack.

Leukocyte Signalling during Human Anaphylaxis

**School/Centre:** Centre for Clinical Research in Emergency Medicine (CCREM)

**Supervisor/s:** Professor Simon Brown, Assistant Professor Shelley Stone

**Contact details:** 9224 0356, Shelley.Stone@uwa.edu.au, Simon.Brown@uwa.edu.au

**Project outline:**
Anaphylaxis is a severe allergic reaction affecting multiple organ systems, characterised by hypotension (shock), bronchospasm and upper airway obstruction, with an estimated mortality rate in the order of 1%. Due to the rapid, unexpected and life-threatening nature of severe anaphylaxis, mechanistic research is difficult to perform in humans. Recent work from our laboratory has demonstrated a clear correlation between serum levels of immune mediators and reaction severity. Furthermore we demonstrated different patterns of immune mediator release during severe cardiovascular reactions compared with severe respiratory reactions. This research aims to identify the leukocyte signalling pathways that are activated during human anaphylaxis and determine the direct effects of key mediators on IgE receptor (FcεRI) expression and mediator release from in vitro differentiated human mast cells.
Title: Brain Injury: Trauma and Stroke  
School/Centre: Centre for Clinical Research in Emergency Medicine (CCREM)  
Supervisor/s: Professor Simon Brown, Assistant Professor Shelley Stone, Professor Daniel Fatovich, Assoc/Prof Glenn Arendts & Dr Pauline van Eeden  
Contact details: 9224 0356, Shelley.Stone@uwa.edu.au, Simon.Brown@uwa.edu.au  
Project outline: This research program aims to improve our understanding of the immunological responses triggered by brain injury by identifying key leukocyte signalling pathways and the timing of their activation post-injury. For traumatic brain injury (TBI) our main hypothesis is that the activation of leukocyte signaling pathways will be closely correlated with clinical outcomes defined by the Glasgow Outcome Scale (GOS) and Disability Rating Scale (DRS). Damage to the brain occurs in two phases; (i) the primary phase which is the initial injury itself and (ii) the secondary phase which consists of delayed responses over ensuing days/weeks, including physiological, cellular and molecular responses aimed at healing the damaged tissue. To establish effective treatment for patients with traumatic brain injury, the complex molecular cascades of gene activation regulating and contributing to neuroinflammation and clinical outcome must be elucidated.

Title: Inflammation and Bacterial Load during Sepsis  
School/Centre: Centre for Clinical Research in Emergency Medicine (CCREM)  
Supervisor/s: Professor Simon Brown, Assistant Professor Shelley Stone, Professor Daniel Fatovich, Assoc/Prof Glenn Arendts & Dr Pauline van Eeden  
Contact details: 9224 0356, Shelley.Stone@uwa.edu.au, Simon.Brown@uwa.edu.au  
Project outline: We hypothesise that, in septic patients, high bacterial load is associated with leukocyte inflammatory pathway activation and cytokine surges not seen with low bacterial loads, and that these changes are amplified by initial antibiotic therapy. We also hypothesise that high bacterial load will be such an important determinant of outcome in patients with sepsis that a clear correlation between bacterial load and early (28 day) mortality. We will measure (in serial blood samples) bacterial load, leukocyte signalling pathway activation and key serum cytokine levels in patients with sepsis on arrival to the ED and during the first 24 hours of treatment. We will also determine the timing and magnitude of the inflammatory (leukocyte activation and key cytokine) response with respect to first antibiotic administration, and whether this differs in those with high versus low bacterial load. The results will help us design future studies of strategies to modulate the impact of inflammatory responses to sepsis and bacterial lysis.

Title: Acute Illnesses in the Elderly – Sepsis  
School/Centre: Centre for Clinical Research in Emergency Medicine (CCREM)  
Supervisor/s: Professor Simon Brown, Assistant Professor Shelley Stone, Professor Daniel Fatovich, Assoc/Prof Glenn Arendts & Dr Pauline van Eeden  
Contact details: 9224 0356, Shelley.Stone@uwa.edu.au, Simon.Brown@uwa.edu.au  
Project outline: More than 60% of patients with severe sepsis seen in the Emergency Department (ED) are elderly (>65 years) and they are twice as likely to die as younger patients with this condition. Chronic illness and poor physiological reserve alone are not responsible for this disparity. Ageing is associated with impaired inflammatory and neurohumoral responses to infection and immunological senescence may predispose to high bacterial load. Septic patients differ greatly with regard to co-morbidities, physiological reserve, immune response, infective agent (type and virulence), initial site of infection, time to presentation and treatments given. Our initial studies of sepsis(above) are focussing on elderly patients with special attention the impact of comorbidities on inflammatory response and outcome.

Title: Acute Illnesses in the Elderly – Delirium  
School/Centre: Centre for Clinical Research in Emergency Medicine (CCREM)  
Supervisor/s: Associate Professor Glenn Arendts  
Contact details: 9224 0356 Glenn.Arendts@uwa.edu.au  
Project outline: Acute delirium is poorly recognised and is associated with inpatient morbidity and mortality. A research project is available for the development of tools to identify and intervene in the delirious patient, using a combination of clinical, cognitive and laboratory markers.

Title: Acute Illnesses in the Elderly – Pain Assessment in Cognitively Impaired Patients  
School/Centre: Centre for Clinical Research in Emergency Medicine (CCREM)  
Supervisor/s: Associate Professor Glenn Arendts  
Contact details: 9224 0356 Glenn.Arendts@uwa.edu.au  
Project outline: A project exists for a student to improve the recognition and management of pain in elderly patients with cognitive impairment presenting to ED.
BMedSci projects are available for students with an interest in improving the provision of care for the chronically ill frail elderly patient. These include the development of alternate care plans or ED avoidance strategies for people living in aged care facilities.

CENTRE FOR ABORIGINAL MEDICAL AND DENTAL HEALTH RESEARCH PROJECTS

The Centre for Aboriginal Medical and Dental Health is involved in the development of cross-country, interdisciplinary research programs on factors and processes that promote resilience, self-determination and improved health and well-being for Indigenous people. Our interests cover a wide range of areas and settings, including Indigenous health competency in the health professions through to factors influencing health and wellbeing of Indigenous communities. Students may choose a topic solely within the Centre or may undertake the degree in another school in the Faculty with a joint supervisor from CAMDH. The following research projects are currently underway and you may be able to undertake your BMedSci project in one of these areas:

Title: Educating for Equity – Exploring how health professional education can reduce disparities in chronic disease (NHMRC International Collaborative ICHRP Grant).
School/Centre: Centre for Aboriginal Medical and Dental Health
Supervisor/s: Winthrop Professor Helen Milroy, Dr David Paul
Contact details: helen.milroy@uwa.edu.au 6488 2038
Project outline:
Indigenous people in Canada, Australia and New Zealand experience a greater burden of chronic diseases such as diabetes, heart disease and mental illness than non-Indigenous people. This project is about comparing, building and sharing experiences and approaches to Indigenous health teaching and learning in the area of chronic disease. It begins by describing existing educational approaches and the contexts in which the study is being undertaken. Indigenous health curriculum developers will be interviewed to identify the specific approaches used and the reasons underlying their use. We will conduct focus groups with learners, educators, patients and other stakeholders to study the impact of different educational approaches. This will result in development of an Indigenous chronic disease education ‘toolbox’ and methods to evaluate the effectiveness of Indigenous health education. The project will place a major focus on ensuring that lessons from the project are translated into practice. This research will make a substantial and enduring contribution to improving the quality of health care for Indigenous people with chronic disease and thus outcomes.

Title: Evaluation of the impact of Aboriginal health curricula
School/Centre: Centre for Aboriginal Medical and Dental Health
Supervisor/s: Dr David Paul
Contact details: david.paul@uwa.edu.au 6488 7084
Project outline:
The Centre, in collaboration with the Faculty’s Education Centre, developed an ‘Impact of the Aboriginal Health undergraduate curriculum (IAHUC)’ questionnaire. This survey has been conducted each year since 2003, and its results are used to guide the further development and modification, as well as assess effectiveness, of the Aboriginal health curriculum.

COMBINED UNIVERSITIES CENTRE FOR RURAL HEALTH RESEARCH PROJECTS

CUCRH is funded by the Commonwealth Department of Health and Ageing, and managed by a consortium of the five Western Australian Universities. CUCRH engages with rural practitioners, health services, local organisations and Aboriginal communities to work collaboratively on projects impacting social, public and organizational as well as individual health. CUCRH is rural-centred, so students may choose to be based in the main office in Geraldton or the satellite centre at Port Hedland. Accommodation and travel would be provided. Perth projects operate from the SPARHC office at Queen Elizabeth II Medical Centre. There are opportunities for a Bachelor of Medical Science student to participate in primary health care research. The following research projects are currently underway and you may be able to undertake your BMedSci project in one of these areas:
Title: The Midwest Aboriginal Organisations Alliance Partnership study  
School/Centre: Combined Universities Centre for Rural Health  
Supervisor/s: Winthrop Professor Sandra Thompson, Dr Fiona Nichols  
Contact details: sandra.thompson@cucrh.uwa.edu.au 9956 0200  
Project outline:  
Many health promotion interventions are focussed on downstream antecedents of poor health such as poor nutrition, physical inactivity or other risk behaviours, despite our understanding that social context and environment are major determinants of behaviour and health. Hence, health promotion recognises that health goes beyond the health sector and includes lifestyle, societal and personal resources. This project uses a rare alignment of circumstances to explore elements of Aboriginal and mainstream partnerships to ensure that Aboriginal aspirations and visions are represented and included in the planning for the future of Geraldton and the Midwest region.

As part of the 2010 City of Geraldton-Greenough’s 2029 Sustainable Future City community consultation process, Aboriginal people responded to ‘future planning’ questions:

- What (if anything) needs to change to make Geraldton-Greenough a great place for Aboriginal people to live in 2029 and beyond?
- What should we be doing now to achieve those goals?

Aboriginal people consistently recommended initiatives targeting racism, access to Aboriginal-friendly life-course education, improving social service responsiveness, increasing Aboriginal employment/mentoring, and increasing the visible representation of Aboriginal leadership and culture.

The greater Midwest region’s 13 key Aboriginal organisations have united to form the Midwest Aboriginal Organisations Alliance (MAOA). As a collective, representative and proactive voice regarding government and industry developments and projects, MAOA are keen to address broader social issues affecting Aboriginal people within the Midwest. MAOA have partnered with the Combined Universities Centre for Rural Health (CUCRH) around research to help address the key areas of concern to Aboriginal people.

Multiple potential research projects are possible linked to this overall Aboriginal-mainstream partnership, including exploring the nature, tensions and benefits of the partnership itself. Our approach is generally that of participatory action research with the aim of that Aboriginal co-researchers are empowered.

If you feel committed to improving the health of Aboriginal people and recognise that improving Aboriginal health requires a more upstream approach than patching up ill people once they seek medical attention, this project will be of interest.

Title: Sexual Health among young Aboriginal people  
School/Centre: Combined Universities Centre for Rural Health  
Supervisor/s: Associate Professor Barbara Nattabi  
Contact details: barbara.nattabi@cucrh.uwa.edu.au 9956 0200  
Project outline:  
Associate Professor Nattabi is a medical doctor and public health practitioner based in Geraldton. She is currently working on two projects, both concerned with sexual health among young Aboriginal people. The first project is concerned with the sexual health knowledge, attitudes and behaviour of Aboriginal youth in rural Western Australia and the second with the development of a sexual health audit tool for continuous quality improvement of sexual health services, with particular relevance to the needs of Aboriginal and Torres Strait Islander people. Any students interested in working on a literature review should contact Associate Professor Nattabi. These two projects will make a substantial contribution to improving the quality of sexual health care for young Indigenous people all over Australia.

Title: Taking an Aboriginal Family Medical History  
School/Centre: Combined Universities Centre for Rural Health  
Supervisor/s: Winthrop Professor Sandra Thompson, Assistant Prof Sandy Hamilton  
Contact details: sandra.thompson@cucrh.uwa.edu.au 9956 0200  
Project outline:  
Taking a family history is an important part of a medical history. But why is it done, and are we taking the sort of histories that we need to take? Often Aboriginal people know a lot more about their family connections than non-Aboriginal people, but they may have less understanding about the genetic and environmental contributions to those diseases. This project proposes an exploratory study based upon taking a detailed family history utilising a few individuals with initial diagnosis of diabetes or heart disease when aged under 40 years. It could explore their understanding of heart disease and risk factors within their wider family network, including opportunities for prevention that may otherwise be missed. The project could potentially help elucidate how much of premature heart disease is a result of genetic diseases like familial hypercholesterolaemia, a condition which has not previously been carefully explored within Aboriginal families.
Title: Disparities in cardiovascular disease for Aboriginal people
School/Centre: Combined Universities Centre for Rural Health
School of Primary, Aboriginal and Rural Health Care
Supervisor/s: Winthrop Professor Sandra Thompson,
Associate Professor Judy Katzenellenbogen
Contact details: sandra.thompson@cucrh.uwa.edu.au 9956 0200

Project outline:
You can contribute to a project that explores the complex interactions between coronary heart disease and other heart conditions and major co-morbid conditions including diabetes and chronic kidney disease. The project has a strong basis in epidemiological analysis and will explore issues relating to access to health services for heart diseases and describe health service utilisation and associated costs of heart disease and associated conditions in the Aboriginal and non-Aboriginal populations in WA.

Potential components are:
1. To describe and compare the epidemiology and clinical manifestations of CHD, chronic heart failure (CHF), dysrhythmias and major co-morbid conditions including diabetes and CKD in Aboriginal and non-Aboriginal people in WA.
2. To compare (using hospitalisation data) access of Aboriginal and non-Aboriginal people to acute and continuing medical care for heart diseases, focusing on acute and chronic CHD, CHF and cardiac dysrhythmias.
3. To describe health care service utilisation and direct costs for heart diseases in Aboriginal and non-Aboriginal people in WA as the basis for future studies of cost-effectiveness of public health and clinical interventions to improve cardiovascular health in Aboriginal people.
4. To investigate the responses of health decision-makers to epidemiological and cost information about Aboriginal inequities in CHD care and outcomes.

The Rural Clinical School of Western Australia

The Rural Clinical School of Western Australia (RCSWA) was established in 2002 to provide undergraduate medical students with the opportunity to have an in-depth learning experience in rural and remote medicine as part of the clinical training. The School has 13 sites around the state and an intake of 80 students. A year doing a BMedSci with us would be an amazing combination of research and adventure - whether looking into diabetes management in Geraldton, doing hands-on projects in the Kimberley, or contributing to the kidney health programme in the Western desert near Kalgoorlie.

The RCSWA would welcome you as a member of a larger community, and encourage you to join in one of our main research themes somewhere in the bush! We would treat you as one of our RCS students, providing accommodation locally and support to travel back to Perth. There is also top-up funding available to your project, which may be used to attend relevant courses, or to access other resources or expertise. All RCSWA sites have technology available for videoconferencing, meaning you can still be part of the wider university network.

Many of our academic staff are able to supervise a BMedSci project and just some of them are listed below. If you are interested, a first step would be to contact Professor Kirsten Auret (Chair of the RCSWA Research Steering Committee), who would then be able to discuss your areas of interest and the possibilities that exist for you in our school, and explain the selection process that we undertake.
Title: Various projects – see below
School/Centre: Rural Clinical School of Western Australia
            School of Primary, Aboriginal and Rural Health Care
Supervisor/s: Professor Kirsten Auret; Dr Craig Sinclair
Contact details: kirsten.auret@uwa.edu.au 9842 5555
Project outline:
Professor Auret is a general physician based in Albany. She also teaches in the RCSWA and chairs the school’s research committee. She has projects that would welcome your help! These include research into palliative care and dying in rural locations, advanced health directives, cancer related fatigue and medical professionalism. Dr Craig Sinclair is a senior research fellow who works alongside Professor Auret and would also be available to support and extend you. He has a particular interest in rural mental health and utilisation of online mental health resources.

Title: Western Desert Kidney Health Project
School/Centre: The Rural Clinical School of Western Australia
            School of Primary, Aboriginal and Rural Health Care
Supervisor/s: Associate Professor Christine Jeffries-Stokes
Contact details: christine.jeffries-stokes@uwa.edu.au 0407387602
Project outline:
A range of exciting opportunities exist with the Western Desert Kidney Health Project. This is a multidisciplinary project based in 10, predominantly Aboriginal, communities in the Goldfields and Western Desert area of WA. The project brings together epidemiological research, health promotion, community development and arts to determine the prevalence of risk factors for kidney disease and diabetes and assist these communities to understand and make changes to reduce the risk of these diseases. For more information see the website at http://www.artshealthfoundation.org.au/westerndesertkidney/

Title: Aboriginal health research in the Kimberley
School/Centre: Rural Clinical School of Western Australia
            School of Primary, Aboriginal and Rural Health Care
Supervisor/s: Professor David Atkinson, Associate Professor Julia Marley
Contact details: david.atkinson@uwa.edu.au 0438380209/91936043
Project outline:
Professor Atkinson is a Medical Coordinator in the Kimberley and also works for the Kimberley Aboriginal Medical Services Council (KAMSC), based in Broome. Professor Atkinson has extensive Aboriginal health, population health and practical community based research project supervisory experience. The RCSWA research team in Broome is based at KAMSC and works closely with KAMSC and WACHS-Kimberley on projects of relevance to improving health services in the region. There are a wide range of collaborative research projects being carried out in the area of Aboriginal health including 3 completed PhD projects and 3 completed honours or BMedSci type studies to date. In particular there is a regional focus on chronic disease management with projects on diabetes, renal disease, chronic lung disease and rheumatic heart disease. There have also been projects looking at the mental well being of Aboriginal youth and at the health of older Indigenous people.

Professor Atkinson, Associate Professor Julia Marley the RCSWA research fellow, Dr Carmel Nelson, Dr Trevor Lord and other senior medical staff, staff of the Kimberley Population Health Unit and other practitioners in the region can support a range of practical research projects. Broome provides a supportive research environment and we are looking for people with an interest in Aboriginal health and enthusiasm who would like to be part of our team.
Bowel Cancer: Causes and Treatment

Winthrop Professor Barry Iacopetta 9346 2085  barry.iacopetta@uwa.edu.au

Molecular Profiling of Bowel Cancers
The two major phenotypes of colorectal cancer show widespread chromosomal instability (CIN) or CpG island methylation (CIMP).

The aim of this project is to investigate alterations that occur to components of the PI3K signalling pathway in these tumour subgroups.

This information will be important for future clinical studies that use novel targeted agents to inhibit the PI3K pathway.

Breast Cancer: Causes and Treatment

Winthrop Professor Christobel Saunders 9346 2146  christobel.saunders@uwa.edu.au
Dr Toni Musiello 9346 4174  toni.musiello@uwa.edu.au
Dr Angela Ives 9346 3161  angela.ives@uwa.edu.au

Professor Saunders is a Consultant Breast Surgeon with a clinical research focus on the causes, diagnosis and treatment of breast cancer. Additional research interests include survivorship issues for breast cancer patients, particularly young women, such as infertility, psychosocial issues and menopausal symptoms.

Professor Saunders is also involved in health services research and the evaluation of State cancer and palliative care programs. Students are welcome to make an appointment to discuss the exciting breast cancer research opportunities available in the BMedSci degree.

Examples of the types of research projects Professor Saunders is currently involved in are detailed below:

1. International clinical trials of breast cancer preventions and treatment such as IBIS II Prevention study
2. Targeting breast cancer recurrence through epithelial mesenchymal plasticity (EMPathy)
3. TARGIT (Targeted Intraoperative radiotherapy) in early breast cancer
4. OCT (Optical coherence tomography) pilot study to detect cancerous lymph nodes
5. Development of a new breast cancer imaging probe
6. The impact of treatment-focused genetic testing in patients newly diagnosed with breast cancer
7. Partnership Intervention Trial to redress treatment delay and improve outcomes in rural cancer patients
8. Gestational breast cancer studies
9. Exploring patient and carers’ understanding of Multidisciplinary Teams (MDTs)
10. Western Australian Breast Cancer in Young Women Database Project
11. Menopause after breast cancer research clinic (including ovarian function and chemotherapy)
12. Occupational causes of breast cancer
13. Mammographic Density Study
14. Evaluative study of quality of life in pre-menopausal women with low risk of early breast cancer (Goserelin study)
15. Treatment of vaginal dryness in Aromitase Inhibitors users

Burn Injury Research Unit

Winthrop Professor Fiona Wood 9202 1145  fiona.wood@health.wa.gov.au
Professor Suzanne Rea 9202 1145  suzanne.rea@health.wa.gov.au
Research Asst Professor Hilary Wallace 6488 8597  hilary.wallace@uwa.edu.au
Dr Mark Fear 6488 7514  mark@mccomb.org.au

The Burn Injury Research Unit is led by Winthrop Professor Fiona Wood, a Plastic and Reconstructive Surgeon who is also Director of the McComb Research Foundation.
Major research interests of the Unit are:

- Biotherapeutics
- Cell Therapy
- Tissue Engineering
- Skin Reconstruction
- Regenerative Medicine

Current projects include:

**The Epigenetics of Scar and Normal Skin Fibroblasts**

Scars are a result of excess collagen deposition and other changes in the skin that never resolve post-injury. Scars obtained in childhood often increase in size during periods of growth, suggesting the possibility that fibroblasts in scar tissue continue to be active and generate scar tissue long after injury repair. One possibility is that the cells have undergone epigenetic changes that lead to irreversible loss of normal phenotype and gain of a ‘scar-forming’ phenotype. Epigenetics refers to irreversible changes in the structure of DNA that alter gene expression. These changes are principally methylation and histone acetylation. This project aims to identify epigenetic changes in fibroblasts from scar tissue compared to non-injured skin. Understanding the epigenetic changes in these cells may lead to novel therapeutics, and if successful has the potential to reverse scar formation back to normal skin at any time post-injury.

**The Role of Ephrins in Reinnervation of Skin Post Wounding**

(Project in association with Dr Jenny Rodgers, School of Animal Biology)

The ephrins are known to be involved in establishing the topographic map during retinal development. However, to date, little is known about the role of ephrins and their receptors in the skin. We are currently using Ephrin A2, Ephrin A5 and Ephrin A2/A5 knockout mice to investigate the roles ephrins play in skin development, maintenance, and the response to injury. The aim is to progress the understanding of healing and reinnervation response in a burn injury model.

**Reinnervation After Burn Injury and its Effects on the Wound Healing Response and Scarring**

We have identified a systemic change in cutaneous innervation after even localised burn injury. The effects of these changes on sensory function, and on scar formation, are still not clear. We have a number of projects to further investigate cutaneous innervation and burn injury, specifically to answer the following questions;

1. Is the systemic loss of cutaneous innervation caused by inflammatory mediators or neuronal signaling?
2. What is the effect on wound healing of these systemic changes?
3. What is the role of inflammation in the systemic nerve loss after burn injury?
4. How does neuronal signaling impact on wound healing and scar formation?

**The Investigation of the Impact of Trauma on the Peripheral Nerve Field**

The change in nerve density in the peripheral nerve field (PNF) was noted in normal non burnt skin with a negative correlation with the extent of injury. The aim is to investigate the PNF over time from day 1 post injury onto 18 months post with serial clinical assessments and skin punch biopsies for histological analysis. The burn patients will be compared to those suffering non burn trauma and neurological trauma of comparative injury severity scores.

**The Impact of Sensory Training on the Long Term Recovering Post Injury**

(Project in association with Professor Sarah Dunlop, School of Animal Biology)

Two years post injury the scars are beginning to mature and we have established a long term loss of cutaneous sensory function. The aim is to investigate whether sensory training of the scar surface can improve function. A program of sensory retraining will be undertaken as a potential therapeutic intervention with baseline and post intervention sensory testing and histological analysis of the peripheral nerve field.

**The Impact of Burn Injury on Muscle Function**

(Project in association with Dr Anthony Bakker, School of Biomedical, Biomolecular & Chemical Sciences)

Profound muscle wasting is a common problem post burn injury. Treatment to this time has been directed at nutrition and exercise. These interventions can result in some improvements, but wasting and weakness remain a challenge. The aim of the project is to investigate the effect of the burn injury on the muscle in isolation and related to the nervous system changes in a burn injury model.

**The Incidence of Hypertrophic Burn Scar in Children with a History of Eczema and Asthma**

Early work has suggested that there is a link between poor scar outcome and asthma and eczema in the paediatric scald population. A retrospective review will be linked to prospective assessment to answer this question. The result will impact directly on clinical care with respect to scar management strategies.
Identification of Factors Influencing Outcome Post Burn Injury
(Project in association with Mr Dale Edgar)
Outcome post injury can be measured in terms of physical and emotional function. The aim of the project is to investigate the outcome related to the scar quality post burn injury. The adult burn service has an extensive database linking injury to outcomes which can be measured against population norms. Understanding the factors impacting on outcome in individuals will facilitate targeted clinical care to optimise the outcome.

The Role of Bone Marrow Derived Cells (Hematopoietic and Mesenchymal) in Burn Injury Repair and Scar Formation
We have previously published data implicating cells derived from the bone marrow, rather than from the wound periphery, as being important in scar development and maintenance. We are continuing to investigate the roles of these cells using established transgenic mouse lines and cell fate monitoring after burn injury.

Cancer and Palliative Care Research and Evaluation Unit (CaPCREU)

Winthrop Professor Christobel Saunders 9346 2146 christobel.saunders@uwa.edu.au
Research Asst Professor Claire Johnson 9346 4700 claire.johnson@UWA.edu.au
Research Asst Professor Angela Ives 9346 3161 angela.ives@UWA.edu.au

CaPCREU is led by Winthrop Professor Christobel Saunders, a Consultant Breast Surgeon with an interest in clinical and health services research. CaPCREU is a collaboration between UWA, Edith Cowan University and Curtin University of Technology and is funded by the WA Cancer and Palliative Care Network (WACPCN). It was established to increase the capacity and profile of cancer health services and clinical research in WA and to help evaluate programs and projects implemented by the WACPCN. New programs may be evaluated to establish how well they meet their objectives and whether outcomes for people with cancer in WA have improved as a result of the intervention.

Researchers from the Unit have collaborated with numerous clinicians within the WACPCN to undertake a wide variety of projects. Current projects in which CaPCREU is involved include:

1. An evaluation of the Liverpool Care Pathway for care of the terminally ill in Western Australia (in collaboration with the Palliative Care Network and ECU).
2. Patterns of care in colorectal cancer project (in collaboration with the Lower GI Tumour Collaborative and the WACPCN).
4. An investigation of the Emergency Department admissions following cancer treatment of people within one year of their cancer diagnosis (in collaboration with the WACPCN).
5. An evaluation of the Metropolitan Area Health Palliative Care Services (in collaboration with the WACPCN).
7. Delays in medical oncology and chemotherapy outpatient services.
8. Palliative Care Outcomes Collaborative (PCOC) Quality Improvement Activities (in collaboration with WACP and University of Wollongong).
9. An investigation of the current adolescent and young adults (AYA) cancer services in Western Australia.
10. Fertility and contraception management for women diagnosed with breast cancer and the health of children born to women after they have been diagnosed with breast cancer.
11. An evaluation of Osteo-radio-necrosis of the jaw in people with head an neck cancers (in collaboration with researchers and clinicians from The University of Western Australia, Sir Charles Gairdner Hospital and Oral Health Centre of Western Australia).
12. General practitioners’ preferences for managing the care of people with cancer (in collaboration with W/Prof Jon Emery, School of Primary, Aboriginal and Rural Health Care).
13. Routine screening and management of distress in people with cancer in WA: a pilot study of people with lymphoma treated in an outpatient setting (in collaboration with the Psycho-oncology Collaborative and the Haematology Care Centre, Sir Charles Gairdner Hospital).

In addition to actively undertaking research, CaPCREU provides research support for health professionals through administering two streams of research funding - the Small Grants Scheme and the Clinical Trials Scheme and by conducting a series of research training workshops for health professionals caring for people diagnosed with cancer or at the end of life.
Research at The Ear Sciences Centre (ESC) draws its strength from the close working relationship between clinicians and researchers. It has a strong emphasis on improving patient outcomes and a committed focus to teaching and training.

The ESC is a partner with the Ear Science Institute Australia which is dedicated to the diagnosis, treatment and research of ear and hearing disorders. The clinical activities involve a large team of surgeons and audiologists in centres throughout Perth and the newly completed dedicated research facility at 1 Salvado Road, Subiaco.

Currently the ESC has six major research streams:

- Molecular and Cellular Otolaryngology: tissue engineering, genetics, and cell culture of all types of ear cells.
- Computer and Information Sciences: covering telemedicine, computer aided diagnosis and e-health databases.
- Clinical Outcomes: implantable devices (such as cochlea implants), surgical outcomes and evaluation of new surgical methodologies and devices.
- Audiology: single sided deafness, residual hearing, conductive and mixed hearing loss, tinnitus, vestibular and noise-induced hearing loss.
- Epidemiology: epidemiology of hearing loss, tinnitus and dizziness, their investigation of genetic and environmental determinates, and linkages to other conditions.

Students will have the unique opportunity to work in a state of the art research facility with a close-knit team of multidisciplinary professionals who are dedicated to achieving the translation of research outcomes into clinical practice. The ESC also has strong collaborative links with European and American centres which include scientist exchange programs.

**Molecular and Cellular Otolaryngology**

**Title:** Role of β-actin in apoptosis  
**Supervisors:** Dr Rob Marano, W/Prof Marcus Atlas  
**Contact details:** rob.marano@earscience.org.au (9346 7956)

**Project Outline:** It has been found that β-actin is downregulated immediately after a stress stimulus. It has also been suggested that β-actin is responsible for transporting apoptotic signals into the cell thus beginning the cascade ultimately leading to cell death. This project aims to research this hypothesis using several cell types and stress stimuli.

**Title:** Evaluation of Silk compounds and structures in the development of a bioscaffold for grafting chronic TM perforations  
**Supervisors:** Dr Rob Marano, W/Prof Marcus Atlas  
**Contact details:** rob.marano@earscience.org.au (9346 7956)

**Project Outline:** Chronic perforations of the tympanic membrane are a global problem with current grafting materials providing less that ideal hearing outcomes. The use of a synthetically produced graft will reduce surgical times and costs. Silk has been identified as a suitable graft material and this project centres on evaluating the optimal structural chemical characteristics that facilitates cell growth and migration. The outcomes of this research provide an essential link to an eventual clinical product.

**Information and Computer Science**

**Title:** Validation of a clinical decision support system for otology  
**Supervisors:** Adj Prof Rob Eikelboom, Prof Peter Friedland, W/Prof Marcus Atlas  
**Contact details:** rob.eikelboom@uwa.edu.au (6380 4900)

**Project Outline:** Expert systems are designed to enhance the interaction between clinicians and patients, improve the diagnostic process by reducing errors, and reducing paperwork. A prototype system developed at ESC for ear and hearing disorders is ready for extensive validation. A detailed clinical history will be taken from the patient using the expert system, and its findings compared to those of ear specialists.
Title: Validation of telehealth for nose, throat and head & neck disorders  
Supervisors: Adj Prof Rob Eikelboom, Prof Peter Friedland  
Contact details: rob.eikelboom@uwa.edu.au  (6380 4900); peter.friedland@uwa.edu.au  
Project Outline: This project will require the validation of devices and protocols for nose, throat and head & neck cancer telehealth. The diagnoses and recommendations made by telehealth will be compared to those made by a face-to-face consultation. The quality of instruments, as well as live and stored images will be assessed. This project will build on the successful development and implementation of an ear telehealth system at ESC.

Title: Mobile devices in outpatients’ clinics  
Supervisors: Adj Prof Rob Eikelboom, Prof Peter Friedland  
Contact details: rob.eikelboom@uwa.edu.au  (6380 4900); peter.friedland@uwa.edu.au  
Project Outline: Mobile devices offer new opportunities to gather data. This project aims to use a mobile device to capture clinical survey data from patients whilst they are waiting in outpatients’ clinics. The project will explore if the use of validated surveys and algorithms will enhance the interaction between patients and clinicians and what efficiencies can be gained.

Clinical Outcomes
Giving hearing to those who have never heard, or returning hearing to those who have lost it, is now possible with a range of implantable devices including cochlear implants, middle ear implants and other devices. These can greatly enhance the patient’s quality of life. The ESC researchers are involved in the advancement of these devices and the development of rehabilitation techniques that must accompany these implants following surgery. The research groups are part of worldwide research programs. The fellowship programs attract clinicians and researchers from around the globe. The focus is on medical devices and prostheses, middle ear mechanics, and quality of life for patients with chronic ear disease, Meniere’s, semi-circular canal dehiscence, cochlear implants, and acoustic neuroma.

Epidemiology of Hearing Loss and Ear disease
ESC is involved in the Busselton Healthy Ageing Study (BHAS), and the Raine Study, two epidemiology projects that is exploring the genetic and environmental influences on health. ESC is focusing on the linkages to age- and noise-related hearing loss, common ear diseases, Meniere’s disease, tinnitus and balance problems.
Projects are available in all of these areas.

Title: The epidemiology of dizziness and related disorders  
Supervisors: Adj Prof Rob Eikelboom, Prof Peter Friedland, W/Prof Marcus Atlas  
Contact details: rob.eikelboom@uwa.edu.au  (6380 4900); peter.friedland@uwa.edu.au  
Project Outline: The epidemiology of dizziness and the types of dizziness in the Australian population is largely unknown. The prevalence of Meniere’s disease is also unknown. Data from 800 to 1000 people per year will be available for analysis. Further testing of those reporting dizziness is available to determine a diagnosis. Linkages to other health related measures will also be conducted.

Title: The epidemiology of hearing loss  
Supervisors: Adj Prof Rob Eikelboom, Prof Peter Friedland, W/Prof Marcus Atlas  
Contact details: rob.eikelboom@uwa.edu.au  (6380 4900); peter.friedland@uwa.edu.au  
Project Outline: There is limited data on the prevalence of the various types of hearing loss in Australia. The BHAS focuses on baby boomers and the Raine Study on young adults. All participants undertake a large range of audiological tests. This project will characterise the types and nature of hearing loss, and explore associations with other health measures. In young adults there will be a focus on exposure to noise, and the detection of early signs of hearing loss.

Scholarships for students are available from various sources. For more information, see the Centre and Institute websites: www.surgery.uwa.edu.au/research/ear and www.earscience.org.au
Neurosurgery

Professor Christopher Lind 9346 2865 christopher.lind@health.wa.gov.au

The Role of Posterior Subthalamic Region in Eye Movement Control

The Surgical NeuroDiscovery Group provides the statewide deep brain stimulation surgery service at Sir Charles Gairdner Hospital. We are pioneering a special technique for inserting deep brain stimulation (DBS) electrodes in our neurosurgical patients that enables very accurate localisation of their position in the human brain. Using this technique we are halfway through a phase I/II clinical trial of posterior subthalamic surgery centred on the caudal zona incerta for Parkinson's disease and essential tremor. Animal studies in the literature indicate that this part of the brain may have connections with eye movement centres. Alongside our clinical trial we are probing the physiological function of this brain region in human eye movement control which has never been done before. In recent experiments we have found previously undiscovered effects on saccadic eye movements which now need to be further explored. Here is your opportunity to join an academic neurosurgery team studying the physiology and clinical effects of an exciting new target for deep brain stimulation in 2011. I will teach you about patients with movement disorders and how this brain surgery is done and you will discover the function of the human zona incerta.

Orthopaedics & Related Biomedical Research

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Disciplines of Research:
- Pathology of Bone, Cartilage and tendon
- Matrix induced autologous chondrocytes implantation
- Bone allograft and related clinical and laboratory research
- Tendon tissue engineering
- Molecular mechanism of bone resorption
- Intracellular vesicle trafficking of osteoclast
- Intracellular signaling of osteoclast

Matrix-induced Autologous Chondrocyte Transplantation

Articular cartilage defects of the knee occur commonly in sports injury and trauma, often affecting the young. From 1993 to 1997, over 210,000 knee arthroscopies were performed on patients below the age of 55 in Australia. At least 5% have full thickness cartilage defects. In an unfavourable location these may progress and lead to early degeneration of the joint. End stage osteoarthritis of the knee is commonly treated by total arthroplasty, but this causes problems in the younger age group, including limited life span, loosening, fracture and infection. Autologous chondrocyte transplantation may limit the progression of such chondral defects and the need for further surgical procedures.

Despite interest generated by the promising early results of autologous chondrocyte transplantation, there has not been a randomized clinical trial comparing outcomes with that of current treatments of chondral defects. Additionally, no non-invasive morphological assessment of repair or objective measures of functional outcome has been made. Thus the project will focus on:

1. Comparing the outcomes of autologous chondrocyte transplantation and the currently used treatment of debridement and abrasion arthroplasty.
2. Non-invasive morphological assessment of healing of chondral defects via magnetic resonance imaging.
3. Assessment of objective and subjective outcomes of MACI.
4. Investigating the durability of repair tissue and the need for further reconstructive procedures.

The research team have developed several methods for the induction of tendon repair and regeneration. These include:

1. **Autologous Tenocyte Implantation (ATI):** This process involvesregenerating a patient’s tendon cells to assist in the treatment of torn or damaged tendons common in shoulder, ankle and elbow injuries. The proposed clinical application of the ATI process will incorporate a same-day surgical procedure whereby a small piece of tendon tissue is removed from the patient and the cells are then cultured over a period of weeks to amplify them to a level suitable for reimplantation.
2. **Matrix Augmented Autologous Tenocyte Therapy (MATT):** The second part of the MATT solution involves the use of a novel collagen based scaffold which delivers the patient’s tendon cells and also provides the optimal environment for cellular augmentation - in effect providing a surface for the tendon cells to continue to proliferate and exhibit the characteristics of the regenerating tissue. The scaffold also provides mechanical strength that mimics the tendon it is designed to augment or replace, thus providing the optimal cellular delivery system for high demand augmentation in areas such as the rotator cuff, Achilles, patella and quadriceps tendons.

The current research projects on tendon repair and regeneration include a Phase I clinical trial of ATI, the pre-clinical development of ATI and the molecular characterization of mice which have the phenotype of tendon degeneration.

**Collagen scaffold and tissue regeneration**

Scaffolds are widely regarded as an integral component for tissue regeneration in reconstructive medicine, supporting cell infiltration, proliferation and subsequent differentiation in response to signalling molecules and mechanical stimulation. Amongst the plethora of synthetic, biological and composite scaffolds in production, collagen-based bioscaffolds have emerged as favoured vehicles of choice because of their versatility, biocompatibility and ability to promote cell growth whilst maintaining the mechanical strength required for an “ideal” tissue engineered construct. A number of collagen-derived biomaterials are currently available, largely developed for matrix-induced and assisted bone, cartilage and tendon tissue regeneration. To address this market gap, we have developed a next-generation collagen-based scaffold to support tissue growth and repair using our patented cellgrowTM technology. We believe that this scaffold device is superior to other existing collagen products and offers widespread therapeutic and commercial potential with particular emphasis on orthopaedic and reconstructive applications, such as tendon augmentation and abdominal wall defect repair. The major goal of this proposal is therefore to translate this patent platform technology into a commercially viable product with potential far-reaching clinical applications using OrthoCell Ltd as a delivery platform. This approach will undoubtedly demonstrate the proof-of-principle necessary to translate this patented technology into bona fide clinical and commercial outcomes.

**The molecular biology of osteoclast**

Osteoporotic fractures in the elderly are often linked to increased mortality rates. Excess bone resorption is a major contributor to the onset of the disease. The proposed project focuses on the investigation of molecular mechanism of acid secretion that is required for the bone degradation in body. The vacuolar-ATPase proton pump (V-ATPase), located on the bone-apposed ruffled border (RB) membrane of osteoclasts (OCs), is an established prerequisite for proton secretion and subsequent OC bone resorption. In search of OC-specific configuration of the V-ATPase complex, we have identified two hitherto uncharacterized but inter-related subunits of the V-ATPase V0 domain, namely e1 (ATP6V0e1) and e2 (ATP6V0e2). Using bioluminescence resonance energy transfer and co-immunoprecipitation assays we will attempt to examine and map out the interaction of e1 and e2 with the V-ATPase V0 complex. To fully unravel the mechanism behind e1 and e2 in osteoclastic function, we will generate e1 and e2 OC-specific (CathepsinK-Cre) cKO mice. The bone phenotype of these mice will be analysed using state of art image facilities and BMM extracted will be subjected to in vitro testing for OC differentiation, bone resorption and/or V-ATPase function defects. We will study the subcellular distribution of e1 and e2 in resting and polarized OCs to determine whether there is preferential targeting of the e1 or e2 specific V-ATPase complexes to the RB for bone resorption. It is anticipated that this proposal will provide us with important new insights into the assembly and structural configuration of the osteoclastic V-ATPase complex thereby enabling us to identify key structural determinants to be targeted for selective inhibition.

**Associate Professor Nathan Pavlos** 9346 2083 nathan.pavlos@uwa.edu.au
**Dr Taksum Cheng** 9346 2083 taksum.cheng@uwa.edu.au

**Molecular Mechanisms of Bone Resorption**

Osteoclasts are large multinucleated giant cells whose exclusive function is the physiological dissolution (resorption) of bone. Excessive osteoclast numbers and/or activity are a major pathological hallmark of a number of highly debilitating orthopaedic-related diseases including osteoporosis, osteoarthritis and tumour-mediated bone destruction. During their differentiation into functionally mature cells, osteoclasts acquire a set of specialised machinery which bestows them with the unique capacity to resorb bone. We have long been interested in deciphering the identity and nature of the molecular machinery that underlie bone resorption function in osteoclasts. To achieve this we have utilised quantitative proteomic-based approaches to identify novel candidates regulating osteoclast formation and function with a key focus on the molecular machinery governing intracellular vesicle trafficking and the molecular structure of proton-pumping v-H+ATPase complex. Methods used for the investigation include in vitro cultivation of osteoclasts from monocyte/macrophages, bone resorption pit assays, confocal microscopy, micro CT assessment, histomophometry and loss of function studies by gene silencing and gene knock-out models.
Otolaryngology, Head & Neck Surgery Unit

Professor Gunesh Rajan 9431 2144 gunesh.rajan@health.wa.gov.au
Clin Professor Harvey Coates
Clin Professor Francis Lannigan
Clin Assoc Professor Shyan Vijaysasekaran
Clin Senior Lecturer Stephen Rodrigues
Clin Senior Lecturer Alexander Ring
Clin Lecturer Jay Krishnaswamy

The Otolaryngology, Head & Neck Surgery Unit represents all subspecialties of academic Otolaryngology in WA. As an Interhospital Unit its members work at all teaching hospitals in WA. The Unit integrates the busiest Head & Neck Cancer Unit with the busiest otology, paediatric otolaryngology and skull base unit in the State. The Otology Section of the Unit is one of the leading hearing implant centres in the world. This underscores its role as a centre of excellence in the area of hearing restoration and hearing implant work. The Paediatric Section of the Unit (based at PMH) is the busiest in Australia and has evolved into a benchmark centre with regard to paediatric airway management, Aboriginal ear health and neonatal hearing screening. The different sections of the Unit focus on various research areas. The FH & RPH sections run research projects in the areas of stapes surgery, skull base surgery, hearing implants, head & neck imaging and head & neck cancer prevention. The Paediatric section investigates the various aspects of pathogenesis of Otitis media, the health economics of Aboriginal ear disease and the outcomes research in paediatric airway interventions for malformations and OSAS.

Current projects:
1. Otitis media & biofilms
2. Outcomes research after paediatric airway interventions for malformations or OSAS
3. Aboriginal Ear Health
4. Telesurgery
5. Hair cell research
6. Cochlear implant & middle ear implant research
7. Head & Neck Imaging (DWI, PET)
8. Head & Neck Cancer QOL & Outcomes research
9. Stapes surgery and middle ear mechanics
10. Skull base surgery techniques

Students interested in undertaking a research project in Otolaryngology, Head & Neck Surgery are encouraged and very much welcome to contact our administrative officer Alison Wallace (alison.wallace@uwa.edu.au; p: 08 94312500) for further information.

Wound Healing and Occupational Performance Research Group

Winthrop Professor Michael Stacey 9431 2500 michael.stacey@uwa.edu.au

Wound Healing and Vascular Surgery

The focus of our research is the investigation of the risk factors that are associated with the development and reoccurrence of chronic wounds in humans and their impaired wound healing. The two main areas of research include chronic wounds in individuals with venous disease and sitting acquired pressure ulcers following spinal cord injury.

This research team is a supportive interdisciplinary team that includes vascular surgery, nursing, occupational therapy, biomedical engineering and mechanical engineering. There are state, national and international linkages and collaborations.

Venous Disease

We have an interest in venous leg ulceration, a chronic wound that occurs most often in the elderly due to venous hypertension in the lower limb (venous disease). Susceptibility to ulceration in patients with venous disease varies. Our unit integrates basic and clinical research into the clinical and diagnostic services provided for patients with chronic leg wounds at Fremantle Hospital. Students have an opportunity to interact with patients in a clinical setting, as well as gaining a sound grounding in laboratory research techniques. The emergence of new techniques in both cellular and molecular biology now makes it possible to use the available small tissue samples obtained from humans to understand the pathogenesis of ulceration in more detail.
Sitting Acquired Pressure Ulcers

Winthrop Professor Stacey is the lead investigator on a multisite international (Australia and Canada) prospective study to identify intrinsic and extrinsic factors associated with the development of sitting-acquired pressure ulcers following spinal cord injury. The aim of the study is to develop a risk assessment tool that will identify high risk individuals for developing a sitting-acquired pressure ulcer within the first 3 years following spinal cord injury (acute stage) and after ten years following spinal cord injury (chronic stage). Students who have an interest in biomechanics, psychosocial aspects of chronic health conditions, core data sets and epidemiology would be suited for research in this tranche.

Summary of current areas of research include:

- Genetic epidemiology of venous leg ulceration and sitting acquired pressure ulcers following spinal cord injury
- Investigation of the relationship between gene polymorphisms and molecular phenotype of chronic wounds (venous leg ulcers and pressure ulcers following spinal cord injury)
- Prevention of sitting acquired pressure ulcers following spinal cord injury
- Finite element modelling of the buttocks following spinal cord injury
- High frequency ultrasound quantification of oedema, ultrasound quantification of soft tissue deformation following spinal cord
- Randomised controlled trials of new wound treatments and new pressure ulcer prevention self-management programs.
- Development of self-management programs for prevention of chronic wounds

SCHOOL OF PSYCHIATRY AND CLINICAL NEUROSCIENCES

Head of School:
Winthrop Professor Aleksandar Janca 9224 0293 email: aleksandar.janca@uwa.edu.au
http://www.psychiatry.uwa.edu.au/

The School is spread across six major teaching hospital sites in Perth and incorporates four academic units and two research centres. It also serves as a WHO Collaborating Centre and has close links with the World Psychiatric Association and a number of leading academic departments and universities in Australia and worldwide. The School staff members are internationally renowned for their research in the areas of diagnosis, assessment, epidemiology, genetics and treatment of mental disorders including schizophrenia, dementia, somatoform, anxiety and substance use disorders. Our School has well-structured and organised undergraduate and postgraduate teaching and training programs in psychiatry and related disciplines. A number of our School staff members are actively involved in the policy development and provision of highly specialised clinical care to people suffering from mental illness.

Winthrop Professor Aleksandar Janca 9224 0293 email: aleksandar.janca@uwa.edu.au

Epidemiological, social and transcultural psychiatry

Over the years, Professor Janca has been coordinating a number of WHO international research projects in the areas of psychiatric epidemiology, transcultural psychiatry, diagnosis, assessment and classification of mental disorders and public health aspects of mental and neurological disorders. His current research has a specific focus on development of novel concepts and instruments suitable for use in the above-mentioned areas. Other research interests include somatic expression of emotional distress across cultures and settings and Indigenous mental health.

Professor Sean D Hood 9346 2393 email: sean.hood@uwa.edu.au

Professor Hood has a variety of planned projects relating an international research collaboration linking autonomic panic, hypertension and serotonergic systems.
He has a strong history of supervising medical student research and BMedSc students.
Alcohol and Illicit Drug Use and Related Morbidity
Professor Hulse has worked in the area of problem alcohol and drug use for the past 24 years. For the past twelve years, he has held an academic appointment as ‘Co-ordinator of Alcohol and Drug Education and Training’ within the Faculty of Medicine, Dentistry & Health Sciences, and heads the Unit for Research and Education of Drugs and Alcohol within the School of Psychiatry and Clinical Neurosciences.

Research is directed at developing evidence-based information which will enhance clinical practice. Research includes:

- Treatment of Substance Abuse (major focus on heroin, alcohol and benzodiazepine abuse).
- Use of new sustained release pharmacotherapies (i.e. Flumazenil, naltrexone, buprenorphine) in treatment of substance abuse (including heroin, alcohol, benzodiazepines, tobacco).
- Epidemiology of morbidity and mortality associated with substance use.
- Co psychiatric morbidity, criminal behaviour associated with alcohol and other drugs use and their management.
- Genetics of Addiction and Treatment Outcomes.

Genes in Psychiatric Disorders
(In collaboration with A/Prof Sibylle G Schwab, Laboratory for Neuropsychiatric Genetics, WAIMR)
Our research interest is focusing on identification of genes conferring risk to schizophrenia and to heroin dependence.

- There is replicated evidence for linkage in large family samples with schizophrenia on chromosome 6p and 10p. We have obtained evidence for association of the two candidate genes dysbindin on chromosome 6p and a gene for a phosphatidylinositol phosphate kinase on chromosome 10p. This research will be directed towards identification of DNA variants as well as their possible functional implication.
- In collaboration with the Department of Psychiatry, University of Jakarta Indonesia, we have collected 152 families from Indonesia for linkage studies in schizophrenia. A genome wide linkage scan revealed evidence for a gene locus on chromosome 3. We are currently analysing this area for presence of schizophrenia susceptibility genes by association studies. For these studies we have ascertained in the area of Jakarta, Indonesia, a sample of 1105 individuals with schizophrenia and 1136 non-psychiatric controls.
- In collaboration with Prof. Gary Hulse we have collected a sample of more than 900 individuals with heroin dependence for genome-wide association studies with DNA sequence variants.
Winthrop Professor Osvaldo P Almeida 9224 2720 email: Osvaldo.Almeida@uwa.edu.au

Old Age Psychiatry
Professor Almeida’s research program focuses on the identification of modifiable risk factors for cognitive decline, dementia and depression. In addition, he runs a number of intervention studies (trials) designed to improve the health outcomes of older people.

Winthrop Professor S Starkstein 9431 2013 email: Sergio.Starkstein@uwa.edu.au

Professor Starkstein is primarily interested in brain mechanisms underlying emotion, behaviour, and cognition. His research includes neuroimaging studies in patients with dementia, stroke, Parkinson’s disease, and traumatic brain injury, neuropsychology, psychiatric phenomenology, and philosophy of mind.

Professor Mohan Isaac 9433 0322 email: Mohan.Isaac@uwa.edu.au

Dr Isaac has been involved in organization of mental health services in resource poor settings and training of primary health care personnel in basics of mental health care, in developing countries for over two decades. His current research interests consist of community mental health, public health aspects of psychiatric disorders including suicides and primary care mental health.

Associate Professor Andrew Ford 9224 2753 email: Andrew.Ford@uwa.edu.au

Professor Helen Slattery 9346 1424 email: Helen.Slattery@uwa.edu.au

SCHOOL OF WOMEN’S AND INFANTS’ HEALTH

Head of School:
Professor John Newnham 9340 1220 Email: john.newnham@uwa.edu.au

www: http://www.swih.uwa.edu.au

The School of Women’s & Infants’ Health (SWIH) is based at King Edward Memorial Hospital for Women, a hospital which delivers 6000 women per year, is the only tertiary obstetric centre in WA and the largest NICU in Australia. SWIH has extensive laboratory based research at KEMH and also an extensive animal research program at UWA in the Large Animal Facility (Crawley Campus) and at Shenton Park. The School also has a close affiliation with the Women and Infants Research Foundation which is co-located on the KEMH campus.

SWIH has a wide range of research opportunities including clinical research, laboratory research and animal research within areas such as:

OBSTETRICS – Preterm birth, Maternal-Fetal Medicine, Intrapartum Care, Fetal therapy, Placental function, Drugs in pregnancy

GYNAECOLOGY – PCOS, Menopause, HRT

NEONATAL MEDICINE – Ventilation

In addition to the funding opportunities available for all BMSc students, the SWIH has a number of internal scholarships available for students undertaking clinical research within the school. Because fresh research fields continually emerge interested students should make a point of contacting the School. Students should contact the School’s Administrative Officer on 9340 1220 to make an appointment.

Professor John Newnham 9340 1220 Email: john.newnham@uwa.edu.au

Head of School.
Prevention of preterm birth: The fetal origins of adult disease; fetal medicine and surgery.
Research before and soon after birth is one of the most fertile areas in which a medical researcher may work. Not only do findings at early times in life have the greatest impact on humans in terms of life-long health, the introduction of new measurement systems now allow investigations which previously were not possible. Two of the most fertile fields are prevention of preterm birth and discovering how the fetus is programmed for later health or disease. The School of Women’s and Infants’ Health runs a range of research programs aimed at preventing major diseases by steps taken before birth. Areas of investigation encompass clinical, population, laboratory and animal studies. The School is fully equipped to apply expertise from most fields to the quest of discovering the mysteries of life before birth. If you wish to be a pioneer in this rapidly growing area of science, join our team.

Professor Karen Simmer 9340 1262 Email: karen.simmer@uwa.edu.au

Neonatal Intensive Care; Lactation and Infant Nutrition; and Factors Involved in Infant Growth and Development.
**Associate Professor Roger Hart**  9340 1322  Email: roger.hart@uwa.edu.au  
Fertility; Reproductive Endocrinology; Polycystic Ovarian Syndrome

**Associate Professor Jan Dickinson**  9340 1324  Email: jan.dickinson@uwa.edu.au  
Fetal Medicine; Fetal Surgery; Twin-Twin Transfusion Syndrome.

**Clinical Associate Professor Barry Walters**  9382 1097  Email: barry.walters@uwa.edu.au  

**Professor Jeff Keelan**  9340 1880  Email: jeff.keelan@uwa.edu.au  
Principle Research Fellow and Laboratory Head  
Placental development, function and infection: roles in pregnancy disorders

**Project: Nanoparticle drug delivery in pregnancy**

Placental disorders are frequently involved in common pregnancy complications such as preterm birth and intrauterine growth restriction, yet no placental-specific medications are available. As a transport organ bathed in maternal blood, the placenta offers a unique target for nanoparticle drug delivery. The placental membrane has the ability to endocytose particles of a variety of sizes, but the characteristics that determine uptake and passage of nanoparticles across the human placenta have not yet been determined. In this project, fluorescent nanoparticles with a variety of surface modifications will be evaluated for their ability to deliver drugs to placental cells in culture. A range of drugs will be tested, combined with fluorescence microscopy to visualise nanoparticle uptake and penetration. The results of this project will help the design of drug delivery systems based on functionalised nanoparticles able to selectively deliver therapeutic drugs to the placenta to address placental defects in pregnancy.

**Professor Jane Pillow, Dr Yong Song**  9340 1257  Email: jane.pillow@uwa.edu.au  
Respiratory physiology of infants, and ventilation strategies

**Neonatal Ventilation Projects**

This group is part of a large and long standing international collaboration which has used an ovine model to investigate aspects of fetal lung maturation and ventilation. We have made a major contribution to the published literature regarding the impact of antenatal steroids on the developing fetus, and have also developed a unique model of chorioamnionitis (inflammation of the placental membranes) to investigate the effect of infection/inflammation associated with preterm delivery on the structure and function of the preterm lung. The group has also investigated the impact of different ventilatory and resuscitation techniques on injury in the preterm lung.

In 2012, the projects described below will be suitable for a Bachelor of Medical Science or Honours project: Additionally, Prof Pillow (a consultant neonatologist) also performs lung function and ventilation studies in newborn infants. Students interested in undertaking studies in ventilated and spontaneously breathing newborn infants should contact Professor Pillow to discuss possible options.

**Project 1: Mitochondrial alteration in preterm diaphragm exposed to inflammation**

Antenatal exposure to inflammation may cause a diaphragm weakness and compromise successful establishment of spontaneous breathing in preterm infants. Reactive oxygen species (ROS) may play an important role in initiating and regulating the pathological process of diaphragm dysfunction, particularly in the preterm subject which has limited antioxidant defences. As a major pathway of ROS products, the function and ultrastructure of the mitochondria from preterm lamb diaphragms exposed to lipopolysaccharide (LPS – a potent inflammatory stimulus) at different gestational ages. The study will involved using electron microscopy to examine microstructure of cellular mitochondria, performing enzyme activities to determine mitochondrial function, employing molecular techniques to quantify antioxidant gene/protein expression and oxidant proteins. The students enrolled in this study will be provided course training for using electron microscopy. The animal work has been completed and tissue samples are ready to analyse.
Project 2: Molecular mechanisms of preterm diaphragm weakness during exposure to inflammation

Antenatal exposure to inflammation may predispose the preterm infants into diaphragm dysfunction, leading to failed establishment of spontaneous breathing. Based on studies of adult subjects, it is known that underlying mechanisms during the pathological process are associated with accelerated proteolysis in concomitance with decreased activity of protein synthesis. How such dysfunction is triggered and regulated in antenatal exposure to inflammation is largely unknown. Recently we establish various molecular assays to study the pathways of protein degradation and protein synthesis, and have completed a baseline study of these molecular pathways in naive preterm respiratory muscle from different gestational stages. The current study is the extension of our research projects, further looking into the aberrant pathways under disease conditions using well established molecular techniques. The animal work has been completed and tissue samples are ready to analyse.

Associate Professor Craig Pennell 9340 1326 email: craig.pennell@uwa.edu.au

(not available in 2012)

Research interests include: 1) genomic and proteomic research with an emphasis on the prediction and prevention of preterm birth; 2) gene-environment interactions underlying preterm birth and the developmental origins of health and disease; 3) the prediction and prevention of adverse outcomes after labour; and 4) fetal medicine and fetal therapy.

Our research team is involved in a number of local and international collaborative research studies focusing on prediction and prevention of preterm labour using molecular genetic approaches and gene-environment interaction studies underlying preterm labour and the developmental origins of health and disease. Further, we offer a number of clinical research projects directly related to obstetric care and fetal medicine. Our research in these fields is continually evolving and interested students can contact Dr Craig Pennell to discuss specific projects for each academic year.

Dr Matt Kemp 6488-7970 email: mkemp@meddent.uwa.edu.au

Research Fellow

Research interests include: 1) Enhancing our understanding of the mechanisms underlying preterm birth; 2) development of novel therapies for the prevention of preterm birth; 3) the developmental origins of health and disease; and 4) intermediate filament biology of the fetal lung.

We operate within a large, internationally collaborative research team and have a number of exciting ongoing projects. Students are welcome to contact Dr Kemp to discuss research opportunities for the forthcoming academic year.

Dr Helen Atkinson 9340 1288 email: Helen.Atkinson@uwa.edu.au

Endometrial blood flow and vascularity during long-term progestin only contraceptive (LTPOC) use.
The Western Australian Institute for Medical Research (WAIMR) is Western Australia's premier adult medical research institute, investigating the genetic and environmental causes of a range of diseases. Our researchers have made, and continue to make, a number of internationally-important discoveries with the potential to deliver better health to the global community.

Our research can be broadly categorized into the following areas:

- **Cancer**: WAIMR’s approach to the broad area of cancer research is to identify specific genetic defects in cancer/leukaemia cells, as well as environmental factors which cause cancer.
- **Molecular Genetics**: This group conducts research in a variety of fields tied together by the fact that they are looking at the structure and function of genes at a molecular levels.
- **Molecular Endocrinology**: This group focuses on the action of hormones at the cellular and molecular levels.
- **Diabetes**: This research is aimed at understanding and preventing diabetes and its complications, with a particular focus on the genetics of type 1 diabetes.
- **Emergency Medicine**: The CCREM is a new collaboration between RPH, WAIMR and UWA Emergency Medicine. It manages a range of bedside and clinically-oriented laboratory research projects both locally and nationally involving a number of hospitals.
- **Epidemiology Group**: This group studies the causes and patterns of cancer and other chronic diseases in human populations.
- **Iron Metabolism and Liver Disease**: The main research focus of our group is to investigate the role of iron in the aetiology of a variety of diseases predominantly that affecting the liver such as hereditary haemochromatosis, fatty liver disease and Hepatitis C. Other research interests include evaluating the effects of iron on breast and colon cancer with relevance to haemochromatosis.
- **Ageing** (WA Centre for Health and Ageing (WACHA)): This Centre is dedicated to issues associated with ageing and is made up of scientists investigating common conditions including dementia, falls, depression and immobility.

Currently, WAIMR is situated at two locations – the Perth Campus is located at the Medical Research Foundation Building of Royal Perth Hospital, while the Nedlands Campus is at B Block, Queen Elizabeth II Medical Centre.

Some potential BMedSci projects are detailed below but please contact any of the staff listed for further advice on other areas of research and potential projects.

**LABORATORY FOR CANCER MEDICINE**

**Leukemia and Blood Disorders**

**Professor Peter Klinken**  
9224 0334  email: pklinken@waimr.uwa.edu.au

**Supervisor:**  
**Dr Louise Winteringham**  
9224.0326  email: louisew@waimr.uwa.edu.au

**Location:** CMR/WAIMR Perth Campus, MRF Building, Level 6, Rear 50 Murray St, Perth

The aim of the Leukemia Research Group is to understand the process of blood cell differentiation from stem cells. Our research focuses on the identification and characterisation of genes that regulate the development of mature blood cells. We are also interested in how leukemia develops when normal blood cell maturation is perturbed. This laboratory has identified two novel genes involved in the control of blood cell production, which are also implicated in the development of leukemia.

**HLS5/TRIM35** is a novel member of the RBCC family of molecules, which includes a number of genes involved in cancer/leukaemia. We have shown that HLS5 is a key regulator of GATA-1, a molecule required for the development of red blood cells. Microarray data have demonstrated that HLS5 influences expression of genes in several important signalling pathways involved in immune regulation and blood cell maturation. Recently HLS5 has also been shown to interact with several members of the SMAD family involved in TGF signalling.
Myeloid Leukemia factor 1 (MLF1) was identified as a gene that caused some forms of acute leukemia. We have identified a number of novel interacting proteins and genes that are regulated by Mlf1; many of these molecules are important in stem cell self-renewal and differentiation. We know that Mlf1 is involved in the developmental of the blood system, and data from transgenic and knockout mice indicates Mlf1 regulates development of mature blood cells from stem cells.

Projects currently available

**Characterisation of Hls5 knockdown on the development of haemopoiesis.**
*(Honours/PhD. Supervisors: L Winteringham, P Klinken)*

This project will investigate the loss of Hls5 both in vitro using shRNA and in vivo. Conditional Hls5 knockout mice are currently being developed. Initially, these studies will focus on the blood cell compartment. In conjunction, knock down of Hls5 in vitro will be undertaken using lentiviral infection of shRNAs. Specifically, this project will:

1. Determine the effect of HLS5 depletion on the differentiation of blood cells in vitro.
2. Investigate the development of blood cells in Hls5 knockout mice.
3. Identify specific pathways that are affected by Hls5 depletion that might contribute to the development of leukemia or other cancers.

**Investigating the role of Mlf1 in the development of early blood cells**
*(Honours/PhD. Supervisors: L Winteringham, P Klinken)*

We have established knockout and transgenic models of Mlf1 expression to investigate the role of Mlf1 in the development of blood cells. Preliminary data indicate that Mlf1 does indeed affect the ability of stem cells to form mature blood cells, and if over-expressed in immature red blood cells, Mlf1 inhibits the expression of genes required for red cell differentiation. Specifically, the aims of this project are to:

1. Characterise the stem cell compartment of Mlf1 knockout and transgenic mice under normal physiologic conditions and under stress.
2. Identify critical pathways regulated by Mlf1 that contribute to normal blood production, as well as the development of leukemia/cancer.

**Investigate the role of paraspeckles in blood cell development.**
*(Honours. Supervisors: L Winteringham, A Fox)*

Paraspeckle-mediated gene regulation plays a critical role in blood cell production. As stem cells differentiate into different blood cell types, the number and physical characteristics of paraspeckles change within the population. This suggests that paraspeckles are playing a role in regulating gene expression in blood cells. The specific aims of this project are to:

1. Investigate changes in paraspeckles in different models of blood cell production.
2. Determine the effect of knocking down paraspeckles in different blood systems.
3. Using the most optimal model system identified in aims 1 and 2, to isolate paraspeckles. Purify the RNA associated with paraspeckles and identify by next generation sequencing.

**Characterise the HLS5 – SMAD interaction in TGFβ signalling in Melanoma.**
*(Honours/PhD. Supervisors: L Winteringham, P Klinken)*

The development and progression of Melanoma involves complex changes in a number of regulatory signalling pathways including the TGFβ pathway. We have recently demonstrated that Hls5 is up-regulated in Melanoma cells where it interacts with a number of molecules (SMAD1, 3 and 4) responsible for the transduction of the TGF signal into the cell nucleus. The aims of this project are to:

1. Characterise the effect of down regulating Hls5, using shRNA, on various TGFβ associated cellular outcomes including proliferation invasion/migration, cell death, colony forming ability and response to exogenous TGFβ.
2. Use an RNA interference (RNAi) based genome-wide screen to identify novel molecules and pathways that contribute to this effect.
1. Defining role of SLIRP and other novel nuclear hormone receptor coregulators in cancer and metabolism (with Dr Shane Colley)

Hormones, acting through nuclear receptors (NRs), play critical roles in the development of human cancer and the control of body homeostasis and metabolism. The discovery of nuclear NRs that selectively modify NR activity has transformed our understanding of hormone action. We have recently identified several novel NR coregulators that regulate a range of NR signaling pathways. These molecules include SLIRP, a NR repressor of estrogen action in breast cancer. SLIRP also represses PPAR signaling, and its expression in fat and muscle suggests an important role in energy and metabolism.

We have generated a SLIRP knock out mouse which is providing added resources for interesting projects. There are many exciting questions regarding the function of these proteins in cancer, as well as fat and muscle cells. Available projects involve studies on the biology of SLIRP as a regulator of hormone signaling in cancer, muscle, fat and the pancreas, and its functional role as a regulator of body homeostasis and metabolism (diabetes). Additional projects include understanding the functional biology of some of the other coregulators in the metabolism of microRNA processing, regulators of hormone action, and investigating the intersection between miRNA biology and NR signaling.

2. The functional role of miRNAs in human disease (with Dr Keith Giles)

The identification of small RNAs (RNAi, microRNAs (miRs)) is transforming our understanding of the regulation of gene expression. In particular, miRNAs have been shown to be aberrantly expressed in a range of human diseases, including cancer. Furthermore, altering the level of a miRNA within a cell is a powerful way to regulate gene expression of target proteins. We have recently identified miRNAs that target key growth factor receptors that are responsible for the proliferation of several different human cancers. Transfection of cells with the miRNAs dramatically reduces the growth factor receptor expression and can lead to cell cycle arrest and cell death. Moreover, the miRNA may coordinately regulate several other genes with the same miRNA target sequence, suggesting a very well orchestrated system in which the miRNA targets downstream members of the same signaling pathway. We now are addressing the role of these miRNAs in a range of human cancers (lung, breast, glioma, head and neck, prostate, pancreas), and in normal tissues in which they are highly expressed. Available projects involve studies to understand how these miRNAs function, identification of other targets in cells within cancer and endocrine paradigms and studies to examine the therapeutic potential of these miRNAs.

General Background:

Each of these projects has a background of signaling in cancer and normal tissues, and involves a large number of molecular and cellular biological techniques, including functional analyses with siRNA and DNA, as well as miRNA microarrays, next generation sequencing and ChIP-seq. The laboratory also has components focussing on a translational focus using human tissue microarrays to provide direct clinical relevance to specific aspects of the work.

The laboratory has excellent infrastructure and several senior scientists, PhD students and research assistants who provide help and guidance in all aspects of the work.
1) **Making small proteins to kill cancer and leukaemia cells.** We have identified a new molecular pathway (Cbp-Csk-SOCS1) that normally down-regulates Src family tyrosine kinases in cancer and leukaemia cells (*J.Biol.Chem* 2006, 281: 31920-9). We have identified the functional components of the pathway and this project aims to combine them into a single novel small protein. The chimeric protein will be purified and tested for its ability to down-regulate Src family kinases, and potentially kill or inhibit the growth of different cancer and leukaemia cells.

2) **A Novel pathway controlling cell shape and movement.** We have identified a new molecule, LACM (Lyn Associated Cytoskeletal Modulator) that directs Lyn tyrosine kinase signals to the cytoskeleton via Nck2 and Vav2, changing the shape of cells and their ability to migrate in response to growth factors. This project will explore this novel pathway in different cancer/leukaemia cells and its implications for human cancer development, in particular on metastasis.

3) **A Novel pathway controlling nuclear:cytoplasmic shuttling.** We have identified the novel molecule Liar as an important nuclear:cytoplasmic (N:C) shuttling protein that interacts with signalling molecules and moves them in and out of the nucleus in response to growth factors (*Blood* 2009, 113:3845-56). The movement of Liar in and out of the nucleus is also regulated by its phosphorylation. This project will explore the pathways that Liar controls in cancer/leukaemia cells.

4) **A proteome-wide analysis of the mammalian SH2-interactome.** We have developed a novel phopho-tyrosine-specific yeast system that can identify SH2 domain-specific interactions. This project will look at using our system to identify the specific interacting partners of some of the 120 SH2 domains of the human genome in view to eventually identify the partners of all of the SH2 domains within a larger project. Specific SH2 domain probes, as fluorescent protein fusions, will also be developed in the project to use as tools to study SH2 signalling in cancer/leukaemia cells.

**Background:** Both receptor and non-receptor protein tyrosine kinases are essential enzymes in cellular signalling processes regulating cell growth, differentiation, migration and metabolism. Considerable evidence implicates tyrosine kinases in the development of many types of cancer and leukaemia via their involvement in numerous growth factor signalling cascades. Members of the Src family of tyrosine kinases are signalling intermediates that can control aspects of these processes. These molecules were originally identified as viral oncogenes and are potent carcinogens in animal models. The level and/or activity of these kinases are often elevated in human tumours. Recent advances in the development of small molecule inhibitors of tyrosine kinases (eg Imatinib mesylate) have resulted in great success in treating particular leukaemias and cancers.
Liver Diseases and Carcinogenesis

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Location:  Biochemistry and Molecular Biology, University of Western Australia

Liver Laboratory

Our research group focuses on the biology of the liver progenitor cell (LPC) called an "oval cell" which describes its shape. We envisage an enormous potential for this cell as the vehicle for cell and gene therapy to treat liver disease. We contend it is superior to other cell types such as the hepatocyte and the embryonic (ESC) or adult stem cell (ASC) for many reasons. In particular, it is robust and simple to freeze and store, then thaw and grow by in vitro culture when required. It can be differentiated into either hepatocytes or cholangiocytes (bile duct cells) quite easily and rapidly when maintained under appropriate conditions, therefore it is more versatile than the hepatocyte. Most importantly, the LPC is developmentally close to the hepatocyte and the cholangiocyte in contrast to the ESC or ASC, which will require many more steps and much coaxing to produce useful cells for liver therapy. Our long-term vision is to hasten the day when human LPCs are utilised to treat liver disease, especially end-stage liver disease for which currently organ transplant is the only solution. A realistic expectation in the short term is to use LPCs to "bridge" patients thereby extending their survival and enhances their probability of finding a suitable organ donor. A more ambitious and longer-term aim is to use these cells to circumvent the requirement for organ transplant. This may be possible with some liver diseases.

To utilise LPCs we must identify and understand the action of growth factors and cytokines, which influence them. To accomplish this, we have characterised the pattern of cytokine expression in two mouse model of liver disease that induces the appearance of LPCs. These studies indicate that inflammatory cells and cytokines they produce namely IL6, TNF alpha, Interferon alpha and gamma and lymphotoxin beta are LPC regulators. To understand their mechanism of action we are testing these on primary cultures of LPCs and LPC lines. This knowledge can be used to increase their contribution to liver regeneration in vivo which can lead to positive outcomes for liver disease patients. Both in vivo and in vitro extended growth of LPCs results in transformation to cancer; in this context hepatocellular carcinoma Recent developments in our laboratory which underpin the projects on offer are:

1. Isolation and characterisation of LPCs from human fetal liver
2. Establishment of LPCs from a transgenic mouse which expresses beta-galactosidase when it becomes a hepatocyte and LPCs which express EGFP which facilitates cell tracing.
3. Acquisition of the Cellscreen instrument which allows for progressive, accurate, high throughput and comparative growth characteristic of multiple cell cultures.
4. Identification of gene expression pattern differences between normal and transformed LPCs as a result of expression profiling.

Accordingly research projects will exploit these new developments for they are designed to increase our understanding of LPCs and establish their utility for treating liver disease.

**GENERATING FUNCTIONAL LIVER CELLS FROM LPC**

Assessing the ability of LPCs to metabolise drugs

Drug metabolism is a key function of liver cells that enables us to detoxify chemicals, particularly toxins.Therefore it is important to know the capabilities of our LPCs under various conditions of culture, when they are growing and when they have been differentiated into hepatocytes. Then we will know what are the appropriate culture conditions for producing the best LPCs for transplant, for use in drug toxicity testing and also in extrnal liver assist devices (bioartificial liver). The principal enzymes which metabolise drugs are the cytochrome p450 family of enzymes. There are many forms which deal with different types of chemicals. Of special interest is there are forms which are specific to embryonic liver and others which are only present in adult liver. The aims of this project are:  

i) to establish the pattern of expression of fetal and adult forms of cytochrome p450 in LPCs during growth and following differentiation 

ii) the assess the ability of metabolites to induce appropriate cytochrome p450 enzyme(s) 

iii) the drug metabolising capacity of LPCs with regard to a model compound 7-benzyloxyquinoline 

Experiments will first utilise mouse LPCs and knowledge gained will be applied to human LPC cell lines
Assessing the growth and function of LPCs in a bioartificial scaffold

Tissue engineering is based on the principle that cells grown in a three-dimensional scaffold perform better than those grown as a monolayer. Preliminary experiments suggest that this is true for LPCs as the reporter gene beta-galactosidase which converts x-gal into a blue stain is highly active when LPCs are grown in scaffolds (Fig.1) compared to monolayer cultures. A range of scaffolds will be tested and the growth of LPCs and expression of beta-galactosidase will be used to assess hepatocytic function. The latter will be correlated with the expression of hepatocyte specific genes as well as functional capacity of the generated cells in terms of urea synthesis and drug metabolism. This work has now reached a phase where we are growing the cells so they form a lawn of cells and the scaffold can be loaded into a chamber which acts as an artificial liver device. This is then assessed for its ability to perform liver functions.

WHAT MAKES LPC’s BECOME CANCEROUS?

Comparing tumorigenic and non-tumorigenic LPCs

LPC lines have been established from p53 -/- as well as +/+ mice. Some grow in soft agar and produce tumours when injected subcutaneously into nude mice; some do not. We are defining the differences between these cell lines at the molecular and cellular level to identify features which are causative and those which are consequential in terms of cancer. Specifically we are documenting chromosomal changes and focusing on oncogene candidates raised by gene profiling. Two anti-apoptotic genes IAP and Yap are prime suspects and their expression at the mRNA level (through qPCR) and protein level (by Western Blot) are being be defined for a range of cell lines and during tumorigenesis during culture. Current studies follow changes in LPCs as they are passaged and progressively become tumorigenic. We are also documenting changes in expression of p53 and the level of its activity by measuring the expression of downstream genes such as p21. We are also testing the effects of culture conditions on tumorigenesis. In particular, we will determine whether the level of oxygen and the composition of the culture medium with respect to growth factors contribute to transformation.

Angiogenesis and Tumor Immunology

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Background:

We have previously identified the molecule Regulator of G protein Signalling-5 (RGS5) as a marker for active vessel remodelling during neovascularisation. We then generated RGS5-deficient mice to show that RGS5 is a key regulator of tumour angiogenesis, a study published in the journal Nature. Our subsequent finding that RGS5 also regulates blood pressure suggests a far more extensive role for RGS5 in vascular biology. RGS molecules negatively regulate G protein coupled receptor (GPCR) signalling. RGS5 is part of a larger family of RGS molecules; their biological role in vivo is only emerging but they are already recognized as attractive targets for drug development. Current literature points to a crucial role for RGS2, RGS4 and RGS5 (our own data) for vascular function.
Honours and PhD projects:

1) **Role of RGS5 in blood vessel maturation and functionality:**
   (Honours/PhD. Supervisors: R Ganss)
   In the course of this project mural cell lines will be generated with overexpression or deletion of RGS5 and mutant proteins. These cells will be co-cultured with endothelial cells and assessed in *in vitro* migration assays. Blood vessel formation will be analysed in *in vivo* angiogenesis assays by transplanting cell mixtures in solidified substrate subcutaneously into immune deficient mice. Establishment of a functional vascular network will be assessed using quantitative assays and immunohistochemistry.

2) **Assess vSMC biology and activity in RGS2 and RGS5 double-deficient and RGS5 mutant vSMC**
   (Honours/PhD. Supervisors: M Manzur, R Ganss)
   We have successfully established RGS5-deficient primary vSMC cells which will give us a unique opportunity to study the implications of a combined gene loss of RGS2 and RGS5 on cardiovascular activity. This project will (i) knockdown RGS2 expression in RGS5-deficient primary vSMC (RGS5/-) using small interfering RNA (siRNA) and (ii) generate "gain-of-function" cell lines by overexpressing RGS2 and 5 in RGS5/- cells. These modified cells will be subsequently analyzed for gene and protein expression and biological changes in adhesion, migration and extracellular matrix composition, all within the context of cardiovascular signalling. This project is highly topical and an ideal opportunity to gain expert training in a wide variety of essential laboratory techniques including molecular biology, tissue culture, quantitative PCR and western blotting.

1) **Role of RGS5 in atherosclerosis:**
   (Honours/PhD. Supervisors: J Burchell, R Ganss)
   This project focuses on the role of RGS5 as negative modulator of vSMC phenotypic switching during atherogenesis. Using a unique double gene knock-out model (RGS5 knockout mice crossed with ApoE knockout mice, a mouse strain prone to develop atherosclerosis under high fat diet) we will establish (i) when during progressive arterial disease RGS5 expression is lost, (ii) how RGS5 loss affects mechanical properties of arteries, and (iii) whether RGS5 loss increases atherosclerotic lesion frequency. The project will analyze vessels and atherosclerotic plaques from already established mouse colonies using quantitative PCR and a variety of histological methods (e.g., immunohistochemistry for ECM molecules, staining for plaques).

**Selected reading:**


*Please also see information on: [http://www.waimr.uwa.edu.au/team/rganss.html](http://www.waimr.uwa.edu.au/team/rganss.html)*
When the Human genome was sequenced, it sent shockwaves through the scientific community when it was revealed that our DNA only contains about 22,000 protein-coding genes; the same number as simple worms, only ten times as many as bacteria, and fewer than rice. The big question was how does this relatively small number of genes account for all of the differences that we like to think makes us more complex than these simple organisms? Importantly, how do these genes account for our complex genetic disorders and cancers? Critically, it is the decisions about which gene will be made (‘expressed’) into protein where and when in development, that is the basis of our complexity. The control of gene expression is thus fundamental to all cellular processes and many diseases such as cancer and metabolic disorders are associated with some aspect of aberrant gene expression.

Transcription of DNA into RNA, the first major step in gene expression, takes place in the cell nucleus. The nucleus is not simply a bag of DNA, in fact, many important nuclear factors are organised into sub-nuclear ‘bodies’. Our lab works on one such body, the ‘paraspeckle’ (Figure 1) and we use it as a model system for learning more about the control of gene expression in the nucleus and how this relates to aberrant gene expression in cancer.

An emerging and exciting research area is the role of noncoding RNAs in controlling gene expression. ‘Noncoding’ RNAs are molecules that are functional as RNAs, and do not encode for proteins. Paraspeckles are the first sub-nuclear structure known to form around a long noncoding RNA (IncRNA), making them an important model system within IncRNA research. This is particularly relevant when it comes to cancer, as several IncRNA have been shown to act as molecular scaffolds, recruiting proteins to form oncogenic complexes that drastically alter gene expression leading to metastasis and ultimately poorer outcome for patients.

Nobel prize winner Tom Cech, a leader in RNA biology, is quoted in Nature Methods 8, 379 (2011) article on long noncoding RNA: "What we need are multiple examples that can be taken down to the structural and mechanistic level so that we have the same sort of understanding as we do for transcription and RNA splicing and translation and other cellular processes. Until we drill down to that level, we don't have much understanding.” We are in an enviable position to tackle this challenging, broadly significant question as we are one of the few groups in the world currently working on an experimentally tractable group of proteins with a known IncRNA target.

**Student projects:**

*Scope will vary depending on Honours or Phd*

1. **Structure of the paraspeckle interactome**
   co-supervisors: Dr. Sven Hennig (WAIMR) and Prof. Charles Bond (BBCS, UWA)

Paraspeckles contain a number of different proteins that are either (1) responsible for paraspeckle formation (2) required for paraspeckle function, or (3) are regulated by sequestration within paraspeckles. In collaboration with Prof Charles Bond, we have recently solved the 3D structure of a heterodimer of two paraspeckle proteins (see figure 2). In an effort to determine the roles of the other known paraspeckle proteins in paraspeckle formation and function, we undertaking a large-scale interactome analysis of paraspeckle components.

In this project you will investigate a number of interactions between paraspeckle protein components, including PSP2/CoAA. You will map the domains in each protein responsible for interaction with other paraspeckle proteins, and also determine the domains responsible for paraspeckle targeting of each protein, using the techniques of cell culture, molecular biology, microscopy, Immunoprecipitation and protein-protein interaction assays. You will move on to the expression in bacteria of recombinant proteins for eventual structural analysis. In many cases you will use sophisticated expression strategies such as co-expression of interacting proteins, in an effort to stabilise interaction partners, leading to large-scale protein production.

This project will provide important building blocks for understanding how nuclear proteins together build up a IncRNA-structure, and how their sequestration affects function.
2. How are DBHS proteins targeted to the cell surface in cancer?

The DBHS (Drosophila Behaviour/Human Splicing) proteins are abundant and ubiquitous proteins that are important in many nuclear functions such as DNA repair, splicing, transcriptional regulation and in forming paraspeckles.

Recently, our collaborators have found a therapeutic antibody that detects DBHS proteins on the cell surface specifically in cancer cells. This raises important questions: Why do cancer cells target these proteins to the cell surface? How is the protein targeted there? What are the proteins doing at the cell surface?

In this project you will seek to identify the mechanisms that cancer cells are using to target these proteins to the cell surface. Our hypothesis is that a change in post-translational modification is occurring that then leads to a change in protein localisation. To test this hypothesis you will use cell culture, subcellular fractionation, immuno-precipitation, proteomics, FACS and molecular biology techniques. This project will yield important insights into the nature of this new anti-cancer therapeutic target.

3. Molecular Mechanisms of the nuclear retention of RNA

Paraspeckles are implicated in controlling gene expression by retaining certain mRNA molecules within the nucleus, thereby preventing their translation in the cytoplasm. We have been investigating the molecular components of this process. Further, we recently identified a novel IncRNA that is localised to paraspeckles that may be subject to nuclear retention – but why would it be regulated in this way if it were never intended to be translated?

In this project you will investigate molecules known to be important for nuclear retention and will examine how these proteins intersect with paraspeckle biology. You will use cell culture, molecular biology and microscopy to examine the localisation of these proteins and domains that map to paraspeckles. In addition, you will investigate the novel IncRNA targeted to paraspeckles using molecular biology, Fluorescent in situ hybridisation, RT-qPCR, cell culture, and RNA interference assays. These insights will dramatically improve our understanding of the process of RNA nuclear retention – and as a consequence could explain complex gene expression patterns.

4. DLX3 – A transcription factor in the spotlight

Primary supervisor: Dr. Sven Hennig, co-supervisors Dr. Archa Fox and Prof. Charles Bond

DLX3 (distal-less-homeobox protein 3) is a homebox containing transcription factor that functions in processes such as skin and bone development. Two patient mutations downstream of the DNA binding homebox cause a frasmsulting in a shorter protein and severe developmental diseases like TDO (tricho-dento-osseus) or AIHHT (amelogenesis imperfecta hypomaturation-hypoplastic type with taurodontism). As these mutations are autosomal dominant genetic diseases, the patient cells still express the wild type protein.

This leads to the idea to develop drugs to “silence” specifically the mutated DLX3 protein within the cell.

In this project you will express and purify the DLX3 protein as wild type, TDO and AIHHT mutants. You will then move towards crystallisation studies to produce atomic structures of the transcription factor in mutated (disease-causing) form to guide future drug design and assays. From these you will learn where the structural differences in the individual proteins are and identify drugable sites within the C-termini. If time permits, follow-up studies could include confirming these sites by introducing mutations on those surfaces to restore the wild type function. You will prove this in vitro by analytical gel filtration, gel shift assays (EMSA) and luciferase assays. Additionally you will underline the effects of the identified hot spots within the mutant proteins by comparing their function within a cell using a tissue culture model looking at the endogenous levels of DLX3 driven genes by qPCR and western blotting.

This work will provide detailed insights into the structure and function of DLX3 and its mutants, providing substantial data for the identification of suitable drugs.
Background:
Mitochondria are essential for the normal function and survival of all eukaryotic cells. Given their central role in providing energy for cells it is not surprising that mitochondrial dysfunction is involved in neurodegenerative disorders, diabetes, and cancer. Despite their importance the regulation of gene expression in mammalian mitochondria remains poorly understood. We investigate RNA-binding proteins that regulate the stability, expression and translation of mitochondrial genes. As well as unraveling the mysteries of mitochondrial biology we are interested in the development of gene therapy approaches and therapeutics to combat mitochondrial dysfunction in disease.

Projects:
1. Mitochondrial RNA-binding proteins and their role in mitochondrial gene expression.
2. Development of gene therapy approaches for neurodegenerative diseases caused by mitochondrial dysfunction.
3. Development of tools to study mitochondrial function.

These projects involve the use of a range of techniques in cell biology (such as cell culture, cell death assays, fluorescence microscopy, gel electrophoresis, western blotting), genomics (RNA-Seq and PARE), molecular biology (cloning, quantitative PCR, RNA interference) and biochemistry (protein purification, enzyme activity measurements).

Selected publications from the lab:
Synthetic Biology and Drug Discovery

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Background:
One of the key aims of synthetic biology is to engineer artificial processes inside living cells. This requires components that interact in a predictable manner, both with each other and with existing cellular systems. However, the activity of many components is constrained by their interactions with other cellular molecules and often their roles in maintaining cell health. To escape this limitation, we pursue an "orthogonal" approach, building a parallel metabolism within the cell. Components of this parallel metabolism can be sourced from evolutionarily distant species or reengineered from existing cellular molecules by using rational design and directed evolution. These approaches allow us to study basic principles in cell biology and to engineer cells that can function as environmental sensors, simple computers, and drug factories.

PhD projects:
1. Re-engineering the genetic code of cells.
3. Development and production of new drugs by re-engineering cell metabolism.

These projects involve the use of techniques in molecular biology (such as mutagenesis, directed evolution, DNA microarrays, quantitative PCR) and cell biology (yeast, bacterial and mammalian cell culture, cell death assays, fluorescence microscopy, western blotting).

LABORATORY FOR NEUROMUSCULAR DISEASE

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Location: Molecular Neurogenetics Laboratory, CMR/WAIMR, Nedlands Campus, B Block, QEII Medical Centre

Our Laboratory investigates the genetic causes of neurological, neuromuscular and muscle diseases using a range of traditional and cutting edge techniques. We have been involved in world-first breakthroughs in the identification of disease-causing genes and mutations over the past 23 years. Furthermore, we have a number of animal models of muscle diseases and are investigating the pathophysiological mechanisms in these models and also potential therapies.

Human disease gene identification has included:
- familial amyotrophic lateral sclerosis (ALS; motor neurone disease) caused by mutations in the Cu/Zn superoxide dismutase gene (SOD1) - 1993
- autosomal dominant nemaline myopathy due to mutations in the slow alpha tropomyosin gene (TPM3) - 1995
- recessive nemaline myopathy due to nebulin mutations (NEB) – 1999
- actin myopathy, autosomal dominant and recessive nemaline myopathy and intranuclear rod myopathy due to mutations in skeletal muscle alpha-actin (ACTA1) – 1999
- core-rod disease due to the ryanodine receptor gene (RYR1) – 2000
- craniometaphyseal dysplasia due to ANKH – 2001
- congenital fibre type disproportion due to ACTA1 – 2004
- early onset (Laing) distal myopathy due to slow skeletal/beta cardiac myosin (MYH7) – 2004
- autosomal recessive nemaline myopathy due to skeletal muscle specific cofilin (CFL2) – 2007
- cap disease due to beta-tropomyosin (TPM2) – 2007
- hereditary spastic paraplegia (CYP7B1) – 2008
- congenital fibre type disproportion due to slow alpha-tropomyosin (TPM3) – 2008.
- Rod-core disease due to mutations in KBTBD13 – 2010
- Filamin distal myopathy due to mutations in muscle-specific filamin (FLNC) - 2011

Our gene discovery work has helped innumerable families around the world with accurate diagnosis of their disease and the possibility of preimplantation, prenatal or presymptomatic diagnosis where this is warranted.
We always have new gene discovery projects running, in collaboration with clinicians and pathologists from around the world. In particular we have a strong link with the diagnostic Neurogenetic Laboratory and Neurogenetic Unit at Royal Perth Hospital headed by Clinical Associate Professor Phillipa Lamont, from both of which undiagnosed patients and families feed into gene discovery projects in the research laboratory. We are currently using Next Generation Sequencing technology in collaboration with the LotteryWest State Biomedical Facility Genomics node at Royal Perth Hospital in gene discovery projects in dominant and recessive ataxia, familial motor neuron disease, recessive Charcot-Marie-Tooth disease, recessive limb girdle muscular dystrophy and foetal akinesia.

In addition to gene discovery, our laboratory has been investigating the pathobiology of diseases whose genes we have identified, with the ultimate aim in each case being the development of treatments. Knowing the genetic cause of a disease is crucial for understanding how the defective gene and either absent or mutant protein leads to the disease. It is also essential for being able to attempt a logical therapeutic approach for patients.

Therefore for the past decade or so we have expanded our research interests into protein studies, producing wild-type and mutant proteins relevant to the diseases we have studied and then performing various biochemical analyses with them, either here in WA or in conjunction with leading researchers around the world. Additionally, we have conducted tissue culture experiments expressing wild-type and mutant proteins in various cell lines, usually incorporating a fluorescent tag to easily visualise the protein of interest. This has allowed us to determine the localisation of the mutant proteins in cells in vitro and the interaction they might have with other proteins, and to develop cell culture models of human diseases.

Lastly, we have a number of mouse models of some of the diseases we have been researching and these provide unique opportunities to better investigate the onset, progression, tissue involvement and possible treatment of diseases. We have been able to compare muscle biopsies from the mouse models with those from human patients.

Most recently we have been researching a possible therapy for the skeletal muscle actin (ACTA1) diseases. Reactivation or upregulation of alternative genes has been shown to be therapeutic for various diseases and disease models. Good candidates for such approaches are fetal isoforms from the same protein family as the defective or absent protein. We have been investigating using the actin gene for the heart (which is also the fetal actin in skeletal muscle) as a possible therapeutic route and have achieved promising results with mouse studies. We are now working to develop methods of upregulating cardiac actin in postnatal skeletal muscle in human patients by conducting a drug screen and other approaches.

Examples of techniques used in our Laboratory or in conjunction with local collaborators

Molecular genetics (PCR, sequencing, mutation detection, cloning etc); SNP array analysis, next generation sequencing data analysis, RNA extraction and analysis; recombinant protein production (bacterial, insect and mammalian cells); protein purification and subsequent biochemistry, mass spectrometry; western blotting; histology and immunohistochemistry; flow cytometry; fluorescent, confocal and electron microscopy; tissue culture (primary and stable cell lines); muscle physiology; aspects of mouse model behavioural analysis.

Projects for 2012

There are multiple possibilities for Honours and especially PhD projects in our Laboratory. We always endeavour to tailor projects to the student’s interests and the skills and techniques they would like to learn. Therefore, if you are interested in our field of research we encourage you to contact us so we can discuss various potential project ideas. In the past we have had students with a background in molecular biology, genetics, physiology, pharmacology, biotechnology, pathology, medical science and biochemistry complete projects with us. Any new student would form part of a strong team working in our Laboratory.

Specific projects include:

1. Next generation sequencing and candidate gene analysis in genetic disorders including:
   a. Muscle diseases
   b. peripheral nerve disease
   c. excessive muscle growth syndromes
   d. dysmorphology syndromes
2. Animal – mouse and ovine models of muscle disease
3. Tissue culture models of muscle diseases
Honours project available for 2011 – Discovery of novel gene in primary congenital glaucoma.

**Background:** We are the world’s leading team investigating the genetics of an interesting founder population – the Gypsies – their origins, current population structure and hereditary disorders. Over the years, this research has led to the discovery of a broad range of new diseases and their genetic causes. This project deals with primary congenital glaucoma (PCG), an eye disorder with onset in the first 3 years of life, which manifests with greatly increased intraocular pressure, clouding of the cornea and progressive optic nerve degeneration. Despite available medical and surgical treatments, PCG is a serious cause of early blindness worldwide. Characterisation of the underlying aetiology and pathogenesis of PCG is an important research focus, which will allow prevention and adequate disease management. PCG is genetically heterogeneous with mutations in two known genes, *CYP1B1* and *LTBP2* accounting for only a proportion of PCG cases. Additional, novel PCG genes remain to be discovered.

In the Gypsy population, a small number of founders and subsequent endogamy have resulted in limited genetic diversity and a small number of mutations inherited from common ancestors explaining many autosomal recessive disorders. So far, we have identified the disease-causing mutations in two thirds of our PCG patients. To discover the new gene(s) contributing to the disease in the remaining patients, we are using a new technology that has revolutionized genetics in recent years - whole-genome massively parallel sequencing. This analysis will identify novel rare sequence variants with potential functional impact, that are shared between affected subjects.

**Aims**

This honours project will aim at investigating further the candidate genes and mutations identified by the whole genome sequencing and confirm or refute their role in causing the disease. This will be done by analysing other family members and checking familial segregation of the interesting variants, screening of healthy controls, and searching for mutations in PCG patients from other ethnic groups.

**Significance**

The study will identify novel molecular mechanisms contributing to PCG, and thus facilitate the development of better approaches to treatment and management of a devastating childhood disorder. In addition, genes involved in childhood glaucoma may contribute to the aetiology of the common types of glaucoma that develop later in life and affect millions of people world-wide.

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**Medical Genetics**

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Location: School of Pathology & Laboratory Medicine, QEII Medical Centre

**Improved understanding of the neuronal functional deficiencies associated with Rett syndrome and autism**

**Research Focus**

The clinical and biological overlap between Rett syndrome, autism and molecular defects involving expression of the *MECP2* gene. The aim is to gather sufficient insight into the disturbed neurobiology contributing to the occurrence of Rett syndrome and related disorders to permit identification and evaluation of therapeutic interventions that may ameliorate or reverse the clinical consequences of these disorders.

**Major Breakthroughs**

MeCP2 is well known for its role as a methyl binding protein, linking methylation signals on DNA changes to histone tail modifications that have an important epigenetic influence. More recently, the group has discovered that the MeCP2 protein has a stabilizing role in microtubule dynamics and that MeCP2 deficiency is associated with impaired microtubule stability and delayed reassembly. These novel findings point to several small molecules that have the potential to ameliorate the dire clinical consequences of MeCP2 deficiency.
Diabetes imposes an increasing problem in our society. Recognizing this, the Centre for Diabetes Research (CDR) has been established recently at WAIMR and UWA. The Centre is directed by Prof Grant Morahan, who is also on the Steering Committee of the international Type 1 Diabetes Genetics Consortium. The focus of the CDR’s research program is in identifying genes which cause susceptibility to diabetes (type 1 and type 2) and its complications. We examine genetics in both mouse models and in humans. The Centre is also undertaking programs in stem cell research and in immunology.

This is the “golden age” in human molecular genetics. The Human Genome project has provided unprecedented insights and tools to accelerate genetics research. One of the great challenges for geneticists is now understanding complex genetic diseases. Diabetes and many other common human disorders are complex genetic traits, caused by variations in multiple genes rather than any single gene, and the interactions between such genes and the environment. Our approach is to map genes that contribute to disease in experimental models and then to confirm the relevance of our findings in humans by performing genetic analyses in human populations. After confirmation, we can dissect further the underlying mechanisms by returning to our mouse models. Projects available in our laboratory relate to both Type 1 and type 2 diabetes and “metabolic syndrome”, a key symptom of which is insulin resistance.

Project Titles:

a) Identification and analysis of human Type 1 diabetes (T1D) susceptibility genes.

By analysis of DNA from families of children with T1D, we have mapped a number of diabetes susceptibility genes. We are now concentrating on two of these which appear to be linked on the same chromosome. This project will involve identifying and testing markers in candidate genes in the region of highest linkage. Techniques involved include PCR, sequencing, and application of sophisticated genetic linkage methods.

b) Identification of mouse T1D genes.

We have strains of mice that differ in a small genetic region and which differ in rates of both diabetes susceptibility and insulin resistance (a feature shared by people at risk for either type 1 or type 2 diabetes). This project will involve testing candidate genes in this region to identify which one causes susceptibility. Techniques learnt could include both molecular genetic and physiological methods.

c) Testing genes in human Type 2 diabetes (T2D).

We have identified two different genes causing T2D related traits in mouse models. We now need to test whether the human counterparts of these genes affect the risk of developing T2D.

d) Molecular genetics of IL12B, a T1D susceptibility gene.

We found that IL12B affects T1D risk in the Australian population. It also affects risk and severity of a number of other important diseases, including asthma, malaria, and some cancers. This project will involve replacement by homologous recombination in stem cells of the mouse Il12b gene with each of the four human IL12B genes, and characterizing the way in which these genes are regulated and affect the immune system. The homologous recombination work will be done during a training period with our collaborators in Edinburgh.

e) Diabetic Kidney Disease.

Our laboratory developed a new mouse model for analysing genes that control the kidney’s response to increased blood glucose levels that result from diabetes. Diabetic kidney disease (nephropathy) is a major life-threatening complication arising from the increase in blood glucose concentrations caused by diabetes. This project involves the genetic analysis of approximately 600 mice derived from this mouse model of diabetic kidney disease for which the traits and phenotypes were measured. Each animal requires genetic typing at ~100 markers. Once the genotyping is complete, genome-wide scans (linkage analysis) will identify loci that contribute to diabetic nephropathy. These loci will be narrowed to identify the genes underlying each locus, at which time the genes can be functionally evaluated. Techniques used in this project include: PCR, genotyping, DNA sequencing, basic molecular biology, linkage analysis, bioinformatics, comparative genomics. This is an exciting project, because very few, if any, experiments have been conducted to investigate the genetic contributions to this catastrophic complication of diabetes and therefore, should yield novel findings with clinical relevance.

f) Systems genetics research.

This is a very sophisticated program looking to the next generation of genetics research, defining networks of interacting genes. This program would be suitable for someone wishing to undertake a career in bioinformatics, and will combine molecular biology techniques with extended microarray analyses.
g) Stem cell research.
We have a system for isolating mouse adult stem cells from different sources and differentiating them into insulin-producing beta cells. This project will involve optimizing these methods and defining the molecular events involved in beta cell development.

h) Involvement of genetic variants in melanoma susceptibility.
Together with colleagues in Germany and Queensland, we have found an association between particular genetic variants and melanoma survival. This work needs to be extended and confirmed in a larger cohort. Mechanisms of disease protection may also be characterized using transgenic mouse models. This work will involve a wide range of molecular genetic and immunological methods.

ISLET CELL DEVELOPMENT PROGRAM

**Associate Professor Fang-Xu Jiang** 9224 0388   email: jiang@waimr.uwa.edu.au
Location: CMR/WAIMR, Perth Campus, MRF Building, Level 6, 50 Murray St, Perth

The mission of the Islet Cell Development Program is to understand the proliferation, differentiation, self-renewal and regeneration of pancreatic insulin-secreting β-cell stem/progenitor cells, including the molecular mechanisms of these biological processes. The ultimate aim is to generate unlimited number of β cells in vitro or stimulate patient’s own progenitor/stem cells to become β cells in vivo to cure type 1 diabetes. We seek bright, motivated and committed students to take up several exciting projects described below.

1. **Identifying critical microRNAs that regulate differentiation of islet progenitor Ngn3+ into β cells.**
We have established novel technologies and a unique system to purify and differentiated islet progenitor Ngn3+ into β cells respectively. However, the underlined molecular mechanisms are largely unknown. As emerging critical regulators of cellular development and function, microRNAs, ~ 22 nt small RNAs, have attracted our attention. Co-supervised by Prof Peter Leedman, a leading expert in microRNA biology, you may become a pioneer in this promising topic in a few years.

2. **Investigating roles of novel transcription factors on development of pancreatic lineages.**
Proof of concept has demonstrated that embryonic stem cells can give rise to all lineages of cells in the body including β cells. However, the efficiency of current differentiation protocols is still very low. Mimicking the normal developmental process of the pancreas, we have developed protocols to differentiate effectively embryonic stem cells into pancreatic progenitors. Using microarray analysis, we have identified approximately 20 potentially novel transcription factor genes during this differentiation process. We seek a highly motivated PhD candidate to carry forward this project for focusing on a couple of them and investigating their roles for development of endocrine pancreas.

3. **Investigating roles of secreted frizzle related proteins on specification of pancreatic lineages**
Wnt signalling plays important roles in development and cancer. Secreted frizzle related proteins (sFRPs) are a family of regulatory molecules that antagonise Wnt proteins. In xenopus, one of sFRPs was shown to maintain foregut endoderm gene expression and allow pancreas development. Our pilot experiments indicated this family plays a conserved role in mouse pancreas progenitor development. Co-supervised by W/Prof Arunasalam Dharmarajan (School of Anatomy and Human Biology) who is a world-renown expert in sFRP biology, you will address this fundamental and exciting question using embryonic stem cells as a model and state-of-the-art technologies.

4. **Dissecting roles of a key basement membrane molecule on islet cell development and function**
Basement membrane is a thin layer between epithelial and mesenchymal tissues and plays critical signalling roles in development and function, in addition to supporting the epithelial tissue. Over a decade ago, we demonstrated that laminin 111, a major component in developing basement membrane, promotes mouse pancreatic progenitors to give rise to insulin-producing β cells. Other laboratories confirmed this role with human pancreatic cells. Our recent microarray analysis helped identify a candidate molecule among approximately forty for further investigation. You are expected to use conditional gene knockout and other state-of-the-art technologies to address this critical question.

Additional benefit to take up a PhD studentship in Islet Cell Development Program is that you are qualified to apply an Alex Cohen Diabetes Research Top-up Scholarship (up to 75% of your primary award).

If you are interested in any projects or require any further information, please call me at 9224 0388 or email me at jiang@waimr.uwa.edu.au.
LABORATORY FOR MOLECULAR ENDOCRINOLOGY – GPCRs

**Associate Professor Kevin Pfleger** 9346 1980 email: kpfleger@waimr.uwa.edu.au
Location: CMR/WAIMR, B Block, QEII Medical Centre

**Research Focus**
The Laboratory for Molecular Endocrinology – GPCRs studies a particular family of “receptors” on the surface of cells that mediate communication with other cells known as “G protein coupled receptors” (GPCRs). These receptors are extremely important in treating disease and are the target of about 50 per cent of all therapeutic drugs. Our current research focuses on cardiovascular disease, metabolic disorders, addiction, and disorders of the kidney. We are world leaders in studying interactions with GPCRs using bioluminescence resonance energy transfer (BRET), a proximity detection technology utilising natural bioluminescent and fluorescent properties of proteins found in sea pansies and jellyfish. We have published the seminal review and protocol of the technology in *Nature Methods* and *Nature Protocols* respectively. We are at the forefront of research on GPCR-GPCR interactions and work closely with our spin-out company Dimerix Bioscience to translate our research findings.

**Recent Major Breakthroughs**
- Seminal Review in *Nature Methods*.
- Seminal Commentary on the state of the field in *Nature Chemical Biology*.
- Validation of a new derivation of the BRET technology, termed eBRET (extended BRET) enabling detection of protein-protein interactions for prolonged periods in live cells, in real-time. This has been published in the journal *Cellular Signalling*.
- Demonstration of improvements to BRET so that it now has the potential to be used for drug discovery screening. This has been published in the *Journal of Biomolecular Screening*.
- Invention of a patented assay for detecting interactions between different GPCRs, known as GPCR-HIT (GPCR Heteromer Identification Technology). This is being commercialised via Dimerix Bioscience.

**Recent Research Highlights**
The laboratory has won a number of awards for its work, including A/Prof Pfleger being named Western Australian Young Scientist of the Year 2009, being listed in the National Health and Medical Research Council (NHMRC) Ten of the Best Research Projects 2010, and being awarded the 2011 Australian Museum Eureka Prize for Emerging Leader in Science. Our last honours student came top of the class and her honours research has been published in the high impact journal, *Molecular Endocrinology*.

**Research Funding**
We have research funding from the NHMRC, the Australian Research Council (ARC), the Raine Medical Research Foundation and Dimerix Bioscience Pty Ltd.

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LABORATORY FOR MOLECULAR ENDOCRINOLOGY

**Cell Growth**

**A/Professor Tom Ratajczak** 9346 2596 email: tomr@waimr.uwa.edu.au
Other Supervisor: **Dr Bryan Ward** 9346 2465 email: bryanw@cyllene.uwa.edu.au
Location: CMR/WAIMR, C Block, QEII Medical Centre

Our research program involves 3 different research areas – the mechanism of steroid hormone action with applications in breast and prostate cancer, the regulation of calcium homeostasis through the role of the calcium-sensing receptor (CaR) in parathyroid function and genetic studies in Paget’s disease of bone (PDB). Our laboratory is situated in the Department of Endocrinology & Diabetes, SCGH and the latter two areas of research are closely linked to the clinical care interests of endocrinologists in the Department, thus ensuring that students have strong clinical support for these studies. Our work is funded by the NHMRC and the SCGH Research Fund.
Honours projects

1. The influence of CyP40 and cyclosporin A (CsA) on the expression of estrogen receptor (ER)-regulated genes in MCF-7 breast cancer cells. Using Northern analysis we have previously shown that CsA is able to enhance estrogen-stimulated expression of the estrogen receptor-regulated gene, cathepsin D, in the MCF-7 cell line. The aim of this project is to use real-time PCR (RT-PCR) to examine the upregulating effect of CsA on cathepsin D expression in wild type MCF-7 cells and in cells depleted in CyP40 by siRNA and to extend the study to additional ER-regulated genes, including PR and GREB1. Our laboratory has developed an MCF-7 CyP40 tet-off stable cell line which overexpresses CyP40 in the absence of doxycycline. This cell line will allow us to test the effect of overexpressed CyP40 on the expression of ER-regulated genes, with and without CsA. Methods/techniques: 1) cloning of cathepsin D, PR, GREB1 and GAPDH into appropriate bacterial plasmids, 2) maintenance, treatment and RNA extraction of tissue culture cell lines, 3) siRNA methodology, 4) optimisation and running of RT-PCR, and 5) statistical analysis of results.

2. Steroid receptor- and tissue-specific actions of Hsp90 immunophilin cochaperones. This study will determine the effects on estrogen receptor beta (ERβ), progesterone receptor (PRA, PRB) and glucocorticoid receptor (GR) mediated responses of immunophilin loss in mouse embryo fibroblasts (MEFs) derived from FKBP51, FKBP52 and CyP40 knockout mice or immunophilin siRNA knockdown in human cancer cell lines from different tissues: HeLa - cervix; ECC-1 - endometrium; ZR-75-1 - breast. Methods/techniques: 1) tissue culture, 2) siRNA methodology, 3) Western blotting, 4) luciferase reporter assays to determine receptor transcriptional activity, 5) confocal microscopy to determine changes to receptor localization within the cell.

3. Sequestosome 1 gene mutations and arsenic in Paget's disease of bone (PDB). Mutations within the Sequestosome 1/p62 gene are a common predisposing factor for PDB. This project will test a long-held hypothesis that exposure to environmental arsenic is a causal factor in PDB and will investigate the impact on PDB of arsenic in combination with the wild type p62 gene, p62 containing the common P362L mutation and p62 with the novel P364S mutation associated with a mild Paget's phenotype. The project will utilize a packaging cell line (PA317) to allow retroviral transfection of p62 (shRNA, wild type or mutant) expression plasmids. Supernatants from these cells will be used to transfect human GM-CSF cells isolated from cord blood. The transfected cells will then be induced to form osteoclasts in the presence or absence of arsenic, with and without the TNFα cytokine, RANKL, to determine whether arsenic is able to potentiate the effect of p62 mutations. Osteoclast formation and resorptive activity will be assessed. Additionally, possible mechanisms behind arsenic-induced osteoclastogenesis, including osteoclast signalling pathways, will also be investigated. Techniques: 1) tissue culture, 2) cloning, 3) Western blots and lipid-based transfection, 4) Western blotting, 5) assays for osteoclast resorptive activity, 6) luciferase reporter assays.

Background to research studies in our laboratory

Mechanism of steroid hormone action: For optimal signalling steroid receptors need to be assembled with heat shock protein 90 (Hsp90) and mature steroid receptor-Hsp90 complexes contain one of four Hsp90-bound immunophilin cochaperones – two FK506-binding proteins, FKBP51 and FKBP52, cyclophilin 40 (CyP40) that binds the immunosuppressant cyclosporin A and PP5, a protein phosphatase with weak FK506-binding affinity. These immunophilins are associated with preferred receptors in steroid receptor-Hsp90 complexes to mediate distinct influences on receptor function. CyP40 predominates over other immunophilins in estrogen receptor (ER)-Hsp90 complexes from uterus, suggesting that CyP40 has a specific role in ER function in this tissue. The selective association of FKBP52 with androgen (AR), glucocorticoid (GR) and progesterone (PR) receptors promotes the receptors to a high affinity hormone binding state, enhancing receptor transcriptional activity in response to physiological hormone levels. This is mediated through direct contacts between FKBP52 and the receptor ligand-binding domain (LBD). Our laboratory is working to define the receptor- and tissue-specific actions of steroid receptor-associated immunophilins and to identify the contact domains for FKBP52 and CyP40 within the LBDs of AR and ER. We have generated a CyP40 knockout mouse to define CyP40 control over estrogen signalling and steroid hormone action generally, as well as its wider role in biological and physiological processes. Since there is evidence that aberrant expression of steroid receptor-associated immunophilins is linked to endocrine resistance and metastasis in breast cancer, we are profiling the expression of these cochaperones in breast cancer tissue microarrays to assess their potential as informative biomarkers for the disease. Hsp90 inhibitors cause the simultaneous depletion of Hsp90 client proteins, including key regulatory proteins such as AR and ER, which drive the growth of prostate and breast cancers, respectively. Our laboratory has achieved promising results with novel coumarin-based Hsp90 inhibitors causing the depletion of ER from breast cancer cells. microRNAs act as negative regulators of gene expression and have control over multiple biological processes linked to heart disease and cancer. Recent genetic studies have revealed that CyP40 promotes the activity of microRNAs in plants, and may chaperone Argonaute (AGO) or a protein that is critical for AGO function. In the mammalian system AGO2, which plays a key role in RNA silencing, co-precipitates with Hsp90, suggesting that AGO2 might be functionally dependent on Hsp90. This opens the door for potential influences of CyP40 on AGO function or AGO2-related processes following assembly of AGO2-Hsp90-CyP40 complexes.
CaR in parathyroid function: CaR is a bio-medically important cell-surface receptor that plays a pivotal role in various disorders of calcium homeostasis, with specific mutations in the receptor causing a number of disease syndromes and low levels of receptor expression in enlarged parathyroid tissue contributing to the severity of primary and secondary hyperparathyroidism. CaR is a member of the G protein-coupled receptor family, sharing the motif of seven membrane-spanning domains, and has a long 200-amino acid intracellular tail thought to modulate CaR signalling. In addition to providing a diagnostic service to identify gain- and loss-of-function CaR mutations in patients with disorders of calcium homeostasis, we have performed a yeast two-hybrid screen with the intracellular tail to identify accessory proteins that might be involved in CaR signalling. Among other interactors, the screen identified OS-9, an endoplasmic reticulum-associated protein with a putative role in protein trafficking. We are investigating the role of OS-9 in regulating CaR cellular processing and expression.

Genetic studies in Paget’s disease of bone: Paget’s disease of bone (PDB) is a chronic and progressive disorder affecting ~3% of elderly Caucasian populations and is characterised by focal lesions where an initial increase in bone resorption leads to excessive and disordered bone formation. The osteoclast is responsible for bone resorption and pagetic osteoclasts have excessive nuclei, increased resorptive capacity and are over-represented in affected bone. Positional cloning studies have shown that mutations in the sequestosome 1 (SQSTM1)/p62 gene are the cause of PDB linked to the 5q35 locus. PDB-causing mutations cluster within the C-terminal ubiquitin-associated (UBA) domain of SQSTM1/p62 and interfere with its role in attenuating activation of the NF-κB transcription factor in response to the RANKL during osteoclastogenesis. As part of our research program we have screened the C-terminal region of SQSTM1 for mutations associated with both sporadic and familial PDB. We have so far identified two novel mutations - K378X, a truncation mutation identified in a patient displaying extensive bone disease and P364S, associated with a mild Paget’s phenotype. A second major locus for PDB has been recently been identified on chromosome 10p13 and once the gene predisposing to PDB has been assigned, we will embark on a mutational analysis of our patient cohort that tested negative for SQSTM1/p62 gene mutations.

EPIDEMIOLOGY GROUP

Professor Lin Fritschi 9346 1061 email: fritschi@waimr.uwa.edu.au
Location: CMR/WAIMR, Nedlands Campus, B Block, QEII Medical Centre

The Epidemiology Group studies the causes and patterns of cancer and other chronic diseases in human populations.

A particular interest is occupational causes of cancer. We study people in particular occupations (particularly heavy industries such as the asbestos industry) and follow them to see if they are at increased risk of cancer. Other types of studies involve comparing the work histories of people with and without cancer. If a particular work exposure causes cancer, we expect to see more people in that job who have cancer than who don’t have cancer. We are or have undertaken studies of breast cancer, prostate cancer, colorectal cancer, non-Hodgkin lymphoma and childhood leukaemia and brain cancer. In order to improve the methods used in these types of studies we are developing new tools for assessing work histories using cutting-edge computer technologies (see www.occideas.org).

Migration has been important to the wealth and development of Australia. In the post war period up until the 1960s nearly six million European migrants arrived in Australia, largely to build Australia's manufacturing industries. From the 1970s restrictions were eased on non-European migration as migrants with increased skill and educational levels were sought. Australia is a nation of migrants and migrant workers will continue to feature as a significant group of the Australian workforce. Currently in Australia we know very little about them, but internationally we know that they are likely to work in the worst of jobs and suffer from more work-related accidents and injuries. We are undertaking research to study the working conditions of migrant workers. This information is vital in order to promote and maintain good health in these sub populations in the future.

There are endless possibilities for projects and students who are interested in cancer epidemiology, occupational epidemiology or working conditions for migrants are encouraged to contact Lin to discuss their ideas further.

Projects

There are endless possibilities for projects and students who are interested in cancer epidemiology, occupational epidemiology or working conditions for migrants are encouraged to contact Lin to discuss their ideas further.

Example questions that you could address in your BMedSc might be: Does exposure to diesel exhaust increase the risk of breast cancer? Are migrants from particular countries likely to have higher prevalences of exposure to carcinogens at work? Does breast density increase...
WACHA is one of the most productive health and ageing research centres in Australia. We are partnered with the WA Institute for Medical Research and the University of Western Australia and supported by the WA Department of Health. Our researchers collaborate extensively both nationally and internationally, giving our students an opportunity to share ideas with the world’s scientific leaders.

WACHA is committed to research training and has an extensive mentor training program that fosters scientific rigor and innovation. Our research covers the spectrum of health care for older adults. WACHA’s researchers have made a number of ‘firsts’ they include;

‘Firsts’ at WACHA: The first to demonstrated that smoking is not a protective factor (as was commonly believed), but a risk factor for dementia. The first to develop a culturally sensitive dementia assessing tool for remote and rural Indigenous communities. The first to provide evidence of the benefit of memory clinics in reducing stress for older people with dementia and their caregivers, leading to the adoption of state run memory clinics in Victoria and Western Australia. The first to conduct the largest study of residential care residents in Australia, that showed that vitamin D supplementation reduced residents rates of falls by 30%.

Below, we have outlined some of the projects that will be available to Honours students. If you have other novel research ideas that you wish to explore contact us at wacha@uwa.edu.au to arrange a meeting.

**Healthy Mental Ageing**

As people age they are more likely to suffer with effects of poor mental health. WACHA has shown that this is not inevitable and a lot can be done to prevent mental health problems and promote mental well being in older people. Two of the areas that you may wish to be involved are below.

**Depression** is a common and disabling illness, affecting 5-15% of adults older than 60 years at any one point in time. WACHA has demonstrated that lifestyle interacts with genetic factors to affect the risk of depression. Genetic and biochemical markers of cardiovascular disease, inflammation, cell death and glucose metabolism have already been shown to be important. We have been using this new knowledge to develop new approaches to manage depression in later life with the aim of decreasing the prevalence and incidence of depression amongst older Australians. We are currently running 3 projects in this area and have 2 new projects set up to start in 2009.

**Delaying Cognitive Decline** Cognitive function declines with increasing age, and as the World’s population ages cognitive impairment will affect an ever larger number of people in the community and will the major source of disability in Australia. WACHA has been running a series of projects designed to delay cognitive decline in later life. These projects have been investigating the role of hormones, antioxidants, vitamins, smoking, alcohol and medication use, physical activity, inflammation, cardiovascular disease, and mental activity on the rate of brain changes and cognitive decline in older people over time. The results of our studies to date have shown that some of our interventions can indeed decrease the rate of cognitive decline amongst older adults, and further investigations are currently under way.

**Quality of Life in People with Dementia** WACHA is participating in several ground breaking projects to understand and enhance the quality life of people with dementia in community and residential settings. Two ongoing projects are underway to investigate the association of quality of life with cognition, and to examine the effect of an educational intervention to improve the quality of life of people with dementia living in residential care. Studentships and Honors projects, are envisaged collecting, managing and organising portions of data from these ongoing studies. Supervision by both medical specialists and neuropsychology staff is possible, making these programs suitable for students form a range of disciplines.
**Neuroimaging and Structural Brain Disease** WACHA has a strong track record in use of neuroimaging to understand the pathogenesis of cognitive decline in various settings, such as people with heart failure. WACHA also has an interest in CT perfusion imaging and is establishing collaborations to develop mathematical models to facilitate automated processing of CT perfusion maps. Several projects are being offered in processing and analysing imaging data from these various cohorts.

**Licit Drugs for Older People** WACHA has successfully completed work to understand the health effects of licit drug use on older people. Current work builds on this foundation to examine the effects of polypharmacy in large cohorts and initiate intervention trials to examine the effect of reducing drug burden in older people. Honours projects are being offered in each of these areas.

**Preventing Frailty** At WACHA we are exploring the concepts of frailty and are using some of our studies of large groups of older people to test different measures of frailty. We propose to find the major factors that increase the risk of frailty and those that help prevent it. We hope to find a simple score that will be useful in routine clinical practice and work out what interventions we can use on this targeted group of individuals.

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**CLINICAL RESEARCH IN EMERGENCY MEDICINE (CCREM)**

**Prof Simon Brown** (Head of Unit)  
9224 2662 Email: simon.brown@uwa.edu.au

**Dr Shelley Stone** (Research Fellow)  
9224 0356 Email: shelley.stone@uwa.edu.au  
Location: Perth Campus, Medical Research Foundation Building, Level 5&6, 50 Murray St, Perth

The Centre for Clinical Research in Emergency Medicine (CCREM) is focused on research activities within the spectrum of Emergency Medicine. Our research involves collaboration between clinical academics working in the Emergency Department (ED), research nurses collecting clinical samples from patients presenting to the ED with acute illnesses and basic scientists analysing samples in the laboratory using immunological and molecular biological techniques. Students with a keen interest in clinical immunology may join our group and contribute to the research projects below. Both will be suitable starting points for PhD projects, should a student wish to pursue a higher degree.

**PROJECT ONE: Culturing mast cells from human peripheral blood progenitor cells**

**Aims**

1) Develop an *in vitro* method for culturing mast cells from adult human peripheral blood mononuclear cells (PBMC) to facilitate research into the mechanisms of severe allergic reactions (anaphylaxis).

2) Determine the effects of the anti-inflammatory cytokine IL-10 on IgE receptor (FcεRI) expression and mediator release from *in vitro* differentiated human mast cells.

**Background:** Anaphylaxis is defined simply as “a serious allergic reaction that is rapid in onset and may cause death”. After an episode of acute anaphylaxis, secondary prevention is important to minimise the economic costs of the disorder, to improve the quality of life of individuals affected and to minimise the long term mortality risk from repeat reactions. Effective secondary prevention requires an understanding of the underlying immunological mechanisms of acute anaphylaxis so that the initial (or “index”) episode can be properly interpreted and used to assess long term risk.

Mast cells are the primary effector cells in anaphylaxis. They express the high affinity Fc receptor for IgE (FcεRI). When allergen-specific IgE bound to FcεRI is cross-linked by allergen, mast cells degranulate, releasing preformed mediators such as histamine and prostaglandins before synthesis and secretion of *de novo* mediators such as cytokines and chemokines. Mast cells are c-kit (CD117)+ but CD14− and CD23−. Mature mast cells do not circulate in peripheral blood, undergoing terminal differentiation in the tissues. Therefore, primary human mast cells are difficult to isolate as only limited amounts of cells can be retrieved from human tissues. Holm *et al* recently published a method to culture mast cells from CD133+ adult progenitor cells isolated from peripheral blood mononuclear cells (PBMC). This novel protocol reduces the culture time for *in vitro* differentiation of human mast cells, allowing investigation of mast cells function in adult donors with different diseases characterised by aberrant mast cell function.
Our Emergency Department Anaphylaxis (EDA) study has demonstrated that elevated levels of serum IL-10 are evident during moderate and severe anaphylaxis, approximately one hour after the observed peak in inflammatory mediators such as histamine and mast cell tryptase. The involvement of IL-10 in human anaphylaxis to our knowledge had not previously been confirmed. IL-10 is considered to be a regulatory (anti-inflammatory) cytokine and may contribute to resolution of the hypersensitivity reaction by reducing activation and degranulation of mast cells and decreasing the effect of pro-inflammatory mediators. Currently, the effects of IL-10 on mast cell function have only been investigated in mouse models. Human mast cells differ from mouse mast cells in cytokine production, immunoglobulin receptor expression and the ability of different stimuli to cause degranulation and release of mediators. Therefore, we will develop a method to culture mast cells from adult human PBMC to facilitate investigation of the effects of IL-10 on mast cells, including expression of the IgE receptor, FcεRI, and production of histamine and prostaglandin D₂.

PROJECT TWO: Investigating the underlying immunopathogenesis of critical illness in the Emergency Department

**Critical Illness and Shock Study (CISS).** This is a prospective observational study of patients presenting to the Emergency Department (ED) with critical illnesses or injuries that compromise the cardiovascular and/or respiratory systems. Clinical and laboratory data will be used to better define and correlate clinical features, aetiology, pathophysiology and outcomes. The analysis of plasma, serum, leukocytes and DNA samples will enable us to investigate mechanisms of disease and novel biomarkers that may eventually facilitate improved diagnosis and therapy. The student choosing this project will investigate which leukocyte populations express cytokines and activation markers during the early stages of shock and/or respiratory failure.

If you are interested in joining the research group, please contact either Shelley (Shelley.Stone@uwa.edu.au) or Simon (Simon.Brown@uwa.edu.au).

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**CENTRE FOR IRON METABOLISM AND LIVER DISEASE**

**Professor John Olynkyk**
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**Janina Tirnitz-Parker**
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Location: Fremantle Campus, School of Medicine and Pharmacology, Fremantle Hospital Unit

Our research is focused on the role of iron in the aetiology of a variety of liver diseases including the genetic iron overload disorder hereditary haemochromatosis (HH) and colon cancer, as well as the role of liver progenitor cells in liver regeneration, fibrosis and cancer.

**Hereditary haemochromatosis and liver injury (DT, JO, AC, JTP; Honours/PhD projects)**
In this study we will use models of HH, which have pathological characteristics that are similar to the human disease to identify the mechanisms of liver iron overload and iron induced liver injury and role of hepatic oxidative stress, apoptosis and inflammation in the development of fibrosis, cirrhosis and cancer in HH.

**Iron and colorectal cancer (DT, JO, AC, DH in collaboration with Prof Ian Lawrance and Dr Borut Klopcic; Honours/PhD project)**
Population studies have shown that high dietary intake of red meat (haem) and iron-containing foods are risk factors for colon cancer. This project will examine the role of iron and haem in mouse models of colorectal cancer. We will determine the levels of dietary haem and iron that enhance colonic damage and define the oxidative and inflammatory signalling pathways that promote cell survival that result in the development of colorectal cancer.

**Progenitor cells in liver regeneration, fibrosis and cancer (JTP, JO)**
Under chronic liver injury conditions in which the replicative capacity of hepatocytes is compromised, the liver regenerates via a coordinated response of adult liver progenitor cells (LPCs). Following injury, dormant LPCs become activated and subsequently undertake a program of proliferation, migration and differentiation to replace lost ductular and parenchymal tissue. This response is typically associated with chronic or carcinogenic injury, such as occurs in chronic hepatitis B or C virus infection, alcoholic liver disease or non-alcoholic fatty liver disease. These diseases, although diverse in aetiology, show a similar progression of pathologies, characterised by three major cellular changes: inflammation, expansion of the LPC compartment and fibrogenesis involving activation of hepatic stellate cells. The focus of this research is to investigate how interactions between cell types may contribute to the regenerative, fibrogenic or carcinogenic response of the liver to chronic injury and how LPCs transform and become cancer stem cells.
Inflammation and chronic liver disease (CE, JO)
Our laboratory has shown that liver progenitor cell (LPC) numbers correlate with severity of liver disease (i.e. fibrosis, cirrhosis, and ultimately hepatocellular carcinoma) in human conditions such as alcoholic liver disease, hepatitis C virus infection, and genetic haemochromatosis. Subsequently, a role for LPCs in experimental hepatocellular carcinoma has now been demonstrated. Chronic inflammation is also associated with liver disease, and macrophages have been shown to play a role in fibrosis. This research will examine the role of macrophages in liver progenitor cell proliferation and differentiation in models of liver injury which invokes a liver progenitor cell response. We will use immunohistochemistry, real-time PCR, and flow cytometry to investigate how macrophages influence LPC responses and chronic liver injury.

CENTRE FOR ASTHMA, ALLERGY AND RESPIRATORY RESEARCH (CAARR)

Director: Winthrop Professor Philip Thompson  
9346 3198/9346 3822
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The Centre for Asthma, Allergy and Respiratory Research (CAARR) is the first integrated scientific and clinical research centre in Australia dedicated specifically to research into respiratory diseases. Under the Directorship of Winthrop Professor Philip Thompson, the Centre currently has around 60 researchers who are working in several research disciplines to build a holistic understanding of lung health. CAARR is a second term as a member of the Cooperative Research Centre for Asthma and Airways. Through this grant, the Centre has undertaken a number of projects in the Molecular Genetics fields.

CAARR is closely aligned with the Lung Institute of Western Australia (Inc) (LIWA), which has been in existence since 1999 and is based at Sir Charles Gairdner Hospital. One of the Centre's missions is to foster the careers of young scientists and, in conjunction with LIWA, it has established a series of initiatives to support students. These include a PhD Scholarship programme which sees both full and top up funding offered to successful candidates each year. Scholarships for BMedSci/Hons students are also offered annually. A vocational cadetship programme for undergraduates which enables participating students to earn money while gaining experience in a research environment is also held each year. Many of these students are given the opportunity to continue working for LIWA on a part time basis throughout the year. Through LIWA, CAARR also offers annual travel awards which enable scientists to further their careers by attending important meetings in their field.

Students are also supported with weekly scientific meetings to informally discuss current projects, regular seminars on medical research topics and an inclusive philosophy which values students and their role in the Institute.

There are currently four research Units offering BMedSci projects within CAARR. They are;

Tissue Repair Unit  
9346 3906/9346 3198
Head – Professor Steven Mutsaers  
Email: mutsaers@liwa.uwa.edu.au

The Tissue Repair Unit is examining the mechanisms regulating resident, inflammatory and immune cell and extracellular matrix (ECM) interactions in the lung, and how a loss of regulation of the normal repair processes can lead to diseases such as asthma, COPD, lung fibrosis and lung and pleural cancers. Studies are centred on understanding how interaction of cells with other cells, growth factors, cytokines and different components of the ECM lead to cell proliferation, migration, invasion, differentiation and collagen production.

Evaluating the molecular mechanisms which protect against lung fibrosis
Dr Cecilia Prele  
Email: ceciliap@liwa.uwa.edu.au

Background
Excessive deposition of collagen and fibrosis is characteristic of many pulmonary conditions including idiopathic pulmonary fibrosis (IPF), a fatal disease of unknown cause which is unresponsive to current therapy. Recent findings by our group and other shave implicated the interleukin-6 (IL-6) family of cytokines in lung fibrosis. In previous studies using animal models and human tissues we have identified the signalling molecule STAT3 as important in potentiating the fibrotic response. However, it is unclear which IL-6 family mediator induces this response or which cells drive the fibrotic phenotype. Although fibroblasts are thought to be the effector cell in fibrosis, other cell types may induce fibroblast-mediated collage production.

Project focus
This study will investigate some of the possible mechanisms regulating STAT3 mediated fibrosis including identifying cell types within the human and mouse lung that express high levels of STAT3 and examining the effects of different members of the IL-6 family on STAT regulation in these cells.
The interaction between hedgehog and transforming growth factor beta signalling pathways in malignant mesothelioma growth.
Dr Bahareh Badrian
Email: bbadrian@liwa.uwa.edu.au

Background
Malignant mesothelioma (MM) is an aggressive asbestos-associated tumour predominantly of the pleura, with a very poor prognosis. Current treatments are ineffective, therefore novel therapeutic approaches are required. Increasing evidence is pointing to the reactivation and aberrant expression of developmental signalling pathways, such as the hedgehog (Hh) pathway, as critical to the pathogenesis of certain cancers. The significance of aberrant Hh pathway signalling in the development and growth of MM remains to be determined.

Project focus
Recent studies have clearly shown an interaction between Hh and transforming growth factor beta (TGFβ) signalling pathways in a variety of cell types. Furthermore, we and others have clearly shown a role for TGFβ signalling in MM growth, although its relationship with Hh signalling has not been investigated in MM cells. Targeting the cooperation of Hh and TGFβ signalling may provide new therapeutic opportunities for treating MM. This study will examine the interaction of these two signalling pathways to determine if TGFβ can regulate Hh signalling in MM cells and/or Shh induces cellular responses through the TGFβ signalling pathway. In particular, regulation of these pathways by miRNA will be investigated. miRNAs are short non protein coding RNAs of approximately 22 nucleotides in length that are known to alter gene expression at a post transcriptional level.

MicroRNA in Malignant Mesothelioma
Dr Bahareh Badrian
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Background
Malignant mesothelioma (MM) is an aggressive and fatal cancer that is primarily caused by asbestos exposure, is associated with a poor prognosis and a 5 year survival rate of less than 1%. The current estimate suggests that the incidence of MM will peak in the western world in 2020. Even though use of asbestos is banned in most developed countries, secondary asbestos exposure from asbestos containing building materials is still a concern for the general population and asbestos is still being use in developing countries. This makes MM a concern for many years to come. There is currently no effective treatment for MM. Therefore it is important to understand the biology of this disease for the development of an effective treatment for MM.

Project focus
The current projects aims to determine the role of microRNAs (miRNAs) in the development and regulation of MM. miRNAs are short non protein coding RNAs of approximately 22 nucleotides in length that are known to alter gene expression at a post transcriptional level. These molecules contribute to the initiation and progression of cancer and malignant tissues exhibit a unique miRNA expression profile that is different to normal tissue. Therefore, we believe that miRNAs may play an important roles in the biology of MM. Current studies in our laboratory have identified a set of miRNA that appear to be important in MM. This project will investigate one of these miRNAs and determine their role in the regulation MM.

Molecular Genetics
9346 79486/9346 3198
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The Molecular Genetics and Inflammation Unit, through its involvement with the nation-wide Co-operative Research Centre (CRC) for Asthma and Airways, is focused on identifying the genetic basis of chronic respiratory diseases, identifying new molecular targets, generating more effective treatments and preventing disease progression.
Alternative gene splicing and asthma: is it all the RAGE?
Dr Svetlana Baltic
Email: svetlana@liwa.uwa.edu.au

**Background**
The Receptor for Advanced Clycation End-products (RAGE) is a cell-surface receptor implicated in a wide array of inflammatory conditions. Activation of the receptor by ligand binding can initiate a positive feedback-loop of pro-inflammatory signalling that leads to chronic and sustained inflammation. However, despite high levels of RAGE expression in the lung, little is known about the role of RAGE in airway inflammation, particularly in asthma.

One important mechanism of RAGE regulation is the process of alternative mRNA splicing. RAGE exists as several alternatively spliced variants, including a soluble variant (sRAGE) that is capable of binding ligand, but lacks the intracellular signalling domains necessary for activating the pro-inflammatory signalling cascade. As such, sRAGE is thought to act as a protective mechanism against the pro-inflammatory effects of RAGE. Disruption of the fine balance of RAGE/sRAGE, either by increased RAGE or decreased sRAGE expression, was observed in several chronic diseases associated with persistent inflammation similar to that seen in asthma.

**Project focus**
This study will investigate mechanisms involved in regulating RAGE/sRAGE balance and assess the potential for antisense oligonucleotides to regulate RAGE splicing, as a new therapeutic tool for restoration of the RAGE/sRAGE balance and reduce inflammation.

The role of miRNAs in regulation of l-selectin expression
Dr Svetlana Baltic
Email: svetlana@liwa.uwa.edu.au

**Background**
A hallmark of neurodegenerative diseases is the overexpression of l-selectin protein which compromises neurone viability and activates microglia. Over the past decade it has become clear that neuroinflammation and peripheral immune responses contribute to development of neurodegeneration. The inflammatory response in the CNS, also features rapid infiltration of dendritic cells (DC) into the brain. We have previously shown that dendritic cells express l-selectin and its essential role in the function of dendritic cells. We have also identified novel l-selectin splicing variant which may contribute to l-selectin over expression in inflammation. The mechanism of l-selectin differential splicing remains unknown, but may involve regulatory elements such as miRNA. In the brain, in addition to neurons and immune cells, glial cells also show extensive l-selectin pathology and may contribute to disease progression. However, the mechanism that produces the glial l-selectin pathology and the interaction between neurons, glia and DC in the disease-inflicted microenvironment remain unknown.

**Project focus**
The aim of this project is to use molecular and cell culture techniques to investigate the role of miRNA in regulation of expression of l-selectin splice variants in neuronal, glial and dendritic cells under inflammatory conditions.

Characterising the function of the SNP in the Bradykinin B1 Receptor (BDKR B1) promoter
Dr Svetlana Baltic
Email: svetlana@liwa.uwa.edu.au

**Background**
Kinins are inflammatory mediators activated in the airways in response to a variety of inflammatory stimuli. They act through two receptors, B1R and B2R. In inflammation, the inducible kinin receptor B1R is rapidly up-regulated. Furthermore, the expression of pro-inflammatory kinins which act via B1R is increased in the bronchoalveolar lavage of asthmatic compared to healthy subjects. Two functional promoters have been identified in the human BDKRB1 gene. The more potent promoter is located in the 5’-flanking region and has been well-studied. The second, weak promoter is located within intron 2 and we have identified the SNPs within it and an association between these SNPs and severity of asthma.

**Project focus**
This project seeks to test whether identified SNPs in the weak promoter region of BDKRB1 increase expression of B1R and consequently increase severity of asthma. To test this hypothesis we will clone the wild type B1R weak promoter and use the site-directed mutagenesis to create a constructs containing previously validated SNPs. Functional assays to determine the differences in transcriptional activity between the wild type BDKRB1 promoter construct and the promoters containing SNP(s)- under different stimulation conditions will be investigated.
Characterisation of Glucocorticoid Receptor Splice Variants In Severe Asthma
Dr Li Ping Chung: Email: lichung@liwa.uwa.edu.au

Background
Glucocorticoids are widely used for treatment of acute and chronic inflammatory diseases including asthma. However, 10-25% of asthmatics have poorly controlled symptoms and persistent airway obstruction despite high dose glucocorticoid treatment. To date, the mechanism for steroid resistance remains unclear but may result from reduced glucocorticoid receptor (GR) expression, altered ligand binding affinity, defective nuclear translocation and cofactor association and activation. The gene encoding GR is highly polymorphic and has naturally occurring splice variants. In addition to the functional variant of GR (GRα), as many as 9 inactive isoforms of GRβ have been reported. Earlier studies suggested an association between raised levels of GRβ relative to GRα in individuals with chronic inflammatory diseases who are resistant to steroid therapy. However, the role of GR splice variants in pathogenesis of severe asthma or steroid-resistant asthmatics has yet been adequately investigated.

Project focus
The extent to which GR splice variants contribute to differences in response to glucocorticoid treatment between individuals will be explored. The aim of this study would include characterisation of GR splice variants in steroid resistant asthmatics compared with individuals with milder form of asthma. Given the significant number of individuals who fail to respond to therapy with corticosteroids, as well as the potential adverse effects and morbidity attributable to corticosteroids, identification of individuals most likely to demonstrate a significant response to this class of medication would be invaluable.

How to contact CAARR
Enquires for BMedSci projects are welcomed. In the first instance please email us admin@liwa.uwa.edu.au or call the Lung Institute of Western Australia on 9346 3198 registering your interest and we will ensure that someone will contact you to answer your questions and/or arrange a meeting.

CENTRE FOR OPHTHALMOLOGY AND VISUAL SCIENCE (COVS)

DIRECTOR
Winthrop Professor D A Mackey 9381 0777 Email: david.mackey@uwa.edu.au
www: http://www.lei.org.au

Population Health
Head of Department
Winthrop Professor DA Mackey 9381 0841 Email: david.mackey@uwa.edu.au
We are currently conducting ophthalmic examinations on 1,500 members of the prospectively followed Raine Birth Cohort in Western Australia who are now age 20 years, the Raine Eye Health Study. This cohort has already had a 610,000 SNP GWAS analysis. The data collected will:
• Document the prevalence of refractive error (need for glasses), amblyopia (lazy eye) and strabismus (eye turn) in young adults;
• Determine the population distribution of eye measurements in young adults;
• Determine genetic and early environmental factors that influence ocular measurements and predispose to ophthalmic disease;
• Investigate the interaction of early life, familial, lifestyle, demographic and genetic risk factors with these conditions, and their measurements;
• Establish an ophthalmic baseline examination for a population cohort that can be followed through later adult life, with particular attention to measurement of the optic disc and cup; and
• Create a normal healthy clinical reference database for researchers investigating diseases affecting young adults including: pterygium, keratoconus and diabetic retinopathy.
In addition, we have phenotyped and genotyped over 1,000 sets of twins in the Twins Eye Study in Tasmania and Brisbane with extensive orthoptic measurements available; a similar study will commence in 2012 in Western Australia. Also commencing in 2012 will be the Western Australian Eye Protection Study evaluating eye protection in adolescents and adults participating in sport and outdoor activity. These studies will be collecting similar data to the Raine Eye Health Study and thus will be available as replicative and population control cohorts.

Physiology & Pharmacology
Head of Department
Winthrop Prof Dao-Yi Yu 9381 0716 Email: dyyu@cyllene.uwa.edu.au
The main focus is to understand vascular control mechanisms in the retina of normal and diseased eyes with the ultimate aim of early diagnosis and treatment of retinal vascular disease, for which no current drug treatment exists. The retinal circulation is unusual, possessing no autonomic innervation and a sparse circulation minimising interference with the light path, so that control of blood flow must occur at the local level. We use a range of integrated techniques to investigate control of the circulation from the molecular, cellular and in vivo level, including oxygen and blood flow microelectrode techniques, pharmacological fluorescent ionic imaging, isolated perfused organs, and isolated perfused arterioles.

**Diabetic Retinopathy**

We focus on the initiating stages in the cascade of events which occurs in the preclinical diabetic retina, to test the hypotheses that retinal oxygen consumption is increased, arteriolar control of retinal blood flow distribution is disturbed and relative tissue hypoxia and ischaemia, all within a short time after the onset of hyperglycaemia and hypoinsulinemia.

**Oxygen Consumption and Blood Flow in Normal Retinas of Rat & Guinea Pig.**

The normal mammalian retina has two circulations. Using oxygen and hydrogen sensitive micro electrodes, we have determined the extent to which the choroid and retinal circulations supply the retina under a variety of physiological conditions, switching aerobic to anaerobic metabolism.

**Local Control of the Retinal Circulation**

To investigate cell/cell interaction at different locations in the retinal vasculature we have developed an isolated perfused retinal artery preparation for vessels 50-100 mm diameter. With this we are able to compare the effect of luminally and extraluminally applied vasoactive agents, on human donor and animal vessels and cell–cell communication.

**Cell/Cell Interaction in the Retinal Circulation**

Using fluorescent imaging and a spectrophotometer we are testing the hypothesis that the retina has unique communication systems between adjacent endothelial cells, endothelial cell and smooth muscle cells in the perfused retinal artery preparation.

In particular we will use the relationship between Ca$^{2+}$ movements and membrane potential changes.

**Vasoactive Effects of B-Blocker Used to Treat Glaucoma**

We are testing the hypothesis that the b-blocker betaxolol, which is used to reduce intraocular pressure in glaucoma patients, has a vasodilatory effect in the retinal circulation. If so this may be the explanation for previous observations that visual function is improved by this drug.

**Development of a Robotic Microsurgical System** for the precisely localised delivery of possible treatment to the retina, involving transplantation of cells, delivery of viral constructs, delivery of drugs, etc., through the individual blood vessels. Ultimately, this system will be developed for use in the human as a precise surgical tool.

**Molecular Ophthalmology**

**Head of Department**

Winthrop Prof P. Elizabeth Rakoczy 9381 0726 Email: rakoczy@cyllene.uwa.edu.au

**Assoc Prof May Lai** 9381 0729 Email: mla@cyllene.uwa.edu.au

Age related Macular Degeneration, Retinitis Pigmentosa and Diabetic Retinopathy are the focus of research of our molecular ophthalmology research group.

**Research Projects:**

- Identification of biomarkers for diabetic retinopathy;
- Preclinical Trials;
- Development of animal models for macular degeneration and for choroidal neovascularisation; and
- Development of animal models and treatment strategies for diabetic retinopathy.

The group provides training in the use of complex cutting edge technologies to develop treatments for eye diseases using tissue culture, monoclonal antibody production, histology, minor eye surgery in animals and molecular biology, such as recombinant virus mediated gene therapy, gene array, transgenic animal technologies and stem cell therapies.
Experimental Immunology
Head of Department
Prof Mariapia Degli Esposti 9381 0808 Email: mariapia@cyllene.uwa.edu.au
The Experimental Immunology group studies the immune system and concentrates on defining the interactions that occur between viral pathogens and components of the host immune system with the aim of determining how these interactions contribute to anti-viral immunity. It is expected that the knowledge generated by such studies will be of relevance not only to controlling infection, but also cancer and some eye diseases.

A better understanding of the responses that control the spread and disease caused by viruses is essential for the development of efficacious vaccines and underpins the design of improved therapeutic strategies.

Clinical Ophthalmology & Research
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Prof Graham Barrett 9381 0872 Email: barrett@cyllene.uwa.edu.au

Areas of Clinical Interest
- Cornea and corneal surgery;
- Refractive surgery; and
- Cataract Surgery.

Areas of Research Interest
- Development of Intraocular Lenses & Materials;
- Development of formulae for lens calculation;
- Small incision surgery;

Prof Geoffrey Crawford 9381 0871 Email: gjc@cyllene.uwa.edu.au

Areas of Clinical Interest
- Cornea and corneal surgery;
- Refractive surgery; and
- Cataract Surgery.

Areas of Research Interest
- Development of an artificial Cornea, AlphaCor;
- Uses for the Femtosecond laser in corneal surgery;
- Development of an integrated orbital implant, AlphaSphere;
- Lamellar surgery for corneal disease; and
- Corneal Cross linking for keratoconus

Prof W Morgan 9381 0873 Email: whmorgan@cyllene.uwa.edu.au
Glaucoma afflicts 0.5 % of people aged > 50, 2 % aged > 70 and causes 14 % of blindness in Australia. This group is to expand the high quality clinical care by carrying out basic research into the mechanisms of the disease, to aid the development of new diagnostic devices.

Optic Nerve Head Pressure Gradients
We are currently the only group world wide to be looking at the distribution of pressure across the optic disk. A servo-nulling pressure measuring device is being used to monitor pressure changes. The relationship between retinal vein pressure, CSF pressure and optic disc tissue pressure is being studied.

Cellular Physiology of the Trabecular Network
The role of the trabecular meshwork is critical to the regulation of intraocular pressure. This function is mediated by various intraocular pressures regulating and signaling substances. Abnormal production of these substances by these cells in response to alterations in the regulating signaling pathway is likely to be the major cause of the pressure rise in glaucoma.

- Isometric force measurements of the trabecular meshwork.
- Ratio microspectrometic studies of trabecular meshwork cells for intracellular concentrations of Ca++, K+ and other ions.
- Determining the effect of putative antiglaucoma drugs on the trabecular meshwork.

Dynamic Tonometer
Elevated intraocular pressure is the major risk factor in glaucoma. Intraocular pressure is not constant and is subject to large fluctuations during the day. Currently almost all intraocular pressure measurements use single point measurements inducing unavoidable errors.
The aims of this study are:
- To develop a dynamic tonometer which can be used in the clinic for frequent intraocular pressure measurements with a high degree of accuracy.
- To further develop a home-use tonometer for patient use.

**Glaucoma Data Base/Epidemiology**
Perth, being isolated and having a relatively stable population is an ideal place to set up a large database of all patients sent to the glaucoma clinic. We have set up a data base with a central computer acting as a server, having a large memory capacity with network communications to computers in all clinic areas.

**Stereo Imaging of the Optic Disk**
Measurement of the topography of the optic disk or optic nerve head is an important element in the diagnosis of glaucoma. Objective measurement systems been developed, but they are prone to high variability. We have developed a Scanning Laser Ophthalmoscope which measures and records reflections from the retina and are currently developing a stereo imaging capability for the Scanning Laser Ophthalmoscope, which will generate simultaneous stereo views of the optic disk.

**Assoc Prof Mei-Ling Tay Kearney** 9381 0875  Email: kearney@cyllene.uwa.edu.au

**Ocular Inflammatory Diseases** are a major cause of visual morbidity in young individuals.
Research is mainly clinical, an ongoing project using a slow-release injectable implant to treat non-infectious posterior uveitis. Previous projects have looked at the implications of anterior uveitis in patients with multiple sclerosis and usefulness of NSAIDs in the treatment of acute anterior uveitis. There is also extensive experience with use of biologics in the treatment of uveitis particularly the type suffered by children with juvenile arthritis. Collaborative work is possible with Prof. P McMenamin at the Anatomy department as well as A/Prof. M-P Degli Espoti at Immunology.

**Assoc Prof Steven Wiffen** 9381 0874  Email: wiffen@cyllene.uwa.edu.au
Research interests include:
- Use of amniotic membrane and cultured corneal epithelium for ocular surface reconstruction
- Limbal stem cell transplantation
- Therapy for ocular surface squamous neoplasia
- Surgery for pterygium

**Assoc Prof Fred K Chen** 9381 0817  Email: fredchen@lei.org.au
**Dr Samuel McLenachan** 9381 0731  Email: smclenachan@lei.org.au
**Dr Dana Zhang** 9381 0731  Email: dana@lei.org.au

**Ocular Tissue Engineering Laboratory**
Blindness affects 130 people / million populations in WA each year, with over 65% due to macular degeneration. Despite recent advances in treatment, there is currently no cure for this condition. Our group offers a range of projects focusing on new technology in diagnosis and novel treatment of macular degeneration and diabetic retinopathy.

1) **New diagnostic imaging tools for macular diseases**
Conventional visual acuity measurement has limited ability in detecting disease progression in dry macular degeneration. At the COVS, we have two new devices which use military tracking technology to enable simultaneous retinal imaging and visual field measurement. This instrument allows detailed analysis of point to point correlation between retinal function and architecture. We are currently studying the test-retest variability and comparability of these devices which have significant implications for future clinical trials.

2) **Macular dysfunction in diabetes and prediabetes**
Until recently, it was believed that diabetes directly leads to blood vessel damage which resulted in neuronal loss and hence visual impairment in diabetic retinopathy. However, our group is interested in using advanced corneal and retinal imaging devices to detect the presence of neuronal cell loss and dysfunction even before retinal vessel damage in patients with pre-diabetes and early diabetes. This will provide further insight into the pathogenesis of diabetic retinopathy and neuropathy.

3) **Macular dysfunction in dry macular degeneration**
Dry macular degeneration is characterised by progressive loss of retinal cells over many decades. We are currently conducting a longitudinal study to examine the roles of various retinal imaging and functional testing devices in monitoring progression of dry macular diseases with a view to use these techniques in future clinical trials. There are also ongoing clinical trials using advanced retinal imaging techniques to monitor retinal disease progression and response to novel therapy.

4) **Cellular therapy in macular degeneration**
Retinal cells are unable to regenerate once they are lost. The only hope for restoring vision in severe age-related macular degeneration is retinal cell transplantation. Our group is working on novel cellular reprogramming techniques to generate retinal pigment epithelium from various stem cell sources. Replacing pigment epithelium in macular degeneration may offer a cure for this common blinding disease.
Centre for Neuromuscular and Neurological Disorders (CNND)

Primary supervisor:  
Adjunct A/Professor Bruno Meloni  9346 3535 email: meloni@cyllene.uwa.edu
Other supervisor: Professor Neville Knuckey  9346 7206 email: Neville.Knuckey@health.wa.gov.au
Location: Centre for Neuromuscular and Neurological Disorders (CNND)

Project title: Assessment of neuroprotective strategies to reduce brain damage following stroke and cerebral ischaemia

Project Background: Our research is focussed on neuroprotective therapies for the treatment of acute ischaemic brain injuries (stroke, cardiac arrest/resuscitation, traumatic brain injury).

Project aims: This project aims to assess potential neuroprotective therapies using both in vitro and animal stroke models. These therapies include magnesium, mild hypothermia and several neuroprotective proteins/peptides we have identified in our laboratory.

Techniques involved: Protein purification, in vitro neuronal cell culture, animal sugery, rat stroke models.

Primary Supervisor:  
Professor Gary Thickbroom  9346 4479 Email: gthickbr@cyllene.uwa.edu.au
Location: Centre for Neuromuscular and Neurological Disorders (CNND)

Project Title: Neuromodulation for recovery of function in neurological disorders

Project Background: We investigate human motor control. This is because many neurological disorders affect motor function and we are a clinically drive research laboratory. We study healthy human motor control (Volunteers always welcome) as well as patient populations such as Parkinson’s disease, multiple sclerosis, the dystonias and stroke. With transcranial magnetic stimulation (painless and harmless) we can activate motor cortex and make a muscle of the hand contract. With this we work out things about inhibition and excitability of the brain. More exciting is that we now can use this to actually change brain excitability a little bit for a little while. The aim is to up-regulate brain plasticity and try and promote recovery of motor function.

We take on students from a variety of backgrounds. The main requirements are enthusiasm, interest and initiative. Undergraduate medical students, honours students, MSc and PhD students have been supervised here. We even attract people who want to do projects for their own interest (2 at present!). Their backgrounds have included nursing, exercise and sport science, physiotherapy, psychology, engineering, medicine, neuroscience and neurologists. We have a cohort of overseas students too. With this diversity, we do not have set projects but prefer to tailor projects to the student. So if you are interested in human brain research, particularly motor function and brain plasticity, get in touch. We are very approachable and it does no harm to have a look.

Project aims: To non-invasively modulate brain plasticity and promote recovery of function in neurological disorders

Techniques:  
Transcranial Magnetic Stimulation  
Neuromodulation and Neurorehabilitation  
Neuroimaging  
Motor performance measures and muscle fatigue  
Posturography
Primary supervisor:
Professor Steve Wilton  9346 3967  Email: swilton@meddent.uwa.edu.au
Location: Centre for Neuromuscular and Neurological Disorders (CNND)

Project title: Treatments for DMD

Project Background: The majority of human genes consist of protein coding exons that are separated by non-coding intronic sequences. Before a mature gene transcript can be translated into a protein, the introns must be removed and the exons precisely spliced together.

We are pioneering a genetic therapy to treat the most common and severe form of childhood muscle wasting, Duchenne muscular dystrophy, by specifically modifying the splicing process. Defective disease-associated exons can be removed during splicing of the pre-mRNA to restore production of a functional gene product.

Clinical trials are currently underway in the United Kingdom, with the first published trial confirming proof-of-concept, and the second showing encouraging preliminary results after systemic delivery of a compound developed in our laboratory.

As we gain experience with modifying expression of the dystrophin gene, we are no pushing the boundaries and extending splice intervention applications to other genetic and acquired conditions.

Most genes undergo some form of splicing during expression, including alternative splicing where different exon combinations are brought together in a developmental or tissue specific manner consequently, the scope of projects is enormous. We have several lines of interest with established research programs, but can also tailor projects to meet special interests of the students.

Primary supervisor:
Dr Sherif Boulos  9346 4090  Email: sboulos@cyllene.uwa.edu.au
Location: Centre for Neuromuscular and Neurological Disorders (CNND)

Project title:
Some of our specific projects include:

- Investigating why missense mutations in the leucine rich repeat kinase 2 (lrrk2) gene cause PD.
- Why deletion of the survival of motor neuron 1 (smn1) gene in Spinal Muscular Atrophy (SMA), the leading genetic cause of infant death, induces motor neuron loss.
- Exploring the role of cyclophilin A and its cell surface receptor CD147 in normal and diseased brain.

Project Background: The Molecular Neurobiology Unit focuses on the cellular mechanisms causing neuronal cell death in disorders such as Parkinson’s, Alzheimer’s and motor neuron disease. Another aspect of our work centres on using and developing novel approaches to deliver neuroprotective peptides and proteins to cells in culture and to the brain and spinal cord in whole animals.

We currently run a number of interesting research projects, all at different stages of maturity and all available to committed and enthusiastic prospective PhD, MSc and Hons students keen to pursue a career in medical research.

Techniques involved: In order to answer these challenging questions our laboratory has adopted and mastered a number of very powerful molecular tools such as;

Cultivation of relevant primary and immortalised cell lines, protein, DNA and RNA analysis, gene manipulation and expression, cell viability assays, recombinant adenovirus design and production, flow cytometry and recombinant protein design, production and purification.