The information in this publication is correct as at 13 October 2010, 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 speciality 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: 9346 7323 or 2887 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
Assoc Professor Linda Slack-Smith Ph.9346 7874 email: linda.slack-smith@uwa.edu.au

School of Medicine and Pharmacology
Assistant Professor Jane Allan Ph.9431 2641 email: jane.allan@uwa.edu.au
Professor Peter Henry Ph.9346 3123 email: peter.henry@uwa.edu.au

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
Professor Patricia Price Ph.9224 0378 email: patricia.price@uwa.edu.au
Assoc Professor Richard Allcock Ph.9346 2993 email: richard.allcock@uwa.edu.au

School of Population Health
Assoc Professor Colleen Fisher Ph.6488 1416 email: colleen.fisher@uwa.edu.au

School of Primary, Aboriginal and Rural Health Care
Professor Simon Brown Ph.9224 3340 email: simon.brown@uwa.edu.au

School of Psychiatry and Clinical Neurosciences
Professor Dieter Wildenauer Ph.9347 6782 email: dieter.wildenauer@uwa.edu.au

School of Surgery
Professor Barry Iacopetta Ph.9346 2085 email: barry.iacopetta@uwa.edu.au

School of Women’s and Infants’ Health
Dr Ilias Nitsos Ph.6488 7969 email: ilias.nitsos@uwa.edu.au

Faculty of Life and Physical Sciences

School of Anatomy and Human Biology
Professor Linc Schmitt Ph. 6488 3298 email: limch.schmitt@uwa.edu.au
Associate Professor Silvana Gaudieri Ph. 9224 2137 email: silvana.gaudieri@uwa.edu.au

School of Biomedical, Biomolecular and Chemical Sciences
Clinical Professor David Smith Ph. 9346 2164 email: david.smith@uwa.edu.au
Professor Don Robertson Ph: 6488 3291 email: don.robertson@uwa.edu.au
8.2.3 BACHELOR OF MEDICAL SCIENCE HONOURS DEGREE (90120)

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\(^{1}\) 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\(^{1}\) 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)
BMedSci Research Projects

SCHOOL OF ANATOMY AND HUMAN BIOLOGY

Head of School:
Professor Linc Schmitt 6488 3298 www: http://www.anhb.uwa.edu.au

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 Neuroscience
- 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

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

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.
Ecology
Dr Debra Judge 6488 3304 Email: debra.judge@uwa.edu.au
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.

Education
Development of computer Aided education
Professor Stuart Bunt 6488 2983 Email: stuart.bunt@uwa.edu.au
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
Evolutionary Biology and Life History
Professor Jim Chisholm 6488 3296 Email: jim.chisholm@uwa.edu.au
[Biological Anthropology]
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.
Professor Linc Schmitt 6488 3298 Email: linc.schmitt@uwa.edu.au
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 Email: stuart.bunt@uwa.edu.au

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 medicos 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 Gardner 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](http://school.anhb.uwa.edu.au/personalpages/grounds/) 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 Email: miranda.grounds@uwa.edu.au

**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

**Professor Miranda Grounds** 6488 3486  
Email: miranda.grounds@uwa.edu.au  
**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 cVIq 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 dystropathology) 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 cVIq) with anti-fibrotic drugs, to assess if this has a cumulative benefit to reduce the dystropathology 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  
Email: brendan.waddell@uwa.edu.au

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 underlying 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  
Email: kathy.sanders@uwa.edu.au

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

Professor Brendan Waddell 6488 3297 Email: brendan.waddell@uwa.edu.au
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

Professor Brendan Waddell 6488 3297 Email: brendan.waddell@uwa.edu.au
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.

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.
Biochemistry and Molecular Biology
Chair of Discipline:
Professor Paul Attwood  6488 3329  Email: pattwood@cyllene.uwa.edu.au
Professor Lawrie Abraham  6488 3041  Email: labraham@cyllene.uwa.edu.au
Current interests broadly involve the molecular biology of gene regulation and the effects of inter-individual genetic differences on the expression profile of genes. Specific interest includes members of the TNF gene family (TNF, Lymphotoxin-alpha and -beta, CD30L and CD30) particularly those involved in immune signalling.

Transcriptional Regulation of Lymphotoxin-Beta
Lymphotoxin-beta is thought to be involved in T cell mediated events during the initiation of a variety of inflammatory and immune processes. We are interested in the transcriptional and post-transcriptional regulation of the gene. In particular, we are interested in answering the question, what signals do T cells receive that result in expression of Lymphotoxin-beta on the cell surface. Thus far we have established that activators such as PMA transcriptionally up-regulate expression but ionomycin acts post-transcriptionally. Use of footprint analysis of the promoter region of Lymphotoxin-beta has shown that transcriptional activity involves the binding of a member of the Ets family of transcription factors. We are currently searching for lymphoid-specific transcription factors or unique combinations of ubiquitous factors that may provide an explanation for the very narrow lymphoid restricted expression.

Polymorphism in the TNF Promoter and its Effect on Autoimmune Disease Susceptibility
The TNF gene may be involved in predisposing particular individuals to diseases such as the autoimmune syndromes and other inflammatory disorders. We have established that genetic differences in the regulatory regions of some of these genes can be correlated with different TNF expression levels when comparing different individuals. It is of central interest to determine whether the promoter sequence differences have an effect on the binding of nuclear factors and subsequent expression of the genes under study. We are currently isolating transcription factors that interact specifically with the disease associated promoter allele with the eventual aim of designing therapeutic mimics that may block expression of TNF.

Molecular Genetics of Human Complement C4 & its Role in Immune Complex Diseases
The Human complement component C4 is located in the Major Histocompatibility Complex and is associated with complement deficiency diseases such as Systemic Lupus Erythematosus (SLE). We are particularly interested in polymorphisms that have the potential to effect the expression of C4 in the liver and also in monocytes. We have sequenced the entire gene for the SLE associated C4B1 protein and have identified a number of polymorphisms that occur in potential interferon-gamma response elements. We are currently testing whether the element confers IFN-gamma responsiveness and the effect of the polymorphisms on the process. As the human C4 promoter remains completely uncharacterised, we are also characterising the basal and IFN-gamma responsive promoter elements that transcriptionally regulate this gene.

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.
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.

Cytochrome P-450 and Steroid Hormone Synthesis
Steroid hormone synthesis is dependent upon cytochrome P-450sc 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 placentae. 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-450sc 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-450sc is the rate-determining step of the progesterone biosynthetic pathway.

References:

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.
Associate Professor Michael J Wise 6488 4410 Email: mwise@cyllene.uwa.edu.au

Research interests are related to bioinformatics/computational biology - see www.pam1.bcs.uwa.edu.au If you have particular interests you wish to pursue apart from those listed below please contact A/Prof Wise.

**Biology and Bioinformatics of Poly-Amino Acid Stutters**

Poly-amo-n-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 Huntingtin 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, ie: 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 C Yeoh 6488 2986 Email: george.yeoh@uwa.edu.au

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?
Research in the Discipline of Microbiology & Immunology is undertaken in the general fields of bacteriology, immunology and virology. Sub-disciplines include antimicrobials, asthma and allergy, clinical microbiology, diagnostic microbiology, immunovirology, molecular bacteriology and molecular virology. Research is carried out by groups of academic and research staff, located within the discipline at the QEII Medical Centre, in PathWest and in Perth teaching hospitals. Nobel laureate Professor Barry Marshall’s research group is based in Microbiology & Immunology. For more detailed information please contact the chair of discipline or the individual supervisors listed below.

**Bacteriology**

**Associate Professor Barbara Chang** 9346 2288  Email: bchang@cyllene.uwa.edu.au  
Molecular analysis of bacterial virulence; studies on adhesion and toxins of *Aeromonas, Vibrio, Moraxella*.  
Bacteriophages (phages): the biology of the bacterial viruses known as phages, their potential uses as biocontrol agents, their role in bacterial virulence, genomic analysis. Projects are available on phages of *Vibrio* species, *Aeromonas* species, *Clostridium difficile* and other genera.

**Dr Tim Inglis** 9346 3461  Email: tim.inglis@uwa.edu.au  

**Dr Charlene Kahler** 9346 2058  Email: charlene.kahler@uwa.edu.au  
*Neisseria meningitides* and *N. gonorrhoeae* are two closely related obligate human pathogens. *N. meningitides* causes epidemic meningococcal meningitis and septic shock. In Western Australia, type B remains prevalent and there is no vaccine against this organism. *Neisseria gonorrhoeae* is the causative agent of the sexually transmitted disease gonorrhoea. Globally approximately 20-60 million new cases are reported per annum (WHO) and is a leading cause of infertility in women. To date no successful vaccine strategies have been developed for this organism, primarily because the cell surface proteins expressed by this organism are highly antigenically variable, and elicit limited immunological protection against other strains. As a result individuals can contract the disease multiple times throughout their lifetime.

My laboratory is interested in understanding how these pathogens interact with the host cell and the basic biochemistry underpinning the synthesis of the bacterial structures that enable this. We are currently developing small molecular inhibitors to prevent these diseases. The projects I offer are of interest to microbiologists, molecular biologists, biochemists and chemists can be tailored to suit your skills and interests.

**Winthrop Professor Barry Marshall** 9346 4815  Email: admin@pylori.com.au  
Genomics and molecular epidemiology of *Helicobacter pylori*, the bacterium which causes peptic ulcer and stomach cancer. Clinico-pathological correlation with *H. pylori* virulence factors. New diagnostic and therapeutic techniques.

Ondek Pty Ltd is developing a new delivery system utilizing unique characteristics of genetically modified *Helicobacter pylori* bacteria. *H. pylori* can be manipulated to be harmless to the patient and it is possible to add genes so as to endow *H. pylori* with special properties. New proteins are added to stimulate the immune system to induce protection (vaccination) against one or more pathogenic organisms. Modified *H. pylori* could produce various human proteins causing stimulation or suppression of the immune system. The connection between *H. pylori* and the stomach lining also allows therapeutical proteins to pass into the tissues.

**Professor Tom Riley** 9346 3690  Email: thomas.riley@uwa.edu.au  
Pathogenesis and epidemiology of gastrointestinal infections caused by *Clostridium difficile*; and respiratory tract infections caused by *Moraxella catarrhalis*. The epidemiology, pathogenesis and prevention of healthcare-related infections, particularly infections with methicillin-resistant *Staph. aureus*. Antimicrobial resistance and the epidemiology of infections with antibiotic-resistant organisms. Infections with *Erysipelothrix* species. Antimicrobial properties of natural products including tea tree oil.
Enterotoxigenic *Escherichia coli* (ETEC) and *Shigella* spp. are intestinal pathogens of humans that cause an estimated 2 million deaths every year. We are pursuing studies aimed at (1) understanding a critical step in the development of infections i.e. how these organisms colonise the intestinal tract and (2) identifying new factors that play a role in virulence.

**Immunology**

**Dr Manfred Beilharz** 9346 2217  
Email: manfred.beilharz@uwa.edu.au

Type I Interferons (Alpha and Beta) in innate immunity and their downstream effects on acquired immune responses. *In vivo* molecular and cellular studies, human clinical trials.  
Myoblast transfer therapy in the mouse model for Duchenne muscular dystrophy. Characterisation and manipulation of the acute inflammatory response to transplantation.

**Professor Geoffrey Stewart** 6488 4699  
Email: geoff.stewart@uwa.edu.au

Immunology of allergens associated with asthma; immunobiology of proteolytic enzymes involved in inflammation; immunopharmacology of respiratory and prostate epithelium in health and disease; bacteriolytic enzymes; protease activated receptors.

**Virology**

**Dr Manfred Beilharz (with Dr Mark Watson)** 9346 2663  
Email: manfred.beilharz@uwa.edu.au

Molecular pathology of murine AIDS as a model for human AIDS and B-cell lymphoma. Development of a therapy to combat retroviral infection that acts by modulating the host immune response to the virus.

**Associate Professor James Flexman (RPH)** 9224 1950  

**Dr Cheryl Johansen** 9346 4656  
Email: cheryl.johansen@uwa.edu.au

Epidemiology and ecology of Australian Arboviruses, especially the alphaviruses, Ross River virus and Barmah Forest virus, and the flaviviruses, Murray Valley encephalitis and Kunjin viruses; sero-epidemiology of flaviviruses in Aboriginal communities; vector competence studies on Australian mosquito species; development of improved field-based serological and molecular surveillance techniques for arboviruses.

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with Dr Alec Redwood 9220 3587 / 9346 2509  
Email: alec.redwood@uwa.edu.au

1. Natural resistance to virus infections and the mechanisms by which resistance genes protect the host against viral infection; the role of interferon, natural killer cells and T-cells in resistance; viral pathogenesis; the mechanisms by which cytomegalovirus induces diseases such as myocarditis through immune responses to viral proteins which show molecular mimicry with normal cellular proteins.
2. Another project employs murine cytomegalovirus as a recombinant vector incorporating genes encoding fertility associated proteins, to induce sterility in infected mice through the induction of immunity to proteins of the ovum and sperm. Other areas of interest relating to this project include studies of the spread and transmission of the virus in mice and the genetic variability of the virus in infected individuals.

**Dr David Smith** 9346 2164  
Email: david.smith@uwa.edu.au

Diagnosis and epidemiology of arbovirus infections, both alphaviruses and flaviviruses. Respiratory virus infections. Emerging infectious diseases. Surveillance and molecular epidemiology of infectious diseases.
Physiology

Dr Tony Bakker  
Room 1.20, Physiology Building  6488 7859  
Email: tony.bakker@uwa.edu.au

**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, that alter skeletal muscle contractile output and protein turnover through increases in intracellular levels of reactive oxygen species, Ca2+, 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 effect of a high-fat (junkfood) diet on skeletal muscle activation and performance  
   *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. The Role of Phospholipase A2 in the Skeletal Muscle Necrosis Responsible for Duchenne muscular dystrophy.  
   *Supervisors: Dr Tony Bakker & Dr Gavin Pinniger.*

4. Role of protease-activated receptors in promoting skeletal muscle regeneration after injury  
   *Supervisors: Dr Tony Bakker & Dr Gavin Pinniger.*

Research Associate Professor Livia Hool  
Room 1.96, Physiology Building  6488 3307  
Email: livia.hool@uwa.edu.au

**Ion Channels in Heart Muscle**

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. The normal electrical activity in the heart is controlled by the movement of ions through specialised channels in the membranes of cardiac cells. The autonomic nervous system plays an essential role in regulating cardiac function and many of its effects are mediated via sympathetic neurotransmitters that regulate the activity of these ion channels. 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. Understanding how cardiac ion channels are regulated under these conditions is crucial to understanding the ionic mechanisms involved in the triggering of ischemic arrhythmias. In addition an increase in reactive oxygen species can contribute to 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 molecular biology techniques for expression and purification of ion channel protein and biochemical techniques for assay of generation of reactive oxygen species and cell viability. The method that will be used to study membrane currents is the patch-clamp technique. This technique is an extremely powerful method for studying the electrophysiological properties of biological membranes and its contribution to the advancement of research was justly recognised with the awarding of the Nobel Prize in Physiology or Medicine in 1991 to its developers Erwin Neher and Bert Sakmann. The technique can be used to study ion channels both at a whole-cell level or at the level of a single channel. In addition, since the intracellular composition of the cell can be controlled, this can be exploited to determine any second messengers involved. Patch-clamp technique is also used in the laboratory in conjunction with fluorescent dyes to record changes in intracellular calcium, reactive oxygen species generation and mitochondrial function.
PROJECTS
1. How does the L-type calcium channel regulate mitochondrial function in pathology where actin filaments are disrupted?
2. How does oxidative stress alter the sensitivity of the L-type calcium channel to isoproterenol? What effect does this have on the action potential?
3. How does a brief oxidative stress (e.g., 5 min exposure to 30 uM hydrogen peroxide) alter protein synthesis in cardiac myocytes?

Dr Shane Maloney
Room 1.02, Physiology Building 6488 3394 Email: shanem@cyllene.uwa.edu.au

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. The Physiology of Avian Fever.
   With Prof Dave Gray (Physiology, University of the Witwatersrand)
3. Can we use Vibration to Enhance Cooling from Hyperthermia?
4. A Role for Prostaglandins in the Vasodilator Skin Blood Flow Response to Heat Exposure and Exercise?
   With Prof Brian Dawson (Human Movement and Exercise Science)
5. Why Does Exposure to High Ambient Temperature Inhibit Reproductive Efficiency?
   With Dr Dominique Blache (Animal Biology) and Drs Anne Barnes and David Beatty (Murdoch Vet School)

Respiratory Group
Room 225 & 226, Preclinical Link

Howard Mitchell 6488 3314 mitchell@cyllene.uwa.edu.au
Peter McFawn 6488 3341 pkm@cyllene.uwa.edu.au
Peter Noble 6488 3310 peter.noble@uwa.edu.au

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. Impact of simulated breathing movements on the response to bronchodilators.
   *With Lin Fernandez, Pharmacology (School of Medicine and Pharmacology)*

2. Relative importance of radial and longitudinal stretch to the bronchodilatation produced by deep inflation.
   *With Lin Fernandez, Pharmacology (School of Medicine and Pharmacology)*

3. Is bronchial hyperresponsiveness of immature animals due to reduced deep inflation bronchodilatation?

4. Maturational changes in calcium release during ASM contraction.
   *With Tony Bakker, Physiology*

5. Cellular basis for deep inflation produced bronchodilatation.
   *With Prof Geoff Stewart, Microbiology*

6. Response of isolated human bronchi to deep inflation.
   *With Alan James, Medicine (School of Medicine and Pharmacology)*

7. Breathing pattern and rate of spontaneous sighs in obstructive airway disease
   *With Alan James, Medicine (School of Medicine and Pharmacology)*

**Dr Gavin Pinniger**

Room 1.10, Physiology Building  6488 3380  Email: gavin.pinniger@uwa.edu.au

**Muscle Physiology Group**

Muscle contraction involves the cyclic interaction between myosin heads (crossbridges) on the thick filaments with binding sites on the thin (actin) filaments, a process that is driven by ATP hydrolysis. The original Huxley (1957) model for crossbridge cycling provides the foundation for current theories of muscle contraction and can account for various aspects of skeletal muscle function such as the force-length relationship and the force-velocity relationship during muscle shortening (concentric contraction). However, current models of muscle contraction fail to fully account for the force response when an active muscle is lengthening (eccentric contraction). Repeated lengthening of activated muscle causes muscle damage, loss of force producing capacity, and pain, and has been associated with disruption of structural proteins. This exercise-induced muscle damage (EIMD) also triggers and inflammatory response that is characterized by the slow development of tenderness, swelling and stiffness, in the several days after the initial exercise (often referred to as delayed onset muscle soreness or DOMS). These debilitating effects are enhanced if the eccentric exercise is excessive or unaccustomed, but may be reduced through an adaptation process brought about by frequent exposure to eccentric exercise. The increased susceptibility of dystrophic muscle to EIMD is considered a major contributor to the progressive muscle wasting that is characteristic of patients with muscular dystrophy. This research is aimed at unravelling the complex molecular events occurring during the lengthening of an active muscle with the aim of better understanding the mechanisms of EIMD and the subsequent inflammatory response. Further research is aimed at understanding the adaptation process brought about by repeated exposure to eccentric contractions and investigating various therapeutic interventions aimed at reducing the susceptibility of dystrophic patients to EIMD.

PROJECTS

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

2. The ability of antisense oligonucleotides 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 the inflammatory cytokine TNF (Tumour Necrosis Factor) in muscle damage
   *With Dr Tony Bakker & Prof. Miranda Grounds (Anatomy and Human Biology)*

4. Ventilation induced diaphragmatic dysfunction
   *With Dr Tony Bakker & A/Prof Jane Pillow (School of Women’s and Infants’ Health)*
The Auditory Laboratory
(See also projects by Dr R Patuzzi)

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. Effects of loud sound on gene expression in the cerebellum
   (With Dr Jenny Rodger)
2. Electrophysiology of plasticity in the auditory brainstem after partial unilateral deafness
3. Anatomy of plasticity in the auditory brainstem after partial unilateral deafness
4. Regulation of inner ear function by ATP receptors

Pharmacy

Nanoparticles for the delivery of anti-cancer drugs

Professor Lee-Yong Lim
6488 4413 Email: limly@cyllene.uwa.edu.au

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, used to enhance the accumulation of drugs in tumours. Anticancer drugs are highly potent, but are often associated with high morbidity and mortality due to their non-sensitive activity. By directing these drugs specifically to cancer cells, adverse events can be minimized and drug efficacy further improved. The aim of this project is to optimise the formulation of nanoscale calixarene platforms for the intracellular delivery of paclitaxel, a widely used anticancer agent. The optimized formulations will be evaluated for differential cellular uptake and toxicity in cancer and normal cell models. Data obtained will determine the potential of the calixarene-paclitaxel nanoparticles for cancer chemotherapy.

Many anticancer drugs, e.g. doxorubicin and paclitaxel, are substrates of the P-gp efflux transporter. Efflux transport by the P-gp is not desirable as it lowers the capacity of the anticancer drug to accumulate intracellularly, and is an established contributor to multi-drug resistance in cancer cells. Experiments carried out in our laboratory have shown that common spice components, such as curcumin (from turmeric) and piperine (from pepper), modify the function of the P-gp transporter in human cells. The purpose of this project is to evaluate the effects of curcumin and piperine, administered individually and cooperatively, on the intracellular delivery of doxorubicin in model cancer cells. Both long term and short term exposure of the cells to the spice components will be evaluated to delineate the time-dependent effects on P-gp activity. Data from this study will establish whether curcumin and piperine are viable adjuvants for cancer chemotherapy.
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.

### Acute Medicine

**Winthrop Professor Paul Jenkins (Joondalup Health Campus and Royal Perth Hospital)**  
9406 7818  email: pjenkins@meddent.uwa.edu.au

**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 3488  email: jhung@cyllene.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 3292  email: Leon.Adams@uwa.edu.au

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.

3. Serum markers of hepatic fibrosis.

4. Clinical trials in liver disease.

**Winthrop Professor J K Olynyk (FH)**  
9431 3774  email: john.olynyk@uwa.edu.au

1. Pathogenesis hepatocellular carcinoma

2. Iron Metabolism

3. Colorectal cancer screening.

4. Viral Hepatitis

**Geriatric Medicine**

**Winthrop Professor D G Bruce (FH)**  
9431 3774  email: david.bruce@uwa.edu.au

1. Health of the older person

2. Impact of diabetes on physical and cognitive function in the elderly
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

Winthrop Professor R L Prince (QEII) 9346 3488 email: richard.prince@uwa.edu.au

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 groundbreaking 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.

Associate Professor  S-K Gan (RPH) 9224 0256/0245 email: senq.gan@uwa.edu.au

1. Clinical studies examining mechanisms of insulin resistance, especially with regard to body fat distribution, tissue lipid (muscle & hepatic, using MRI/MRS technology) and adipokines.

A/Professor  Gerard Chew(RPH) 9224 0274 email: gerard.chew@uwa.edu.au

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

Winthrop Professor P J Leedman (RPH) 9224 0333/0323 Email: peter.leedman@uwa.edu.au

1. Regulation of oncogene expression in breast, prostate, and colorectal cancer. Investigation of the molecular mechanisms underlying the regulation of growth factor receptor gene expression in cancer cells.
2. Regulation of hormone action in breast and prostate cancer, with emphasis on nuclear receptor coregulators and translational biology.
3. Regulation of androgen receptor expression and signaling in prostate cancer.
4. microRNAs and cancer, investigating the functional biology of a range of microRNAs in cancers (lung, glioma, breast, prostate, head and neck, pancreas).
5. The laboratory investigates the regulation of expression of key target genes for therapeutics in each of these tumors, with an emphasis on impacting on the central signalling pathways. The laboratory has a strong translational bias with each project having tangible clinical components (eg. tissue microarray assessment of expression of specific genes, in vivo assays of tumor growth) and the long term goal of the laboratory is to work towards the development of novel small molecule modifiers of tumor growth that can be taken to the clinic.

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 Vascular Disease

Winthrop Professor Lawrie J Beilin 9224 0258 email: lawrie.beilin@uwa.edu.au

Studies of childhood origins of adult cardiovascular disease, obesity and diabetes; genetic and environmental effects and interactions.
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. C. Ytochrome P450 arachidonic acid metabolism.

Dr 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 Assistant Professor Anne Barden 9224 0272  email: anne.barden@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.

Professor Kevin D Croft 9224 0275  email: kevin.croft@uwa.edu.au
1. Markers of oxidative stress in disease
2. Lipid / protein oxidation and cardiovascular disease

Winthrop Professor Lawrie J Beilin (RPH) 9224 0258  email: lawrie.beilin@uwa.edu.au
2. Alcohol and cardiovascular disease.
3. Dietary antioxidants and blood pressure risk.

Professor Kevin D Croft and 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.

Professor P H R Barrett (RPH) 9224 0249  email: hugh.barrett@uwa.edu.au
Development of mechanistic 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 9224 0248  email: gerald.watts@uwa.edu.au
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.

Winthrop Professor G F Watts (RPH) 9224 0248  email: gerald.watts@uwa.edu.au
Studies of vascular endothelium function in dyslipidaemic, insulin-resistant and diabetic states. Involves use of venous occlusion plethysmography and ultrasonography.

Immunology and Cancer

Professor B W S Robinson (QEII) 9346 3129
Dr D Nelson (QEII) 9346 4967
A/Professor R Lake (QEII) 9346 3127
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**
email: ian.lawrance@uwa.edu.au

**Dr Borut Klopcic**
email: klopcic@cyllene.uwa.edu.au

**Dr Angela Chew**
email: achew@meddent.uwa.edu.au

**Fremantle Hospital 9431 3647**

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 alterations and to determine ways to modify these factors so as to alter the clinical patterns of ulcerative colitis (UC) and Crohn¹’s disease (CD).

Present investigations include an animal model of chronic inflammation-induced 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-induced 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.

**Dr Ross Graham**
email: rmgraham@cyllene.uwa.edu.au

**and Research Professor Debbie Trinder**
email: debbie.trinder@uwa.edu.au

**Fremantle Hospital 9431 3307**

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.

**Research Professor Debbie Trinder**
email: debbie.trinder@uwa.edu.au

**and Dr Ross Graham**
email: rmgraham@cyllene.uwa.edu.au

**Fremantle Hospital 9431 3640**

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 haemochromaotis 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.

**Associate Professor Callum Pearce**
email: Callum.pearce@uwa.edu.au

**Fremantle Hospital Gastroenterology**

**Medical Oncology**

**Dr Anna Nowak (SCGH)**
email: Anna.Nowak@uwa.edu.au

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

**Cancer Treatments**

**Professor Michael Millward (QEII)**
email: millward@waimr.uwa.edu.au

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

**Associate Professor Philip J Thompson (QEII)**  9346 3822/9346 3198  
Email: pjthomps@cyllene.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 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. Dendritic cell biology, airway modulation and allergy  
5. Airway inflammation including the role of prostanoids, leukotrienes, kinins and their biochemistry  
6. Eosinophils, neutrophils and their relevant mediators and regulation  
7. Pharmacogenetics of asthma and COPD  
8. Clinical drug trials and their design  
9. Role of RAGE in chronic lung diseases  
10. Aspirin sensitive asthma  
11. The role of exercise training in chronic lung disease  
12. Epidemiology and management of pulmonary hypertension.

**Dr Nigel McArdle (RPH)**  9224 0245  email: nmcardle@cyllene.uwa.edu.au

1. Cardiovascular Physiology of Sleep Apnoea/Hypopnoea Syndrome  
2. Neurophysiology of Sleep Apnoea/Hypopnoea Syndrome  
3. Studies on Sleep Disorders

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

**Research Assistant Professor Suzanna Lindsey-Temple  9224 0254**  
Email: Suzanna.temple@uwa.edu.au

1. Genetic Susceptibility to Pulmonary Infections. Investigation and gene polymorphisms within cytokines are related protein 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.

Rheumatology

**Associate Professor Helen Keen (RPH)**  9224 0244  email: Helen.keen@uwa.edu.au

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

Tropical and Infectious Diseases

**Winthrop Professor T M E Davis (FH)**  9431 3229  
Email: tim.davis@uwa.edu.au  
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.

Renal Medicine

**Dr Neil C Boudville (QEII)**  9346 2325  
Email: nboudvil@cyllene.uwa.edu.au

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
Pharmacology and Anaesthesiology
Head of Discipline: Professor Peter Henry 9346 3123 email: peter.henry@uwa.edu.au

Respiratory Pharmacology

Dr Peter J Henry 9346 3123 email: peter.henry@uwa.edu.au
Dr Lynette B Fernandes 9346 4517 email: lynnette.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.

Professor Ken F Ilett 9346 2985 email: ken.ilett@uwa.edu.au
Professor TME Davis 9431 3228 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 piperaquine. 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 piperaquine in humans.

Professor David A Joyce 9346 2569 email: david.joyce@uwa.edu.au

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.
The role of macrophage motility in inflammation and disease progression

Macrophages form part of the host microenvironment and contribute to the pathogenesis of disease. Motility is an essential aspect of their function. Studies in this laboratory are aimed at delineating the molecular mechanisms regulating macrophage motility and determining the role of macrophage motility in the promotion of tumour invasion and metastasis and in chronic inflammatory disorders. As a result, therapies to inhibit macrophage infiltration of tumours and other inflammatory sites should be identified. Techniques used in the laboratory include cell culture, microscopy and protein biochemistry.

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 toxicolgy 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 immunochemical analysis of protein modifications, proteomic identification of protein targets and microarray analysis of transcriptional responses to acrolein.

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 inactivation 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.

Pleural Disease Research

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.
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 Contact: Dr Cleo Robinson on 9346 1518 or email cleorob@cyllene.uwa.edu.au

PROFESSOR ANNA NOWAK

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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.
**Chemotheraphy, 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 tolerated. 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?

**PROFESSOR RICHARD LAKE**

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**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, Associate 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 Dr. 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.

Dr. 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, Dr. 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. McCoy MJ, Nowak AK, Lake RA. Chemoimmunotherapy: an emerging strategy for the treatment of malignant mesothelioma. Tissue Antigens. 2009;74:1-10.

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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 treat 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.

**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-2K^b\) derived tumour cell lines that express the Balb/c (H-2K^d\) 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-2K^d\) restricted epitopes by these cell lines to C57Bl/6 (H-2K^b\) restricted CD8 T cells is prevented in H-2K^d (C57Bl/6) or H-2K^b/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-2K^d\) 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.
specific chemotherapy agent so that their treatment regimes can be best targeted. The aim of this study is ultimately to identify those patients most likely to respond to a first-line therapy. In this current project we plan to define the molecular pathways responsible for resistance to pemetrexed in malignant mesothelioma. The chemotherapy 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. Gemcitabine is a nucleoside analogue, directly inhibits the RR enzyme.

**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 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 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 (JHCC, 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 autoimmune. 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.

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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.
Current studies with potential for BMedSc Honours Projects:

1. **Perth childhood acute asthma study** (PCAAS) – Mechanisms involved in acute asthma attacks in children using assessments of viral infection, immunology, genetics and physiology in children presenting with acute asthma (NHMRC program grant). Asthma attacks are the number one cause of hospitalisation in children and contribute significantly to missed school days and family stress. We have recruited 400 children who have presented to the Princess Margaret Hospital Emergency Department with an asthma attack and plan to recruit at least 200 more for ongoing studies. The children are followed up when they have recovered from the attack. Over 90% of these children have a viral infection on presentation and we are particularly interested in discovering why particular viruses can precipitate acute asthma exacerbations. We have also discovered that human rhinovirus (HRV) is much more common than expected as a cause of acute asthma and over 85% of children with acute asthmas 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, the HRVC is the most common cause of the most common reason children are 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 a common disease are very rare in research these days. Our work has raised many crucial questions about acute asthma and about HRVC. Aspects of this work that have strong potential as BMedSc projects include:

   (i) **Studies of HRV and HRVC in the developing world** – we have a major collaboration with a Spanish group working in Mozambique and we would like to determine the role of HRV and HRVC in respiratory diseases in young children in the developing world. This project would require travel to Africa and collection of specimens there as well as laboratory work back in Perth to analyse the specimens.

   (ii) **Studies in the community control groups of children in Perth** 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.

   (iii) **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 develop acute asthma in response to respiratory viral infections is crucial to our understanding of 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 asthma susceptibility in detail and each would make an excellent BMedSc project.

2. **Evolution of the human immune system and genetic diversity of human populations** – 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.

3. **18 yr assessment of Perth Infant Asthma Follow-up (PIAF) cohort.** 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 30 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.
4. Immunogenetics of malaria infection in early life – 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 will address 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.

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Adolescent Medicine

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Potential BMedSc project: Immunology of Otitis Media

Middle ear infections (otitis media, OM) are the most common reason for a child to see a doctor, be given antibiotics, or undergo surgery. Recurrent OM (rOM) and the accompanying persistent middle ear effusions (glue ear) in young children are associated with hearing loss, which can significantly affect a child’s development and learning. Aboriginal children are at highest risk for severe OM and related disease and subsequent consequences.

Despite the frequency of and the morbidity associated with rOM, the causal mechanisms that lead to recurrent OM are still poorly understood. A poorly functioning immune system is an important risk factor for rOM but to date has not been extensively investigated.

Our research group is interested in how exactly the immune response in children with rOM (including Aboriginal children) differs from healthy children and whether variation in the genes of the immune system underlies these differences. By identifying which aspects of the immune response are most impaired in children suffering from recurrent infections, new vaccines can be developed using specific immune stimulants (adjuvants) that can overcome these problems, since there are currently no effective strategies to reduce the disease burden other than ENT surgery.

Several clinical studies to investigate this are being performed by our group:
The Otitis Media Study (OMS): A study in which the effect of pneumococcal vaccination to prevent recurrence of OM was investigated. Peripheral Blood Mononuclear Cells (PBMCs), serum, plasma and saliva have been collected of 80 children with rOM and 30 healthy control kids.
The Biofilm Study: A study to investigate the role of bacterial slime (biofilm) in the middle ear of children with rOM. PBMCs, serum, plasma and saliva have been collected of 150 Caucasian and Aboriginal children with rOM. The recruitment of healthy controls has just started.
The GROMIT study: A study to look at the immune response and genetic differences in genes of the immune system between children with and without rOM. Recruitment for this project has just started and will involve collection of PBMCs, serum, plasma, saliva and DNA.

With these samples we aim to identify the immune responses that are impaired in children with recurrent OM compared to healthy children. This will be done by investigating:
• Antibody responses to bacterial proteins in serum (IgG) and saliva (IgA) by using Enzyme Linked Immuno Sorbent Assays (ELISA)
• Cellular immune responses by culturing PBMCs with bacterial proteins and measuring cytokines the cells produce using Time Resolved Fluorometry (TRF)
• Genetic differences in immunological pathways which identified disparities between children with and without rOM
• Questionnaire data on environmental and host risk factors to account for baseline differences between cases and controls

A potential BMedSc project could involve part of the described laboratory work on a distinct set of collected samples. Students could also be involved in recruitment of new study subjects, which would involve contact with parents, collection of samples in operating theatre and processing of samples, all under supervision of experienced staff.
Investigating antimicrobial peptide responses in the human preterm infant – All newborns rely heavily on their innate immune defences to prevent infection. However, infants born prematurely have a much higher risk of developing serious infections, even into early childhood. Antimicrobial peptides (AMP), produced in microgram quantities by a range of cell types, are among the most ancient innate defence systems of the animal kingdom, but their role in preventing infection in humans is not well understood. In this project, the candidate will use a range of cellular, molecular, microbiological and immunological methods on primary samples from preterm and term infants and adult volunteers to examine how the human AMP system protects against infection and responds to normal microbial commensals. This represents an exciting new area of human immunology/infection research with ramifications for preventing infections in newborns. There is potential to develop the project into a higher degree.

Professor Lou Landau 9340 8624 email: llandau@meddent.uwa.edu.au
Developmental origins of childhood asthma

Professor David Forbes 9340 8122 email: david.forbes@health.wa.gov.au
Medical aspects of adolescent Eating Disorders
Functional bowel disorders in childhood

Professor Susan Prescott 9340 8171 email: sprescott@meddent.uwa.edu.au
Primary prevention of allergy in children
Early immune development in fetal and early postnatal life
The effects of diet (probiotics, fatty acid and antioxidants) on immune function
Paediatric allergy, asthma and immunology
For further information: Prof Prescott: susanp@ichr.uwa.edu.au or Dr Dunstan: jand@ichr.uwa.edu.au

Clinical Professor Stephen Stick 9340 8696 email: stephen.stick@health.wa.gov.au
Paediatric Respiratory and Sleep Physiology, Epithelial Cell Biology
Paediatric Respiratory Diseases
Role of indoor air pollution in paediatric respiratory diseases

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Epithelial Cell Biology

Dr Erika Sutanto 9340 8400 email: erikas@ichr.uwa.edu.au
Epithelial Cell Biology

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 proliferation 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, ie 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.

**Associate Professor Christopher Blyth:** 9340 7061   email: ccblyth@meddent.uwa.edu.au
Paediatric Infectious Diseases and Microbiology
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

**Dr Sunalene Devadason** 9340 8985   email: sdevadason@meddent.uwa.edu.au
Aerosols in Paediatric Medicine
Investigation into generation, delivery and deposition of medical aerosols in childhood

**Dr Peter Franklin** 9340 8176   email: peter.franklin@uwa.edu.au
Title: Air quality and children’s respiratory health
Project outline: There are opportunities to be involved in studies of the impacts of indoor and outdoor air pollution on children’s respiratory health. Studies include lung function of children living in Kwinana, indoor air pollution and respiratory symptoms in asthmatic children and measurements of biomarkers of environmental exposures

**Dr Guicheng Zhang** 9340 7896   email: gczhang@meddent.uwa.edu.au
Title: gene by environment interaction on asthma and allergy in children
Project outline: 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.

**Dr Catherine Choong** 9340 8090/8606   email: catherine.choong@health.wa.gov.au
Paediatric Endocrinology and Diabetes

**Clinical Research Professor Jonathan Foster** 9340 8175   email: jfoster@meddent.uwa.edu.au
Title: Early life events and markers of adolescent neurocognitive functioning and mental health
Project outline: 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 researchers based at UWA 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 project (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.
**Title: Contribution of glutathione (GSH) pathway gene variants to the variability in lung GSH levels and disease severity in children with cystic fibrosis (CF).**  
Co-supervisors:  Prof Jack Goldblatt (Clinical Genetics, King Edward Memorial Hospital; Dr Anthony Kikic, Dept of Respiratory Medicine, Princess Margaret Hospital; Prof Peter Sly, Division of Clinical Sciences (ICHR)

Project outline: 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-oxidative 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.

**Title: Viral burden in infants with Cystic Fibrosis (CF)**  
Co-supervisors:  Prof Steve Stick, Dept of Respiratory Medicine, Princess Margaret Hospital; Prof Peter Sly, Division of Clinical Sciences (ICHR)

Project outline: 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.
Title: Gene/environment interactions in the glutathione antioxidant defence system in acute asthmatic children  

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 2011 Telethon Institute for Child Health Research Honours Student project booklet outlines 42 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: http://www.ichr.uwa.edu.au/files/user5/2011_Honours_Projects.pdf  

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.
**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.

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**SCHOOL OF PATHOLOGY AND LABORATORY MEDICINE**

**Head of School:**
**Winthrop Professor Martyn French**  9346 2739  email: martyn.french@uwa.edu.au

**Dr Kimberley Strong**  9346 2076  email: kimberley.strong@uwa.edu.au

**Acute Renal Failure**
Dr Strong has expertise in urinary protein assays and early diagnosis of renal disease, mostly in diabetic patients. She is currently establishing a new area of research, investigating protein excretion patterns due to acute renal failure in critically ill patients.

**Projects:**
1. Proteinuria and renal outcomes in patients with acute renal failure.

**Adjunct Associate Professor Jacky Bentel**  9224 3123  email: jacky.bentel@health.wa.gov.au

**Dr Marc Thomas**  9224 8498  email: marc.thomas@health.wa.gov.au

**Characterisation of Hormone Dependent Cancers**
The laboratory investigates hormone dependent cancers (breast and prostate cancers) and students carry out projects on either cancer. 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 cancer
4. Androgen action in breast cancer cells

**Professor Patricia Price**  9224 0378  email: patricia.price@uwa.edu.au

**Clinical Professor Martyn French**  9224 2899  email: martyn.french@uwa.edu.au

**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 Kuala Lumpur and 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. Many 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) Mycobacteria-specific responses of host macrophages (Mφ) in NTM lung disease.

Th1 immunity (production of IFN-γ and TNF-α) and Mφ activation are essential for containment and killing of mycobacteria. Defective Mφ activation results in poorly formed granulomas and survival of mycobacteria. This project will assess abnormalities in general and mycobacteria-specific responses of Mφ from NTM patients.

(Project B) 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.

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

Immunology of Renal Transplantation

This group's interest focuses on improving the outcome of solid organ transplantation, particularly kidneys. They are currently investigating the role of anti-HLA antibodies in chronic rejection and subtle immune defects in dialysis patients.

Projects:
1. Prediction of kidney graft survival based on software-based prediction of the immunogenicity of specific HLA mismatches.
2. Can anti-HLA antibody formation in dialysis patients given blood transfusions be prevented by concomitant immunosuppression?
3. Are poor vaccine responses in dialysis patients associated with dysfunctional dendritic cells?
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.

Cell signalling and regulation of mRNA
This group has various research interests which focus on cell signalling and regulation of mRNA in repair processes and cancer growth. Techniques used in the laboratory include tissue culture and cell function assays, real time PCR, western blot analysis, immunohistochemistry, cell transfection and reporter assays and animal models of disease.

Current projects include
1. Hedgehog signalling in mesothelial regeneration
2. The interaction between hedgehog and transforming growth factor beta signalling pathways in malignant mesothelioma growth
3. The Hedgehog pathway in gastric dysplasia: a role in the pathogenesis of gastric carcinoma
4. Suppressor of cytokine signalling proteins in the control of pulmonary fibrosis
5. miRNAs in malignant mesothelioma
6. miRNAs in primary central nervous system lymphomas

Serum Cytokine Levels and Graft-Versus-Host Disease after Allogeneic Stem Cell Transplant
Allogeneic haematopoietic stem cell transplantation (HSCT) is an effective treatment for a wide range of disorders that would otherwise be fatal. Unfortunately, it is frequently complicated by the development of an inflammatory disorder known as graft-versus-host disease (GVHD). This disorder occurs as a result of interactions between antigen-presenting cells of the recipient and mature T-cells of the donor. It is associated with significant morbidity and mortality and can be difficult to control using current immunosuppressive regimens. Novel approaches, including the use of mesenchymal stromal cell (MSC) therapy, are currently being evaluated by us as part of clinical trials. Characterisation of the changing patterns of cytokine expression following high dose chemotherapy and allogeneic HSCT in humans may be used to guide the optimal timing of MSC therapy in the management of GVHD.

The aims of the study are to:
1. Measure the serum levels of four cytokines (TNF alpha, IFN gamma, IL-2 and IL-6) by BD cytometric bead array (CBA) technology in patients undergoing high dose chemotherapy and allogeneic haematopoietic stem cell transplantation.
2. Identify associations between the serum levels of cytokines and the onset of GVHD.
3. Predict the optimal timing of MSC therapy in the management of GVHD.
4. Identify cytokine changes following MSC treatment of GVHD.
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 Einarsdöttir 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).
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.

General Practice

Chair of General Practice:  
Winthrop Professor Jon Emery  9449 5150  Email: jon.emery@uwa.edu.au

General Practice carries out extensive research into a variety of areas of primary care, community health and general practice education. There are opportunities for a Bachelor of Medical Science student to participate in primary health care research and the following members of staff are able to supervise BMedSc projects:

Professor Emery is the Head of School and Chair of General Practice. His research interests are in cancer research in primary care; chronic disease management in general practice; genetics in primary care including application of the family history and use of new genetic tests in clinical practice.

Associate Professor Caroline Bulsara  9449 5166  Email: caroline.bulsara@uwa.edu.au

Dr Bulsara works with general practitioners and divisions of general practice in developing, implementing and evaluating research programs in the area of primary health. Her areas of expertise are qualitative research, survey and questionnaire design, scale development, consumer involvement in health outcomes and disadvantaged groups.

Research Associate Professor David Whyatt  9449 5141  Email: david.whyatt@uwa.edu.au

Dr Whyatt has a PhD in molecular biology and postgraduate training in biostatistics. His research interests include chronic disease management, 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.

Emergency Medicine

Head of Discipline:  
Winthrop Professor Tony Celenza  9346 4355  Email: tony.celenza@uwa.edu.au

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, venom research, poisons information and toxicology, and in evaluation of teaching and learning in emergency medicine. The following members of the academic staff are able to supervise BMedSci projects:

Professor Ian Jacobs  9346 1587  Email: ian.jacobs@uwa.edu.au

Epidemiological and outcome studies of pre-hospital care  
Clinical studies in pre-hospital care  
Utilisation and outcomes of Emergency Care  
Clinical trials in Emergency Medicine  
Resuscitation  
Trauma and trauma systems  
Primary and secondary retrieval systems
Centre for Clinical Research in Emergency Medicine (CCREM), Western Australian Institute for Medical Research (WAIMR), Royal Perth Hospital Campus:

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. Current research streams include redback spider and elapid snake envenoming (clinical effects, management with antivenom and blood products), adverse reactions to antivenoms, anaphylaxis (pathophysiology and management), venom allergy and immunotherapy (mechanisms), toxicology (drug overdose), amphetamine effects on the brain, sepsis, and the management of acute illnesses in the elderly - particularly heart failure and sepsis.

Potential BMedSci students with particular interests in the broad fields of toxinology, toxicology, acute medicine are invited to contact one of the researchers to discuss potential projects, according to the main fields of interest as outlined below.

**Associate Professor Glenn Arendts**  
9224 14947  Email: glenn.arendts@uwa.edu.au

A number of projects are available for research into life threatening illness afflicting the elderly patient, and systems research for improving the provision of acute care to the elderly patient within ED.

**Acute cardiac failure and sepsis in the elderly**

Critical illness in the elderly is a focus of our Centre. Several projects are available looking specifically at cardiac failure and sepsis, including:

- Identifying the relationship between early biomarker changes in elderly heart failure patients and subsequent development of renal dysfunction.
- Using a combination of clinical, laboratory and echocardiograph data, to increase accurate identification of acute diastolic failure versus systolic or no heart failure.
- Investigating the relationship between cardiac dysfunction and adverse outcome in the elderly septic patient, through the use of laboratory markers taken at early timepoints in the illness.

**Delirium**

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.

**Pain assessment in cognitively impaired patients**

A project exists for a student to improve the recognition and management of pain in elderly patients with cognitive impairment presenting to ED.

**ED avoidance for the frail elderly**

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.

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

**Dr Shelley Stone (Laboratory manager)**  
9224 0356  Email: shelley.stone@uwa.edu.au

**Toxicology**

Royal Perth Hospital has a well developed clinical toxicology unit admitting in excess of 1200 poisoned patients per annum including >70 to Intensive Care. A randomised controlled trial of activated charcoal to reduce drug absorption is planned to start in 2009, using pharmacokinetic endpoints, at several hospitals in WA and interstate. Within the framework of this trial, a BMedSci project would investigate the clinical impact of intervention in particular staff acceptance, patient tolerance and duration of altered physiological parameters including altered consciousness.

**Critical illness – shock states (including sepsis)**

Using the clinical infrastructure and laboratory methods developed in our anaphylaxis study we plan to start collecting serum samples for multiple cytokine analysis from patients with a range of critical illnesses focussing primarily on shock states including sepsis. A BMedSci project is to explore the time course of a range of cytokines in these patients and potential correlation with disease severity and outcome. This would suit students interested in the mechanisms of critical illness, in particular the early human immune response.
Centre for Aboriginal Medical and Dental Health (CAMDH)

Director:  
**Professor Helen Milroy**  
6488 2038  Email: helen.milroy@uwa.edu.au
Associate Professor Milroy’s specialist training is as a child and adolescent psychiatrist and she continues to work in the public system. Her research areas cover social and emotional well-being, resilience, grief and the dimensions of health. Students may choose a topic solely within in the Centre or may undertake the degree in another school in the Faculty with a joint supervisor from CAMDH.

Assistant Professor Paula Edgill  
6488 8140  Email: paula.edgill@uwa.edu.au
Assistant Professor Edgill is a recent graduate who has an interest in Emergency Medicine, prison health, adolescent health, and the role of Indigenous health care providers in the Australian health care context.

Associate Professor David Paul  
6488 7084  Email: david.paul@uwa.edu.au
Associate Professor Paul has worked for many years in general practice and his research interests include Aboriginal community control in Aboriginal health, self-determination, the determinants of health, Primary Health Care and the roles of medical practitioners in Aboriginal Affairs. David also has an interest in the impact and effectiveness of Indigenous Health Education curricula.

Combined Universities Centre for Rural Health (CUCRH)

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.

Director:  
**Winthrop Professor Sandra Thompson**  
9956 0200  Email: Sandra.thompson@cucrh.uwa.edu.au
Winthrop Professor Thompson has extensive experience working in a variety of health settings across a number of jurisdictions across Australia as a clinician, researcher and as a public health physician. Since 1994, Sandra’s work has involved working with marginalised or underserved communities, with a particular focus on Aboriginal health, research and capacity building. She has established professional collaborations and networks and well developed skills and experience in participatory planning and visioning, action learning and research, collaborative and strengths-based research and evaluation, particularly around partnership tools plus organisational and system change methodologies. Sandra has an understanding and familiarity with a variety of methodological approaches and research paradigms, expertise in surveillance systems, a strong background in epidemiological methods and data analysis.

Research Assistant Professor Melissa Barrett  
9956 0226  Email: melissab@cucrh.uwa.edu.au
Melissa Barrett is a Nurse Practitioner whose areas of interest and expertise are Palliative Care, Community Nursing, Remote Area Nursing, Midwifery Practice in Rural and Remote Areas, Nursing Education in Rural and Regional Areas, Telehealth and Wound Care. Melissa is also a PhD Candidate.

Associate Professor Juli Coffin  
9956 0247  Email: julicoffin@cucrh.uwa.edu.au
Associate Professor Coffin is the Aboriginal Senior Health Lecturer at CUCRH with formal qualifications and extensive experience in education and health promotion. Her research interests include the experiences of Aboriginal people as patients and workers in mainstream health services, child health interventions for Aboriginal people and the development of culturally safe protocols for health services. Juli is also involved in mental health challenges facing Aboriginal communities and children around relationship issues and keeping our children mentally safe.

Associate Professor Marisa Gilles  
9956 0232  Email: mgilles@cucrh.uwa.edu.au
Associate Professor Gilles is a public health physician with 18 years experience in the prevention and management of sexually transmissible diseases. She is active in research on social capital, the relationship between health and town planning, multidisciplinary models of health care delivery, and the environmental determinants of health. Dr Gilles holds a regular clinic at the regional prison and BMedSci students could become involved in projects related to prison health, chronic disease management and blood-borne viruses and STIs.

Ms Charmain Green, Lecturer  
9956 0226  Email: charmaine.green@cucrh.uwa.edu.au
Melissa Barrett is a Nurse Practitioner whose areas of interest and expertise are Palliative Care, Community Nursing, Remote Area Nursing, Midwifery Practice in Rural and Remote Areas, Nursing Education in Rural and Regional Areas, Telehealth and Wound Care. Melissa is also a PhD Candidate
Assistant Professor Jan Hall  
9956 0247  
Email: jan.hall@cucrh.uwa.edu.au

Assistant Professor Hall has been employed in a variety of roles within the health industry for the past thirty years. Her formal qualifications in nursing and health science have contributed to her broad experience in nursing and health service development and management throughout WA. Jan currently focuses on projects targeting Aboriginal health, cultural proficiency, evaluation and service modelling.

Assistant Professor Maeva Hall  
9956 0200  
Email: maeva.hall@cucrh.uwa.edu.au

Assistant Professor Hall is a qualified Occupational Therapist having working within the Health industry for over 30 years in a variety of both clinical and non clinical roles. She has a passion for rural health, having spent the majority of her career in rural areas, focussing on primary health, health service development and Telehealth.”

Assistant Professor Ivan Lin  
9956 0204  
Email: ivan.lin@cucrh.uwa.edu.au

Assistant Professor Lin is a Physiotherapist whose activities include a range of strategies to support rural and remote allied health professionals, rural and remote relevant undergraduate education and research interests in musculoskeletal health.

Assistant Professor Gelaye Nadew  
9158 9900  
Email: gelaye.nadew@cucrh.uwa.edu.au

Assistant Professor Nadew holds the position of Mental Health Academic. He is a qualified nurse with specialties in mental health nursing. He has a MSc in Nursing and a PhD in Medicine/Psychiatry. His PhD documents the relationship between exposure to traumatic events, alcohol abuse and prevalence of Post Traumatic Stress Disorder (PTSD) in Aboriginal Communities in Australia. Gelaye is based in the Pilbara.

Associate Professor Barbara Nattabi  
9956 0200  
Email: barbara.nattabi@cucrh.uwa.edu.au

Associate Professor Nattabi is a medical doctor and public health practitioner with 10 years experience in prevention and management of HIV and other sexually transmitted diseases. Her interests include stigma and discrimination and their impact on health behavior, epidemiology of HIV, adherence to antiretroviral therapy, mixed methods research, mental health among refugees, migrants and rural populations. She also has extensive project management experience, specifically Voluntary Counseling and Testing for HIV, Antiretroviral therapy and Prevention of Mother–to-Child transmission and HIV surveillance programs.

Associate Professor Sarah Prout  
9956 0200  
Email: sarah.prout@cucrh.uwa.edu.au

Associate Professor Prout's disciplinary background is in Human Geography and applied social research. Her core research activities focus on Indigenous demography and spatiality and how specific Indigenous population dynamics unsettle existing mainstream education, housing and health delivery frameworks, and call forth more adaptive and flexible service delivery practices. Sarah’s other research interests include the development of relevant, reliable and representative indicators of Indigenous wellbeing, and the social, spatial, cultural and health geographies of urban-based Indigenous peoples.

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 provide you with a bursary for self-arranged accommodation and a stipend to support your living expenses over the year. There are also top-up scholarships available, which may be used to attend relevant courses, or to allow travel 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.

Most 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.

Academic staff that are able to supervise BMedSci projects include:

Head of Centre:
**Winthrop Professor Geoff Riley**  
9842 0820  
Email: geoff.riley@uwa.edu.au

Professor Riley’s research interests involve psychiatry in general practice, affective illness, somatisation, rural and remote medicine and psychiatry, and medical ethics.
Chair of Research Steering Committee:
Professor Kirsten Auret 9842 5555 Email: kirsten.auret@uwa.edu.au
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 researcher who works alongside her and would also be available to support and extend you.

Associate Professor David Atkinson 0438380209/91936043 Email: david.atkinson@uwa.edu.au
Dr Atkinson is a Medical Coordinator in the Kimberley and also works for the Kimberley Aboriginal Medical Services Council (KAMSC), based in Broome. Dr 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.

Associate Professor Christine Jeffries-Stokes 9091 0662 Email: christine.jeffries-stokes@uwa.edu.au
Associate Professor Jeffries-Stokes is a Paediatrician in Kalgoorlie who has strong clinical and family links with the communities scattered throughout the Goldfields. Her research is powering ahead with an exciting project exploring the early markers for chronic diseases such as the metabolic syndrome in Aboriginal communities, but linking this with the practical delivery of health information through an arts and music programme. Involvement in this project would see you travelling around the Western Desert in a specially converted clinical – artist truck, sleeping under the stars and making a difference to the lives of many people.

Associate Professor Andrew Kirke 9722 0500 Email: andrew.kirke@uwa.edu.au
Dr Kirke is a Medical Coordinator with the RCSWA in Bunbury. He also works in General Practice and has special interests in Obstetrics and Anaesthetics. Dr Kirke has been involved in teaching for five years. This has been at a post-graduate level through GP Registrar training and more recently at an undergraduate level with the RCSWA. He is researching obstetric outcomes in the bush, and has recently started a new project focused on the South West that would easily include a BMedSci student in meaningful work, that will make practical differences to the management of births in the country.

Associate Professor Moira Maley 9842 5555 Email: moira.maley@uwa.edu.au
Associate Professor Maley is a scientist and medical educator with a special interest in learning in the RCSWA environment. She is progressing work on questions arising from the huge dataset we have available of e-logged cases from previous cohorts of students.

Associate Professor Bronwyn Peirce 9722 0500 Email: bronwyn.peirce@uwa.edu.au
Dr Peirce is an ED physician from Bunbury who is involved with a number of projects that are being run in the South West, including psychosocial aspects of care for rural women with breast cancer, familial hypercholesterolemia and research into the use of Advanced Health Directives.

Associate Professor Denese Playford 9449 5145 Email: denese.playford@uwa.edu.au
Associate Professor Playford is a medical educator with vast experience of teaching and learning in rural environments. She is currently following the choices made by our students and alumni about fields and location of practice after leaving the RCSWA. She is also working with others at the university on a longitudinal study of medical professionalism – seen from the perspective of students and young doctors. Both these projects would be suitable for a student’s involvement.

Associate Professor Helen Wright 9340 7538 Email: helen.wright@uwa.edu.au
Associate Professor Wright is a General Paediatrician at Princess Margaret Hospital who works with the School of Paediatrics and Child Health and as the Paediatrics Coach with the RCSWA. She visits RCSWA sites and delivers videoconference tutorials to RCSWA students as well as teaching metropolitan students. Dr Wright’s research interests are in general paediatric topics and rural paediatrics, including the effects of installation of swimming pools in remote communities.
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  
Email: christobel.saunders@uwa.edu.au

**Dr Toni Musiello**  
9346 4174  
Email: toni.musiello@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:

**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. 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 Email: christobel.saunders@uwa.edu.au
Research Asst Professor Claire Johnson 9346 4700 Email: Claire.Johnson@UWA.edu.au
Research Asst Professor Angela Ives 9346 3161 Email: 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 the WACPCN projects and activities. 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 rural Western Australia (in collaboration with the Palliative Care Network and ECU)
2. Patterns of care in colorectal cancer project. WACPCN (in collaboration with the Lower GI Tumour Collaborative and the WACPCN)
3. Literature review and development of a research proposal for the development of a cancer care pathway (in collaboration with 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. Research education needs of health professionals associated with the WACPCN
6. Combination therapy in patients with high risk bladder cancer (in collaboration with Prof Dickon Hayne, Fremantle Hospital)
7. 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)
8. 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 Curtin University)

CaPCREU is also involved in the evaluation of WACPCN activities. Programs and projects that have been implemented by the WACPCN will be evaluated to report how well they have met their objectives and whether outcomes for people with cancer in WA have improved as a result of the program or intervention.

Ear Sciences Centre (including Otolaryngology)

Winthrop Professor Marcus Atlas 9346 3633 Email: marcus.atlas@earscience.org.au
Adj Associate Professor Robert Eikelboom 9346 3735 Email: rob.eikelboom@uwa.edu.au
Dr Robert Marano 9346 7956 Email: rob.marano@earscience.org.au
Professor Peter Friedland 9346 3089 Email: peter.friedland@uwa.edu.au

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. 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 cochlear 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.
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.

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 (9346 3735)  
**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 (9346 3735); 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.

**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), an epidemiology project 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 (9346 3735); 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 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 (9346 3735); peter.friedland@uwa.edu.au  
**Project Outline:** Little is known of the prevalence of the various types of hearing loss in Australia. All 800 participants per year in the BHAS undertake a full hearing test. This project will characterise the types and nature of hearing loss, and explore associations with other health measures.

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

**Winthrop Professor Ming H Zheng**  
9346 4050  
Email: minghao.zheng@uwa.edu.au

#### 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.

**Tendon Repair and Regeneration**

Tendon injuries occur commonly and are often caused by acute and repetitive events such as sporting mishaps, over-extensions, or incorrect alignment. Tendonopathy is a type of tendon injury that occurs when the tendon becomes painful or dysfunctional due to a change in the collagen matrix known as ‘tendinosis’. Loss of rotator cuff tendon integrity generally results in impaired strength, a reduced range of motion and a loss of function. Current treatments for tendon related injuries provide poor clinical outcomes and have high failure rates. If surgery fails to correct the problem, management is typically restricted to physical exercise rehabilitation and behaviour modification.

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

1. **Autologous Tenocyte Implantation (ATI):** This process involves regenerating 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.

**Orthobiologics & Tissue Engineering**

Orthobiologics is a relatively new concept of surgical procedure using biological based implants for the induction of repair and regeneration of bone, cartilage and tendon tissue. Over the last few decades there have been dramatic developments in the field of osteobiologics. This has led Orthopaedic Surgery to re-visit the principle of bone cell biology other than just bio-mechanics of skeletal tissue. Examples of orthobiologic developments include the use of OP-1 & BMP-2 for the treatment of non-union fractures, the matrix-induced autologous chondrocyte implantation and implaction bone allograft for revision hip protheses. The objectives of this project are to understand the tissue engineering concept of skeletal tissue regeneration and to develop clinical and practical biotherapeutic products in the field of Orthopaedic Surgery. The major aims of the project are to investigate the feasibility of biological joint replacement and to establish cell and matrix based biological therapy for tendon and bone tissue regeneration. Methodology of the project includes gene therapy, cell culture, flow cytometry, confocal analyses and a series of biocongability studies in vivo.

**Orthopaedic Equipment & Devices**

The fundamental aim of this project is to develop equipment and methods to facilitate internal examination of cartilage in its functional condition and then to use the developed techniques to study arthritis. The internal microstructure of cartilage and determination of its functional biomechanics could potentially reveal the nature and causes of arthritic diseases. Confocal microscopy will be used in-vitro to determine the functional properties of cartilage and theories describing the biomechanics of normal and arthritic cartilage will subsequently be verified and developed. Concurrently, confocal arthroscopy will be developed to be of genuine clinical value for the assessment of cartilage in-vivo. This work is in collaboration with Professor Brett Kirk at the School of Mechanical Engineering, UWA.
Molecular Mechanism of Bone Resorption
Abnormal osteoclastic bone resorption is responsible for many osteolytic diseases, including osteoporosis, osteoarthritis and cancer induced bone destruction. The centre has a long term interest in the investigation of the molecular mechanism of bone destruction and the pathogenesis of bone diseases. The current key focus on the study include intracellular vesicle trafficking of osteoclast, cellular signalling which controls the process of bone resorption and the molecular structure of H-ATPase. Methods used for the investigation include in vitro cultivation of osteoclasts from monocyte/macrophage, bone resorption pit assay, confocal and micro CT assessment, histomorphometry and loss of function study by silencing and gene knock out strategy.

Professor Jiake Xu  
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

Otolaryngology Unit (Fremantle Hospital)

Professor Gunesh Rajan  
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 plays a leading role in academic Otolaryngology in WA. It is the busiest Head & Neck Cancer Unit in the state and, in conjunction with PMH and RPH, performs the majority of oncological as well as neurotological skull base surgery in the state. The Unit was recently identified as one of the 17 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 group of the Unit 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 groups of the Unit focus on various research areas. The FH & RPH group run research projects in the areas of stapes surgery, skull base surgery, hearing implants, head & neck imaging and head & neck cancer prevention. The PMH group investigates the various aspects of pathogenesis of chronic 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
Wound Healing Research

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

Wound Healing and Vascular Surgery

The focus of our research is the investigation of impaired wound healing in chronic wounds in humans. We have a particular interest in venous leg ulceration, a debilitating 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.

Current areas of research include:

- Genetic epidemiology of venous leg ulceration
- Investigation of the relationship between gene polymorphisms and molecular phenotype of chronic wounds
- High frequency ultrasound quantification of oedema
- Clinical trials of new wound therapies

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.

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 chairs the ROSETTA group that has a variety of planned projects relating to innovative medical and psychiatric teaching, as well as participation in an international research collaboration linking autonomic panic, hypertension and serotonergic systems.
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, initially for the first ten in clinical based services. 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).
- Use of new sustained release pharmacotherapies (i.e. naltrexone, buprenorphine) in treatment of substance abuse (including heroin, alcohol, benzodiazepines, tobacco).
- Epidemiology of morbidity and mortality associated with substance use.
- Co psychiatric and alcohol and other drug morbidity.

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.

Dr Bennett’s main research interests involve child psychological health and wellbeing and complementary therapy and the impact of chronic illness on families. In the past, Kellie has also conducted research in the areas of Attention Deficit Hyperactivity Disorder, behavioural genetics, communication in health, and the role of patient spirituality in health.

Broad research interests are in psychophysiology with the aim of developing clinically useful laboratory indices for diagnosis and monitoring the effects of treatment. Specific interests have been in brain electrical activity (EEG and evoked potentials) and cardiac monitoring.
Associate Professor Helen Street 9346 2045 email: Helen.Street@uwa.edu.au

Stress psychology
Professor Street is involved in a number of studies exploring the role of social cognitive factors in the aetiology and maintenance of both wellbeing and chronic stress. She is particularly interested in the role of goals and goal setting in childhood and adult wellbeing and the importance of motivation. Her recent research also considers the role of values in psychological treatment and interventions. Helen is an adjunct consultant with the Centre for Clinical Interventions. She is involved with ongoing school based projects, working with both children and staff, in Australia and in the UK.

Associate Professor Roland Kaiser 9224 0287 email: Roland.Kaiser@uwa.edu.au

- broad interest in medical education, including historical aspects of psychiatry and psychotherapy
- Prior projects include facial affective behaviour in psychotherapy, art therapy for patients with mood disorder, and substance abuse in patients suffering from a psychotic illness.

Associate Professor Jon Laugharne 9336 5555 email: jonathan.laugharne@uwa.edu.au

Current research interests include the psychopathology of traumatic experience, refugee mental health, and various aspects of transcultural psychiatry.

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
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

Medical students during their 5th year clinical clerkship of 10 weeks who wish to enquire about enrolling for a BMedSc degree are most welcome to see the Head of School so that they can discuss research projects. Students in earlier years are also welcome.

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**  
**Head of Discipline.**
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**  
**Neonatal Intensive Care; Lactation and Infant Nutrition; and Factors Involved in Infant Growth and Development.**

**Associate Professor Roger Hart**  
**Fertility; Reproductive Endocrinology; Polycystic Ovarian Syndrome**

**Associate Professor Jan Dickinson**  
**Fetal Medicine; Fetal Surgery; Twin-Twin Transfusion Syndrome.**

**Clinical Associate Professor Barry Walters**  
**Medical Disorders of Pregnancy with Particular Emphasis on Pre-Eclampsia and its origins in the familial vascular diathesis, Thromboembolism and diabetes in pregnancy. Postnatal and long term follow-up of medical complications of pregnancy. The diagnostic process and philosophy thereof.**

**Professor Jeff Keelan**  
**Principle Research Fellow and Laboratory Head**
Placental development, function and infection: roles in pregnancy disorders

Project Titles for 2011:
- Targeting placental inflammatory signalling for prevention of preterm birth
- Delivery of “fetal friendly” drugs using nanoparticles
- Novel placental messengers, diabetes and obesity in pregnancy
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 2010, 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.

Title: Does Chorioamnionitis Weaken the Premature Diaphragm?
Project outline: The diaphragm is the major muscle of the respiratory pump hence a functional diaphragm is fundamental to respiratory well-being. Studies over the last 6-8 years have shown that in adults, diaphragm dysfunction may contribute to difficulty weaning from the ventilator which has given rise to the term Ventilator Induced Diaphragmatic Dysfunction (VIDD). We have shown that the preterm diaphragm may be more susceptible to damage that the mature diaphragm of a preterm lamb born at full term. Premature birth often occurs in the setting of chorioamnionitis – when there is infection/inflammation of the placental and fetal membranes. We have collected a number of samples of diaphragm tissue from naive lambs delivered at different gestations, as well as lambs exposed to chorioamnionitis after either one or two intra-amniotic injections of lipopolysaccharide (LPS – an endotoxin). Potential projects suitable for B Med Sci students in 2010 could utilize these existing samples to define the impact of chorioamnionitis on protein synthesis and degradation, as well as oxidative stress in the diaphragm using Western Blotting, Immunohistochemistry and quantitative PCR techniques. The projects will be undertaken within the School of Women’s and Infants’ Health, with co-supervision from Dr Yong Song.

Title: Effect of Waveform and Inspiratory to Expiratory Waveform on Gas Exchange and Lung Injury during High Frequency Oscillatory Ventilation
(suitable for a student with medical, physiology or engineering background)
Project outline: High frequency oscillatory ventilation is a highly efficient method of ventilating the lung, whilst potentially minimising lung injury. It uses tidal volumes less than or equal to the respiratory deadspace and supraphysiological respiratory rates (600-900 breaths/min) to remove carbon dioxide, whilst a constant, high distending pressure facilitates oxygenation. Despite the theoretical advantages, clinical trials have failed to demonstrate a consistent beneficial effect of HFOV compared to conventional ventilatory modalities. One of the proposed explanations for this lack of a clinical difference between HFOV and conventional ventilation, is that there are a number of different oscillatory ventilators available commercially, but each has a different range of ventilator settings, and differences in the ventilator waveform. Such differences may be important as they can potentially alter the flow profiles and shear stress on the airway walls. This project will use a preterm lamb model to examine two of the major questions – being the selection of inspiratory to expiratory (I:E) ratio and the use of a square versus sinusoidal waveform, to determine if these factors impact on gas exchange and/or lung injury using immunohistochemistry and quantitative PCR techniques. You will have the opportunity to learn basic resuscitation and intensive care techniques including intubation, insertion of umbilical arterial and venous catheters, and analysis and interpretation of blood gases.

Title: Effect of Variability in the Ventilator Waveform on Lung Injury in the Ventilated Preterm Lamb
(suitable for a student with medical, physiology or engineering background)
Project outline: The conventional approach to ventilating newborn infants is to control the ventilator tidal volume, rate and breath duration. In contrast, the breathing pattern of healthy infants breathing spontaneously varies considerably from breath to breath. The application of a variable breathing pattern in adult animal models improves oxygenation and improves lung mechanics compared to a controlled and non-varying ventilation pattern. The use of varying breath volumes and inspiratory pressure may promote recruitment of collapsed lung, by exploiting power-law governed recruitment of respiratory airspaces. We have shown that variable ventilation can improve lung physiology, and are currently analysing samples to ascertain if it reduces ventilator associated lung injury in the premature lamb lung. In 2010, we collected samples from term lambs ventilated with controlled ventilation and variable ventilation. A student in 2011 would have the opportunity to analyse these samples to determine if using variable ventilation enhances surfactant pool size and production in a near term lamb model, ventilated for 24 hours, as well as the effect of variable ventilation on lung histology using immunohistochemistry and quantitative PCR techniques. You would also have the option to be involved in other team preterm lamb studies undertaken in 2011, with the opportunity to learn basic resuscitation and intensive care techniques including intubation, insertion of umbilical arterial and venous catheters, and analysis and interpretation of blood gases (in lambs).
Title: Measuring severity of lung disease in premature infants at discharge

Project outline: Premature infants are prone to developing a chronic lung disease called bronchopulmonary dysplasia (BPD). The severity of their BPD is normally described as mild, moderate or severe depending on their need for oxygen or mechanical ventilation at 36 w postmenstrual age (ie just prior to discharge). However, more precise estimates of lung disease severity are needed for accurate prediction of long term outcome. In this study, the student will perform a physiological assessment of oxygen requirements and ventilation perfusion shunting and compare these to measures of lung volume and ventilation homogeneity in infants with and without lung disease. Inspired oxygen (PIO2) will be compared to peripheral oxyhaemoglobin saturation (SpO2) measurements. The percentage shunt and the degree of right shift (kPa) of the P(I)O(2) versus SpO(2) curve will be compared with the oxyhaemoglobin dissociation curve (a measure of V(A)/Q) using a published method. Ventilation inhomogeneity, tidal volume and lung volume will be assessed using the multiple breath washout technique.

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

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 focussing 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 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 Ilias Nitsos 6488 7969 email: ilias.nitsos@uwa.edu.au

Investigation of Fetal Health and Disease Using the Sheep Model with Particular Emphasis on the Antecedents of Fetal Brain Injury.

Dr Jennifer Henderson 9340 1333 email: jennifer.henderson@uwa.edu.au

Prevention of preterm birth; genetic and environmental influences on preterm birth; clinical research projects related to obstetric and midwifery care.

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.
- **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 blood 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**

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**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 development 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 TGF 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.

**Hormone Dependent Cancers**

**Professor Peter Leedman** 9224 0333  email: peterl@waimr.uwa.edu.au
Other supervisors:
**Dr Shane Colley** 9224 0368  email: scolley@waimr.uwa.edu.au
**Dr Keith Giles** 9224 0327  email: kgiles@waimr.uwa.edu.au

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

**Project title:**
PhD/Honours Projects for 2009

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.
In the past year, we have generated a SLIRP knock out mouse which will provide 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 macrophage cells, 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 coordinate 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), 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. The laboratory also has components focussing on the structural biology of the novel coregulator SRA-binding proteins, as well as 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.

Cell Signalling

A/Professor Evan Ingle
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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 oncoproteins 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 (e.g., Imatinib mesylate) have resulted in great success in treating particular leukaemias and cancers.

**Liver Diseases and Carcinogenesis**

**Professor George Yeoh**  
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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 enhancing 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 external 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 beween 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.
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 act as GTPase-activating proteins (GAP) for heterotrimeric G proteins and as such 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. Of all RGS molecules described to date, RGS5 is the only one with highly restricted expression in mural cells of the arteries (pericytes and smooth muscle cells). This makes RGS5 a prime candidate to study vessel remodelling in the context of tumor growth and cardiovascular disease.

1) Role of RGS5 in atherosclerosis:
Atherosclerosis is the most important cause for coronary heart disease, stroke and peripheral arterial disease in humans. Atherosclerosis produces many pathological changes in the arterial wall, and vascular smooth muscle cells (vSMC) are an integral part of this process. For instance, vSMCs undergo a "phenotypic switching" in the atherosclerotic lesion, proliferate at a higher rate and produce different extracellular matrix proteins (ECM), proteases and cytokines. Interestingly, it has been reported that RGS5 expression is downregulated in atherosclerotic plaques. 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, immuohistochemistry for ECM molecules, staining for plaques).

2) Assess vSMC biology and activity in RGS2 and RGS5 double-deficient and RGS5 mutant vSMC
There are more than 20 RGS proteins identified to date. The cell type-specific expression of RGS molecules argues for distinct biological functions in addition to their GAP function. However, overlapping expression patterns do suggest that net signalling outcomes are a result of internal cross-talk between different RGS members. Current literature points to a crucial role for RGS2, RGS4 and RGS5 (our own data) within cardiovascular functions. Due to the close clustering of RGS2 and RGS5 on chromosome 1 in mice, a double deletion would be very difficult to achieve in a murine system; therefore *in vitro* cellular assays are the method of choice.

We have successfully established RGS5-deficient primary vSMC cell line 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 expression, protein expression and biological changes in adhesion, migration and ECM characteristics all within the context of cardiovascular signalling. The outcome of this project is of crucial significance for further development of RGS5 as a pharmacological target. 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.

Please also see information on: [http://www.waimr.uwa.edu.au/team/rganss.html](http://www.waimr.uwa.edu.au/team/rganss.html)

We are a young and enthusiastic team who seeks similarly motivated and motivating students with interest in molecular biology, immunology, vascular biology and mouse models for human diseases. We will provide a stimulating work environment and anticipate that suitable candidates will, with assistance, secure scholarship funds. For those interested please feel free to contact Ruth Ganss at ganss@waimr.uwa.edu.au to further discuss available research projects.
Cancer Gene Regulation

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When the Human genome was sequenced, it sent shockwaves through the scientific community when it was revealed that our DNA only contains about 22000 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’ 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 cancers and the nervous system.

Student projects (Scope will vary depending on Honours)

1. Noncoding RNA in the nervous system. Our brains are full of RNA that does not encode protein. What is all this RNA doing? Could this RNA provide clues to how our brains work and why they are so complex? This project will combine cell biology, molecular biology, bioinformatics and microscopy to try to address these questions. The aim is to discover new subcellular structures and determine the molecular details of control of gene expression by these long noncoding RNA in the nervous system.

2. Paraspeckle RNomics in Cancer. Paraspeckles ‘trap’ certain RNA molecules in the nucleus, therefore preventing them from being translated into protein in the cytoplasm. Our hypothesis is that cancers will use this mechanism to control the expression of key genes. This project will focus on identifying and characterising the RNA found trapped in paraspeckles purified from different cancer models, thereby finding new targets for developing novel cancer therapeutics.

Mitochondrial Medicine and Biology

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

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 unravelling the mysteries of mitochondrial biology we are interested in the development of gene therapy approaches and chemotherapeutics to combat mitochondrial dysfunction in disease.

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PhD 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 mitochondria targeted chemotherapeutics that selectively target cancer cells but not normal cells.

These projects involve the use of techniques in cell biology (such as cell culture, cell death assays, fluorescence microscopy, gel electrophoresis, western blotting) and molecular biology (cloning, quantitative PCR, RNA interference).

Synthetic Biology and Drug Discovery

Dr Oliver Rackham 92240325  email: rackham@waimr.uwa.edu.au
Location: CMR/WAIMR, Perth Campus, MRF Building, Level 6, 50 Murray St, Perth

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 CANCER EPIDEMIOLOGY

Cancer Epidemiology

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

We study the causes and patterns of cancer in human populations. We are involved in a broad range of studies covering most aspects of cancer epidemiology. Students who want to do a project in public health, epidemiology or occupational health are advised to speak with Lin so a personalized project can be chosen.

A particular interest is occupational causes of cancer. We study people in particular occupations (particularly heavy industries) 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 (case-control studies). 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. Currently we have case-control studies on 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.

We have a number of data sets on occupational exposures to carcinogenic chemicals which could be explored for student projects. For example students could look at the patterns of pesticide use in farmers, or the exposure to diesel exhaust in truck drivers. Or they could examine occupational use of chemicals and the resultant risk of different types of cancer.
Another major area of research is using large databases to investigate the treatment and outcomes of people with cancer. Datasets are available which cover all cancers and hospital treatments in WA over the past 20 years. Using these datasets we can examine whether treatment follows recommended guidelines, whether there are inequities in treatment for cancer, and how treatment differences affect survival. For example, students could look at specific surgical treatments for cancers and examine trends in use of surgery over time; whether there are differences in use of surgery between different groups (e.g., rural or urban, male or female, young or old); and whether treatment according to guidelines improves survival. We also look at links between cancer and other medical or surgical conditions. These associations often suggest new areas of investigation for exploring causes or prevention of cancer. For example, whether women who have had a miscarriage are more likely to develop breast cancer.

There are endless possibilities for projects and students who are interested in cancer epidemiology are encouraged to contact Lin to discuss their ideas further.

**Title: Folate and colorectal cancer**

**Project outline:**

Factors that appear to influence the development of colorectal cancer are folate levels and metabolism. Folate levels in the body are influenced by intake of foods containing folate, folate supplements, alcohol intake, polymorphisms in genes involved in folate metabolism and some medications which interfere with folate metabolism. We have data on all these factors from a large case-control study of colorectal cancer (the Western Australian Bowel Health Study – WABOHS).

This project involves developing a theoretical model of the factors which affect folate levels and then undertaking statistical analysis of data from WABOHS to examine the relationship between folate and colorectal cancer. The student who does this project will review the literature in this area, gain an understanding of folate metabolism and the causes of colorectal cancer, prepare data for analysis, analyse data including logistic regression, and prepare a paper for publication.

**LABORATORY FOR NEUROMUSCULAR DISEASE**

**Neuromuscular Disease**

**Professor Nigel G Laing** 9346 4611 email: nlaing@cyllene.uwa.edu.au

Other supervisors:

**Dr Kristen Nowak** 9346 1981 email: knowak@cyllene.uwa.edu.au

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**Dr Gina Ravenscroft** 9346 2423 email: gina.ravenscroft@uwa.edu.au

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

Our Laboratory has traditionally been a human genetics laboratory, investigating the genetic cause of various neurological, neuromuscular and muscle diseases. We have been involved in world-first breakthroughs in the identification of disease-causing genes and mutations over the past 17 years. For example:

- 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
- cranio-metaphyseal 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 coflin (CFL2) – 2007
- cap disease due to beta-tropomyosin (TPM2) – 2007
- hereditary spastic paraplegia (CYP7B1) – 2008
- and congenital fibre type disproportion due to slow alpha-tropomyosin (TPM3) – 2008.

Our gene discovery work has helped innumerable families around the world with accurate diagnosis of their disease and the possibility of prenatal diagnosis where this is warranted. We always have new gene discovery projects on the go, collaborating with clinicians and pathologists from around the world as well as here in Western Australia and Australasia. In particular we have a strong link with the diagnostic Neurogenetic Laboratory at Royal Perth Hospital with undiagnosed patients and families feeding into projects in the research laboratory.
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. Not only is knowing the genetic cause of a disease crucial for being able to attempt a logical therapeutic approach for patients, but also understanding how the defective gene and either absent or mutant protein leads to pathology and the disease is often vital in developing possible therapeutic routes.

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, amongst other things.

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); 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 analysis.

Projects for 2011

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

LABORATORY FOR MOLECULAR GENETICS

Professor Luba Kalaydjieva  9346 1946  email: luba@cyllene.uwa.edu.au

Location: B Block, QEII Medical Centre

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.

Medical Genetics
Professor David Ravine  9346 2499  email: ravine@waimr.edu.au
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 RESEARCH
Centre for Diabetes Research
Professor Grant Morahan  9224 0206/397  email: gem@waimr.uwa.edu.au
Location: CMR/WAIMR, Perth Campus, MRF Building, Level 6, 50 Murray St, Perth

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. Identifying critical microRNAs that regulate differentiation of embryonic stem cells into pancreatic progenitors.

Proof of concept has demonstrated that embryonic stem cells can give rise to all lineages of cells in our 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 these protocols, it is now possible for you to identify critical microRNAs that regulate this fundamental process.

3. Functionally characterizing Neat1 in embryonic stem and differentiating cells.

Neat1 (nuclear enriched autosomal transcript 1) is a long nuclear-retained noncoding RNA and essential for structural integrity and maintenance of the nuclear paraspeckles, discovered by Dr Archa Fox. Neat1 is undetectable in embryonic stem cells but highly expressed in differentiated cells. Co-supervised by Dr Fox, you will use our embryonic stem cell differentiation model to investigate how Neat1 is regulated and/or its biological role.

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

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.

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 associated with fluid homeostasis in 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 (dimerization) and work closely with our spin-out company Dimerix Bioscience to translate our research findings.

Recent Major Breakthroughs

- 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. 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 National Health and Medical Research Council of Australia (NHMRC), the Australian Research Council (ARC) and Dimerix Bioscience Pty Ltd.

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 TNF 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) retroviral 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 co-chaperones – two FK506-binding proteins, FKBP51 and FKBP52, cyclophilin 40 (CyP40) that binds the immunosuppressant cyclosporin A and PPI, 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 co-chaperones 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.

**CaR in parathyroid function:** CaR is a biomedically 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.
Honours Program
The researchers at WACHA are helping to find new approaches to prevent, diagnose and cure disease to improve the quality of life and health of our elders. This type of research will make a difference to the lives of older people, helping them live longer, healthier and stronger.

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.

Delivering 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 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 groundbreaking projects to understand and enhance the quality of 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 our research group, please contact either Shelley (Shelley.Stone@uwa.edu.au) or Simon (Simon.Brown@uwa.edu.au).

CENTRE FOR IRON METABOLISM AND LIVER DISEASE

Iron Metabolism Research (DT, JO, RG, AC)

Iron is an essential trace element required for life. Iron deficiency or excess can lead to pathological conditions such as anaemia or haemochromatosis, a genetic disorder of iron overload. 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.

Regulation of iron metabolism (DT, AC, RG, JO; Honours/PhD project)

Iron metabolism is regulated by a hormone called hepcidin. It is synthesised by the liver in response to many factors including iron, inflammation, erythropoiesis and oxidative stress to control iron absorption, recycling and storage. The signalling pathways involved in the regulation of hepcidin are unclear. In this project we will use mouse models of the iron overload disorder hereditary haemochromatosis, which have mutations in either or both HFE or TFR2 genes to examine their role in hepcidin signalling pathways. Cellular, molecular and biochemical approaches will be used to examine iron transporters, regulators and cell signalling molecules (including SMADs & STATs) to determine how HFE and TFR2 regulate hepcidin expression to control iron metabolism.

Iron transport (RG, AC, DT, JO; Honours/PhD project)

Non-transferrin bound iron (NTBI) appears in the plasma in disorders of iron overload such as haemochromatosis when the iron transport protein, transferrin, becomes saturated with iron. NTBI can be toxic due to its ability to generate free radicals. It is taken up rapidly by the liver, but the mechanisms responsible are unclear. A number of molecules have been identified which are capable of transporting NTBI, but their contributions are unknown and it is clear that there are other, unidentified, molecules involved. This project will involve a variety of molecular, biochemical and imaging techniques to investigate two known (DMT1, Zip14) and two candidate NTBI transporters (Zip4, Ctr1). The aims of the project will be to determine whether the transporters mediate NTBI uptake in an hepatocyte cell line and, importantly, what their relative contributions are.
**Cholesterol pathways (RG, DT, JO; Honours project)**

We have recently shown a link between liver iron loading and the synthesis of cholesterol in the liver. This finding has important implications in the pathogenesis of fatty liver disease, which is becoming an increasing problem worldwide. This project will use molecular, biochemical and imaging techniques to investigate those conditions under which this relationship holds true and those under which it breaks down. The information generated will be used to tease out the molecular mechanisms involved.

**Iron and Cancer (AC, DT, JO)**

There is a greater incidence of breast, colorectal and liver cancers in individuals with hereditary haemochromatosis, who are homozygous for the C282Y mutation in the *HFE* gene. This has led to projects designed to examine the role of iron and/or *Hfe* gene mutation in carcinogenesis. Evidence for a role of iron in cancer is mani-fold. Iron is pro-oxidant and can generate free radicals causing lipid peroxidation and DNA damage. Cancer cells also require more iron to sustain their rapid proliferation compared to non-cancer cells. The role of iron and *Hfe* in the development of breast cancer. This project will study how iron and *Hfe* affects cellular iron metabolism and proliferation in a breast cancer cell line (Honours/PhD). The effects of iron and/or *Hfe* on the rate of tumourigenesis will also be investigated using mouse models of HH and breast cancer. Markers of lipid peroxidation and oxidative stress which has been postulated to induce carcinogenesis and changes in cancer and iron metabolism genes and proteins implicated in the pathogenesis of breast cancer will be determined (PhD).

**Liver Disease and Regeneration Research (JO, CE, JTP)**

**Progenitor cells in Liver Regeneration, Fibrosis and Cancer (JTP, JO)**

Liver progenitor cells (LPCs), sometimes also referred to as liver stem cells, play an important role in cell renewal processes in the setting of chronic liver injury when hepatocyte-mediated regeneration is compromised. Following activation, they proliferate, migrate through the liver and differentiate into bile duct cells (cholangiocytes) or hepatocytes. If this regenerative process is dysfunctional and LPCs are kept in a proliferative state, they are likely candidates for transformation and hepatic tumour formation. The sequence of events for a healthy liver to become cancerous is thought to be as follows: chronic chemical or carcinogenic injury, inflammation, LPC expansion, fibrosis, cirrhosis and eventually cancer. LPCs do not work in isolation and are impacted by circulating or paracrine growth factors and cytokines produced by other cell types such as macrophages and fibrosis-driving hepatic stellate cells. Our group is interested in the cross-talk of these cell types and our goal is to understand the cellular and molecular mechanisms, which drive LPC-mediated regeneration as opposed to pathological fibrogenesis and carcinogenesis.

**Honours project A:** *In vitro differentiation and characterisation of LPCs*

Clonal, murine LPC lines will be subjected to a “Hepatocyte Differentiation Environment”—Matrigel (a three-dimensional growth matrix) and cultured with differentiating cell culture supplements, which mimic embryonic development of a hepatoblast into a fully functional hepatocyte. The process of differentiation will be monitored and analysed by real-time PCR analysis, immunohistochemical and immunofluorescent staining and functional biochemical assays.

**Honours project B:** *Cross-talk between LPCs and hepatic stellate cells*

We have hypothesised that hepatic regeneration processes are reliant on cross-talk between LPCs and fibrosis-driving hepatic stellate cells. To investigate the contribution of key cytokine and chemokine players, we will use differential gene and protein expression analyses, cell culture as well as co-culture and will also be establishing laser microdissection to focus more specifically on the hotspots in a tissue section of a chronically injured liver.

**Inflammation and chronic liver disease (CE, JO; Honours project)**

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 project will examine the role of macrophages in liver progenitor cell proliferation and differentiation in an animal model 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.
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 Associate Professor Philip Thompson, the Centre currently has over 60 researchers who are working in several research disciplines to build a holistic understanding of lung health. In July 2005 CAARR commenced its second term as a member of the Cooperative Research Centre for Asthma and Airways. Through this grant, the Centre has commenced a number of projects in the Epidemiology and Molecular Genetics fields. With this grant and other funding, the Centre has access to funding of approximately $2.7 million.

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. A vocational cadetship programme for undergraduates which enables participating students to earn money while gaining experience in a research environment has also been successfully implemented over the last five years. 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. We are keen to see scholarships for BMed Sci students being offered by LIWA.

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.

"My involvement with LIWA and CAARR added a lot of value to my BMedSc, allowing me to work with some excellent scientists who have since become mentors to me. I feel proud to be part of a team who are continuing to work to a better understanding of respiratory disease which will allow improved treatment of conditions such as asthma and COPD. My first scientific publication was very exciting, and I look forward to many more publications in the years to come." Lauren Mott (nee Akesson), BMedSc Student 2003/4.

Some current research Units within CAARR:

**Inflammation & Immunology:**

*Head - Professor Kanti Bhoola*

*Email: bhoolakd@yahoo.com*

1. The unit’s research is focused on inflammatory mediators (the kallikrein-kinin cascade, prostaglandins, leukotrienes), immune modulation of dendritic cells in the context of asthma, COPD and human lung cancer.

2. The projects are focused on inflammatory cells (eosinophils, neutrophils) and dendritic cells, and the regulatory enzymes, mediators and receptors that may be important in the pathophysiology of asthma and chronic obstructive lung disease (COPD). Current and recent studies have examined the expression of kinin receptors on eosinophils and dendritic cells and the functional effects of kinins on eosinophil and dendritic cells.

3. Dendritic cells (DC) are the most efficient antigen-presenting cells and crucial players in the initiation of immune responses. In the respiratory tract, DC play the major role in balancing between immunity and tolerance. In inflammatory disease such as asthma, DC function is deregulated and contribute to changes in the balance in T cells response.

We are investigating activation of DC by pro-inflammatory mediators such as *kinins*. This research may offer the potential for discovering new and novel target for inflammatory disease. Furthermore, to understand the pathways involved in the induction and maintenance of respiratory tolerance to pathogens/allergens we are investigating molecular mechanisms underlying transforming growth factor β1-induced suppression of inflammatory mediator production by DC.

4. In addition, there is increasing evidence of an association and interdependence between the immune and nervous systems. Since recent evidence has shown that DC produce a number of *neuropeptides* and their receptors, we are investigating their role in modulation of DC phenotype and functions. Recently, we discovered that the neuroprotein, synuclein is expressed by dendritic cells. Synuclein has interesting regulation of expression at the level of mRNA. As a response to variety of inflammatory stimuli, DC expressed different splicing forms of synuclein. Synuclein is involved in the regulation of immature DC migration and plays also a role in DC apoptosis.
5. Major interests of the Cancer Group are:

a) Analysis of the role of the kallikrein-kinin cascade in human lung carcinomas:
   Cellular and molecular studies on the serine proteases, plasma- and tissue-kallikrein, their multifunctional endogenous substrates, the H- and L-kininogens, and the kinin B<sub>1</sub> and B<sub>2</sub> receptors, which regulate the production and function of mitogenic kinin peptides, and thereby the proliferation of lung carcinoma and mesothelioma cells.

b) Experiments have been designed to determine the cellular expression of the proteins of the kallikrein-kinin cascade and molecular pathways involved in the activation of kinin receptors on lung carcinoma and mesothelioma cells.

c) Changes in transcriptional activity and post-transcriptional modification of genes involved in the kinin-kallikrein cascade are associated with carcinomas affecting the lung, and contribute to tumour development, invasiveness and metastasis. Therefore the cancer group has a focused research programme that involves also the examination of three independent molecular mechanisms (splice variants, promoter methylation and genotyping of genes) involved in regulating expression of the kinin and kallikrein genes in carcinomas of the lung and pleura.

d) Recent findings indicate that de novo formation of blood vessels from endothelial progenitor cells (adult vasculogenesis) may be responsible for the efficient neovascularisation of tumours. Evidence suggests that tissue kallikrein (hK1) and the kinin peptides exercise important regulatory control on the growth and proliferation of vascular endothelial cells and progenitor cells. The aims of this study are: i) identification of (endothelial) stem and progenitor cells in lung tumours using specific markers, ii) expression of hK1 and BKR1 & 2 in stem and progenitor cells in lung tumours applying double labelling techniques, in situ hybridization, real-time PCR, iii) effect of hK1 and kinin peptides on lung endothelial tumour cultures in vitro by live cell imaging.

Tissue Repair Unit: Head – Associate Professor Steven Mutsaers
9346 3906/9346 3198
Email: mutsaers@liwa.uwa.edu.au

The Tissue Repair Unit is examining the mechanisms regulating cell and extracellular matrix (ECM) interactions in the lung, and how a loss of regulation of the normal repair processes can lead to disease. Studies are centred on understanding how interaction of cells with other cells, growth factors and different components of the ECM lead to cell proliferation, migration, invasion, differentiation and collagen production. The focus is in two areas: 1) understanding the mechanisms underlying mesothelial healing and the role of the mesothelial cell and mesothelial stem cells in the formation of post-operative adhesions, serosal fibrosis and malignant mesothelioma, and 2) understanding how lung injury can lead to the development of fibrosis, in particular the role of interleukin-6 family cytokines. More specifically:

1a. Role of epithelial to mesenchymal transition-inducing proteins in mesothelial repair and adhesion formation. We have previously shown that mesothelial cells secrete and respond to hepatocyte growth factor (HGF) a mediator shown to stimulate repair and prevent fibrosis in many different tissues. The expression of this growth factor in healing serosal lesions and the effect of increasing or reducing its expression on the rate of mesothelial repair and development of adhesion formation is currently under investigation.

1b. Evidence for a mesothelial stem cell. Early studies have suggested that mesothelial cells can be induced to change to different mesenchymal cell phenotypes in vitro. This data suggests that mesothelial cells have stem cell or progenitor-like properties. Current studies are examining the mechanisms regulating mesothelial cell plasticity, in particular plasticity following exposure to different mediators, ECM proteins and cells and tissue in vivo.

1c. Role of the ECM and transforming growth factor beta (TGF-β) in mesothelioma growth. Studies using the proline analogue thiaproline have clearly demonstrated a role for collagen in mesothelioma growth and studies using blocking antibodies to transforming growth factor β (TGF-β), a major stimulus for collagen production, have also shown a role for this molecule in the progression of tumour growth. Ongoing studies are looking at the mechanisms by which TGF-β regulates collagen production and tumour growth in mesothelioma.

2. Role of the IL-6 family of cytokines in pulmonary fibrosis. We have previously shown that there is dysregulated IL-6 signalling in lung fibroblasts from patients with idiopathic pulmonary fibrosis (IPF). In addition, using genetically modified animals in experimentally induced models of pulmonary fibrosis we have shown that activation of different signalling pathways downstream of the common IL-6 family signalling receptor component gp130, can dramatically affect the outcome of acute lung injury to either prevent or enhance lung fibrosis. Current studies are examining the mechanisms through which gp130 signalling induces fibrosis and which of the IL-6 family proteins are most important in the fibrotic response. In addition, studies are examining the role of the bone marrow and tissue chemokines in fibrosis in these animals.
This unit is strongly supported by the CRC for Asthma and Airways and its laboratories are located within WAIMR at the QEII campus.

**Genetics of Lung Diseases**

Asthma and other respiratory diseases have been shown to have a strong genetic component. However, the inheritance of these diseases is complex, and the multiple genes involved in their development are still being discovered. To date our work has focused on using state-of-the-art PCR-based technology to find associations between mutations in certain "candidate" genes for respiratory disease in a population of over 1200 well-characterised asthmatics and non-asthmatic controls recruited with the help of our Clinical Trials Unit. In line with our emerging interests in to COPD/emphysema and lung cancer research we are actively recruiting a broader patient population.

**Candidate Gene Approach**

Asthma has been shown to have a strong genetic basis, with heritability estimated to be between 30 and 50%. Atopy and atopic disease also show strong familial clustering which contributes in part to the genetics of asthma. Asthma and atopy are complex genetic diseases, with multiple genes likely to be important in the pathophysiology of these conditions. Similarly, several different genes are important in other respiratory conditions, including smoking-related chronic bronchitis and emphysema (COPD). Our aim is to identify the genes associated with these conditions using a candidate gene approach to better understand the diseases, more appropriately target drug therapies and, where possible, direct appropriate interventions. Lung cancer genetics will be a new initiative in 2007.

**Alternative Gene Regulation & Disease**

Many of the genes thought to be involved in asthma encode for more than one protein. This arises as a result of alternative splicing, in which immature mRNA is cut to remove intronic sequences and reassembled in different ways, often with pieces of exons missing, to produce mature RNA which is translated to produce a variety of end stage protein products. It is well established that alternative splicing is highly tissue specific and developmentally regulated. In contrast, aberrant alternative splicing has been linked with the development of diseases such as muscular dystrophy. The role of alternative splicing in asthma has yet to be investigated. In collaboration with Prof Steve Wilton and Dr Sue Fletcher, experts in the field of gene regulation, we have started to explore this new and exciting possibility; that aberrant splicing of asthma candidate genes may contribute to the development of this disease. Identification of any splice variants which contribute to disease will lead to investigation of the functional role these variants play.

*Current projects include:*  
- Pharmacogenetics of the leukotriene pathway in asthma  
- Genotyping and asthma severity  
- Genetics of proteases and anti-proteases in chronic obstructive pulmonary disease  
- Genetics of airway remodelling in respiratory diseases  
- Gene regulation of candidate genes associated with inflammation in asthma

Our Unit has a long track record of supporting undergraduate students and would be pleased to discuss projects with any potential B.Med.Sci students.

**Clinical Trials:**  
**Head – Dr Helen Peake**  
9346 3198/9346 4649  
Email: hlpeake@liwa.uwa.edu.au

The Clinical Trials Unit recruits and advises patients who have volunteered for lung research including evaluating the effectiveness of new pharmaceutical therapies, and investigating new approaches to the management of asthma, chronic obstructive pulmonary disease, and other respiratory diseases and allergies. With a multi-disciplinary staff from various backgrounds including nursing, allied health, medicine and public health, the unit is dedicated to improving the welfare of its patients.

Undergraduates interested in becoming involved in clinical research are invited to contact Dr Helen Peake on 9346 3198 or email hlpeake@liwa.uwa.edu.au.

**Physiotherapy:**  
**Head – Associate Professor Sue Jenkins**  
9266 3639/9266 9346/9266 3198  
Email: s.jenkins@curtin.edu.au

This unit undertakes research aimed at improving the quality of life and physical activity levels of individuals with asthma, COPD and other respiratory conditions. We have access to telemetric gas analysis equipment enabling measurements of ventilation and gas exchange to be during exercise testing and prescription and during physical activities of daily life. There is also some interest in Bronchiectasis patient orientated research. Please contact Sue Jenkins to learn of potential projects.
This unit seeks to improve our understanding of the environmental factors that influence the high and increasing rates of asthma and other respiratory diseases by investigating how factors such as air pollution contribute to lung disease. Current projects include the impact of traffic related pollution on the health of residents living near vehicle corridors, the effect of indoor air pollution on adult asthma and chronic obstructive pulmonary disease, and geology and respiratory disease in regional areas. Senior researchers for this group are: Dr Angus Cook – geology and respiratory disease (6488 7804), Dr Andrew Jardine – vehicle corridors and respiratory health (6488 1296) and Dr Peter Franklin – indoor air pollution (9346 7949).

Advanced Lung Disease and Pulmonary Vascular Disease:
Head - Dr Eli Gabbay 9224 1467/9224 8793 Email: eli.gabbay@health.wa.gov.au
This unit investigates the prevalence and mechanisms underlying advanced lung diseases including pulmonary vascular diseases, airway complications of lung transplantation and various interstitial lung diseases. We also are interested in mechanisms, which aim to reduce the symptomatic burden for patients with severe lung diseases.

This unit is currently located on the Royal Perth Campus and interacts with relevant groups on that site.

In the area of pulmonary vascular disease, our particular areas of interest includes novel therapies for pulmonary arterial hypertension as well as assessing the prevalence of pulmonary hypertension and other lung diseases in a variety of conditions including the obese and patients with haematological and rheumatological diseases. We are examining novel therapies to deal with pulmonary hypertension, which can complicate pulmonary thromboembolic diseases. We are interested in the genetics of pulmonary hypertension as well as potential environmental stimuli.

In the area of lung transplantation, we are particularly interested in the mechanisms, which underlie obliterative bronchiolitis, the most important complication, which limits the effectiveness of lung transplantation. We are also involved in examining novel therapeutic agents in patients with severe interstitial lung disease.

How to contact us
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
Professor D A Mackey 9381 0777 Email: david.mackey@uwa.edu.au
www: http://www.lei.org.au

Physiology & Pharmacology
Head of Department
Prof Dao-Yi Yu 9381 0716 Email: dyyu@cyllene.uwa.edu.au

Assoc Prof Stephen J Cringle 9381 0720 Email: cringle@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\(_1\)-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
Prof P. Elizabeth Rakoczy
Email: rakoczy@cyllene.uwa.edu.au

Dr May Lai
Email: mlai@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
Assoc Prof Mariapia Degli Esposti
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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.

Viral Immunogenetics
Head of Department
Dr Tony Scalzo
Email: scals@cyllene.uwa.edu.au

The research of the Viral Immunogenetics Group provides an insight into novel mechanisms of viral immune evasion. This is an important step in increasing our understanding towards developing therapies to limit the severity of viral diseases, including those that affect vision.
People living in remote and rural regions often experience difficulty accessing specialist health care services. e-Medicine undertakes research to provide people in these regions with improved disease screening and diagnosis and offer the best possible diagnostic and treatment options.

Our group is advancing in its understanding of numerous clinical conditions by capitalising on its strengths in e-medicine, decision support, medical imaging and computer aided tools. It has also developed innovative digital imaging devices and software programs to facilitate high volume screening and diagnosis of debilitating eye diseases such as Diabetic Retinopathy and Glaucoma. With this technology having potential applications for dentistry, dermatology and otolaryngology, it places e-Med at the forefront of medical imaging hardware and software development. Already e-Med’s efforts have resulted in use of the internet to transfer clinical information and data becoming more prevalent within the medical community.

Combining telemedicine, e-Medicine & e-Health our activities concentrate on:
- Research & development of affordable, portable and non-invasive diagnostic tools, intelligent electronic medical record systems, imaging algorithms and computer-aided diagnostic software;
- Clinical services in rural and remote areas; and
- Education & training of healthcare professionals in the area of telemedicine and medical informatics.

**Clinical Ophthalmology & Research**

**Dr Ian McAllister**

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;

**Dr Geoffrey Crawford**

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

Dr 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.

Dr 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.

Dr 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
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 (stroke, traumatic brain injury) and chronic neurodamaging (Alzheimer’s, Parkinson’s disease) disorders.

Project aims: This project aims to assess the neuroprotective potential of mild hypothermia when combined with neuroprotective proteins/peptides we have identified in our laboratory.

Techniques involved: Protein purification, surger, rat

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 here 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.