BACHELOR OF MEDICAL SCIENCE

HANDBOOK

2010
Index

Introduction ..................................................................................... .3
Admission Options ........................................................................... .3
The BMedSc Course ......................................................................... .4
Award of Degree .............................................................................. .4
Combined BMedSc/MBBS ................................................................. .5
Application Procedures ................................................................. .5
Scholarships .................................................................................... .5
Youth Allowance .............................................................................. .6
Example of an Honours Dissertation Guide ...................................... .6
Course Enrolment Queries ............................................................... .8
Course Rules .................................................................................... .9

Schools and Disciplines

School of Anatomy and Human Biology ........................................... 12
School of Biomedical, Biomolecular & Chemical Sciences ............ 20
  - Biochemistry and Molecula r Biology ....................................... 20
  - Microbiology and Immunology ................................................ 25
  - Physiology .............................................................................. 28
  - Pharmacy ............................................................................... 37
School of Medicine and Pharmacology .......................................... 38
  - Medicine ................................................................................. 38
  - Pharmacology & Anaesthesiology .......................................... 43
School of Paediatrics and Child Health ......................................... 46
  - Telethon Institute for Child Health Research.......................... 52
School of Dentistry ......................................................................... 61
School of Pathology and Laboratory Medicine ............................... 61
School of Population Health .......................................................... 65
School of Primary, Aboriginal and Rural Health Care .................... 70
  - General Practice .................................................................... 70
  - Emergency Medicine ............................................................ 71
  - Centre for Aboriginal Medical & Dental Health (CAMDH) ....... 72
  - Combined Universities Centre for Rural Health (CUCRH) ....... 73
  - Rural Clinical School of Western Australia ............................. 74
School of Surgery ............................................................................ 76
School of Psychiatry & Clinical Neurosciences .............................. 84
School of Women’s and Infants’ Health .......................................... 86
INTRODUCTION
The Bachelor of Medical Science (BMedSc) degree provides the opportunity for medical students and biomedical science graduates to spend a year studying in depth an aspect of medicine, which is of particular interest to them. It enables students to gain experience in experimental design and techniques, and to savour the excitement, which comes from original research. Students who successfully complete the course requirements are awarded the BMedSc degree with honours of the appropriate class (e.g. First Class Honours).

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

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

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

ADMISSION OPTIONS
There are three pathways for entry into the BMedSc degree:

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

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

3. MBBS students who have completed at least the Level 1 requirements of the MBBS course at this University or equivalent and have achieved a final weighted average of at least 65% in those units may be accepted as students in the combined course of BMedSc and MBBS. Students must have a proposed research project which is longitudinal in nature and would suit research over a three year period.
THE BMEDSC COURSE
The BMedSc degree consists of an approved course of advanced study and research to the value of 48 points in any subject offered by the Faculty of Medicine, Dentistry and Health Sciences. The course involves at least 36 weeks as a full-time student (or part-time equivalent for students in the combined course) in one of the schools of the Faculty (or approved schools not within the Faculty). The Faculty may permit a student to undertake some of this study and research at an approved institution either interstate or overseas. In such cases the principal supervisor must nonetheless be a UWA-based researcher. Students must present a dissertation based on their work. Students may also be required to undertake additional assessments such as a research seminar presentation or literature review. In some schools, the only formal components of the BMedSc course are the research project and submission of the thesis. However, in all schools, these are the major components of the course. Other schools require additional commitments, which may be assessed as part of the overall grading of the student. These include presentation of one or more seminars based on the student's research activities, submission of a review of relevant literature in the field of study, an oral examination of the thesis and related areas of research, and participation in formal courses which will be of value for the student's research activities. Intending BMedSc candidates should obtain information on the requirements of an individual school from the School Honours Co-ordinator/Academic Advisor or the Head of School before submitting an application.

Students should be aware that some research projects may require ethics approval from the Research Integrity Office which is responsible for administration and policy issues relating to experimentation on human participants and animals, and for biological safety. Approval should be sought as early as possible in the planning stages as it might take some time to obtain formal approval.

Students must, no later than 31 OCTOBER following their first enrolment in the course submit to the School a dissertation on the work done. An example of an honours dissertation guide is presented on Page 6. Please note that this is only an example and students are required to consult their supervisor regarding specific requirements of the School. The dissertation is examined by at least two experts in the field of study who will make an assessment of the quality of the student's research and thesis via a written report to the school.

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

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

AWARD OF DEGREE
The Bachelor of Medical Science degree is awarded with honours of the appropriate class when a student successfully completes all the requirements of the course. The honours classification is as follows:

- 80 – 100% First Class Honours
- 70 – 79% Second Class Honours (Division A)
- 60 – 69% Second Class Honours (Division B)
- 50 – 59% Third Class Honours
COMBINED BMedSc / MBBS COURSE
This option has been available since 2007 where eligible students may elect to undertake the combined course of Bachelor of Medical Science and the MBBS. This may appeal to students who are interested in pursuing a BMedSc without having to take a year away from their MBBS studies. The course is considered quite intensive and will only be offered to students who are achieving above average standards in their MBBS course.

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

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

Students in the combined course must, no later than 31 OCTOBER of their fifth year of enrolment, submit to the School a dissertation on the work done. Students who successfully complete the course are awarded the degree of Bachelor of Medical Science (with honours of the appropriate class, as noted above) and the degree of Bachelor of Medicine and Bachelor of Surgery.

COURSE RULES
The complete official Rules for the Bachelor of Medical Science degree and the combined BMedSc / MBBS course can be found in the Undergraduate Handbook (www.handbooks.uwa.edu.au) and on Pages 9-11.

APPLICATION PROCEDURES
Students are required to lodge a formal application to the Faculty of Medicine, Dentistry and Health Sciences for permission to undertake the BMedSc course. Application forms are available from the Faculty web page http://www.meddent.uwa.edu.au/courses/undergraduate/honours

Alternatively, hardcopy application forms are available from the Faculty Office reception (N block, QEII Medical Centre). Students must 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
Scholarships are available for current UWA MBBS students who wish to interrupt their medical studies to undertake the full-time BMedSc course. The scholarships available to BMedSc students are listed below. Some awards may be shared between students.

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. If you are interested in these scholarships please indicate this in the space provided on the Bachelor of Medical Science application form (Q. 9).

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. If you are interested in this scholarship please indicate this in the space provided on the Bachelor of Medical Science application form (Q. 9).

Information regarding other non-faculty scholarships can be found @ 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:

Student Service Centre
1296 Albany Highway
CANNINGTON WA 6107
Telephone: 13 2316

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”.

6
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. 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 - $30.00 per copy). You must meet the cost of any additional copies you may require for family, etc. (approx $32.90 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 Stuart Bunt Ph. 6488 2983 email: smbunt@anhb.uwa.edu.au
Winthrop Professor Alan Harvey Ph. 6488 3294 email: alan.harvey@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(1) To be considered for entry into the Bachelor of Medical Science course applicants must—
   (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.

\(^1\) These totals include all units completed in the single degree course for the MB BS prior to enrolment in the combined course.
**Bachelor of Medical Science Component**

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

**Award of Bachelor of Medical Science Degree**

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

**Bachelor of Medicine and Bachelor of Surgery Component**

**11.1.55.8(1)** The Bachelor of Medicine and Bachelor of Surgery component consists of units to a total value of 272 points comprising -

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

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

and

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

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

**Award of Bachelor of Medicine and Bachelor of Surgery with Honours**

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

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

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

**Level Two**

- IMED7296 Honours Thesis - Research
- IMED7297 Honours Thesis - Research (Vacation) (12 points)

**Level Three**

- IMED7396 Honours Thesis - Research
- IMED7397 Honours Thesis - Research (Vacation) (12 points)

**Level Four**

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

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

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

The School's major research areas are:

- Cell and Developmental Biology
- Endocrine and Reproductive
- Human Biology

Morphology
Neuroscience
Education and Information Technology

Research can be undertaken in many areas, such as:

- Cancer Biology (Ovarian, Breast & Prostate)
- Ecology
- Evolutionary Biology
- Functional And Clinical Anatomy
- Human Biology
- Information Technology
- Muscle Regeneration
- Neuroscience
- Reproductive Biology
- Sleep Science

The School has excellent facilities for the conduct of BMedSc research programmes. See information at http://www.anhb.uwa.edu.au/for/students/honours2/bmedsci

and http://www.anhb.uwa.edu.au/for/students/honours2

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
**Cancer Biology**

**The Role Of Apoptosis And Its Signalling Molecules In Cancer**

**Professor Arun Dharmarajan**  
6488 2981  
Email: dharma@anhb.uwa.edu.au

Professor Dharma’s group researches the role of apoptosis and its signalling molecules in cancer. Specifically projects examine the effect of apoptosis on:
- Breast cancer
- Ovarian cancer
- Mesothelioma
- Skin differentiation/melanoma
- Prostate cancer

**Bone in Health and Disease**

**Dr Luis Filgueira**  
6488 3907  
Email: lfilgueira@anhb.uwa.edu.au

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

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

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

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

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

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

**Metals in Medicine**

**Dr Luis Filgueira**  
6488 3907  
Email: lfilgueira@anhb.uwa.edu.au

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

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

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

**Ecology**

**Dr Debra Judge** 6488 3304  Email: djudge@anhb.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: smbunt@anhb.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: jchisholm@anhb.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@anhb.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: milne@anhb.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...

Human Biology

Professor Neville Bruce  6488 3292  Email: nbruce@anhb.uwa.edu.au

My research interests focus on the interface of lifestyle, psychosocial stress and health and wellbeing. I integrate disciplines from the biological and social sciences to examine current issues such as human fertility, overweight and obesity and organisational and industrial stress.

I do not wish to present specific projects, rather I would like to discuss possible projects in relation to the students own interests and future directions.

Information Technology

Development of Medical Diagnostic Software

Professor Stuart Bunt  6488 2983  Email: smbunt@anhb.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 metaanalysis of the data then entering it into a software program (no computer expertise required). You would then have to test the software's accuracy with medics on the wards or in GP's office to estimate its accuracy, false positives and negatives etc. I am also involved with research into using heart rate to diagnose psychological state such as depression, anxiety etc. A project could involve working with researchers in Fremantle hospital and Sir Charles 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 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: mgrounds@anhb.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: mgrounds@anhb.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**

Email: mgrounds@anhb.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: mgrounds@anhb.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 Email: alan.harvey@uwa.edu.au

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: bwaddell@anhb.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 underling cognition and behaviour. It is hypothesized that long-term effects of early life stress on adolescent regulation of stress perturb these neurodevelopmental processes during adolescence. To study the neurobiological mechanisms by which changes in adolescent basal hypothalamic-pituitary-adrenal (HPA) activity and stress responsiveness (as a result of early life stress exposure) may induce alterations in brain morphology and function during adolescent neurodevelopment, a mouse model is proposed.

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

Reproductive Biology

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

Dr Kathy Sanders 6488 1527 Email: ksanders@anhb.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: ksanders@anhb.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 (eg. a friend or relative).

However, social attitudes to the use of donor gametes/embryos have changed. Accordingly an increasing number of countries/states (Sweden, Netherlands, UK, States of Victoria and Western
Australia) have legislated for open-identity donor systems where children born of gamete or embryo donation can access identifying information about their donor on reaching maturity.

This project addresses issues surrounding the release of identifying information in a donor gamete/embryo program from the perspectives of the donor, the recipient and the offspring. Some questions include:

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

**Developmental Origins of Health and Disease**

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*Dr Peter Mark* 6488 2609  
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Our major interests centre on the role of glucocorticoids and dietary omega-3 fatty acids on pregnancy. This includes their effects on placental function, fetal growth and programming the phenotype of adult offspring.

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

**Oxidative Stress and Placental Function**

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

Oxidative stress results from the accumulation of reactive oxygen species (ROS) within cells and is thought to underlie a range of disease states. The detrimental effects of oxidative stress are mediated via damaging effects of ROS on cellular protein, DNA and lipids. Placental oxidative stress is thought to play a key role in several pregnancy disorders such as miscarriage, intrauterine growth retardation and pre eclampsia. 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  
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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 (to be commissioned in March 2010) 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.

SCHOOL OF BIOMEDICAL, BIOMOLECULAR AND CHEMICAL SCIENCES

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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  
**Oxygen Sensors and their Role in Preventing Tissue Damage during Hypoxia**  
The major research theme is to understand how tissue can sense and respond to a lack of oxygen.

A lack of oxygen in mammalian tissue as the result of traumatic injury, heart attacks, or stroke can have lethal effects. For example, coronary heart disease, where delivery of oxygen to the heart is compromised, is responsible for about 1 in 3 deaths in Australia.

Dramatic as these events are, non-lethal reductions in oxygen concentration (hypoxia) also occur, and can have a variety of clinical, physiological, metabolic and molecular consequences. For example, hypoxia during human endurance training has been found to enhance muscle fibre size, capillarity, myoglobin concentration and muscle oxidative capacity. Hypoxia has also been implicated in the development of hibernating myocardium, a process which limits the functional capacity of the heart. This disorder, which was identified from clinical and experimental observations, has been proposed to be an initial and protective reaction to a heart attack. This disorder is particularly intriguing as it is characterised by major changes to the myocardial cell including changes in its metabolism as well as the loss of contractile proteins.

These responses to hypoxia suggest that there is some way of detecting and responding to a decline in oxygen concentration by, as yet, unknown molecular mechanisms. Experimentally, it is difficult to investigate hypoxia using the traditional animal or organ models, because variable oxygen concentrations can occur throughout tissue. To overcome this problem, we developed a perifusion system which allows us to experimentally manipulate the oxygen concentrations of cell suspensions. With this system we can use different types of cells, including platelets, cultured skeletal muscle cells, heart cells and liver cells to examine the impact of hypoxia on cell function. Projects focus on using cell suspensions to probe the molecular mechanisms by which cells can sense and respond to a decline in oxygen concentration. The long term aim of this work is to prevent damage to tissue resulting from a lack of oxygen.

Dr Mark D Cregan  
**Characterisation of Mammary Stem Cells Isolated from Human Breast milk**  
Human breast milk is a complex medium containing a mixture of lipids, carbohydrates, proteins, micronutrients and cells. The cell types in breast milk of particular interest in my laboratory are secretory epithelial cells that have exfoliated from the basement membrane and mammary stem cells. As it is not possible to obtain normal, healthy tissue from the developing or lactating human breast, my laboratory has developed primary cultures from the breast milk cells that mimic the developmental stages of the mammary gland, such that we can culture mammary stem cells, differentiating cells and terminally differentiated secretory epithelial cells. The aim of the research in my laboratory is to characterise the differentiation pathways of these three primary cultures for use in lactation studies.

Professor Peter E Hartmann  
**Breast milk and Pre-term Nutrition**  
Breast milk provides the basis for an optimum food for pre-term babies because it has a desirable nutrient balance and contains many nucleotides, hormones and growth factors, which are not in infant formula. Although the gastrointestinal tract (GIT) of the pre-term baby is under developed it is important that the pre-term baby receives food not only to nourish its growth but also because it's GIT requires an intake of food for its functional development. While breast milk is the only food required for the first six months of life for a term baby to grow and develop normally, it does not contain a sufficient nutrient density to enable the pre-term baby to achieve the same rate of growth as would be expected during late pregnancy. Indeed, the energy, protein, sodium, calcium, phosphorus and magnesium content of breast milk are not high enough to meet the optimal rate of growth required for very pre-term infants. Currently this problem is overcome by fortifying the mother's breast milk with a fortifier derived from cow's milk. This project will explore the possibility modifying breast milk so that it can be used to fortify the mother's own breast milk for pre-term babies.
Expression of Breast milk
Mothers of pre-term babies as well as mothers who return to the workforce need to express their breasts to maintain a supply of breast milk for their babies. However, little is known about the features of a breast pump that are important in achieving efficient and comfortable removal of milk from a mother’s breast. It is apparent that in many mothers, the baby is more efficient in removing milk from the breast than the current hospital grade pumps. This project will examine the characteristics of the breast shield that facilitate efficient breast milk removal. The removal of milk by the baby will be examined using ultrasound imaging of the breastfeeding baby to identify the mechanism of removal of milk by the baby. These findings will then be applied to designing an improved breast shield for electric breast pumps.

Associate Professor Naomi Trengove 6488 4421 Email: naomi.trengove@uwa.edu.au
With Prof Mike Stacey and Dr Hilary Wallace

Research Area
The investigation of the causes of impaired wound healing in chronic wounds in humans represents a particularly challenging area of medical research. Fortunately, with the emergence of new techniques in both cellular and molecular biology it is now possible to use the available small tissue samples obtained from humans to understand the process more accurately. Venous leg ulceration is a debilitating chronic wound that occurs most often in the elderly and is the result of venous hypertension in the lower limb (venous disease). The pathogenesis of ulceration is not well understood, but there is evidence that elevated levels of inflammatory mediators (e.g. tumor necrosis factor-alpha) are involved (1,2). Susceptibility to ulceration in patients with venous disease varies. The supervisors have identified a polymorphism in the tumor necrosis factor-alpha gene (TNFA-308A) that is associated with increased risk of ulceration (3). Further studies are required to determine whether carriage of this allele is part of the cause of venous leg ulceration or just a marker of another causal allele in close proximity on the chromosome.

Project
This project will be undertaken in collaboration with the wound healing research group in the School of Surgery and Pathology (Faculty of Medicine and Dentistry), which undertakes clinical and laboratory studies into chronic venous leg ulceration.

The proposed project will investigate whether the tumor necrosis factor-alpha (TNFA) genotype in humans with chronic venous ulceration is associated with differences in the TNF phenotype. That is, do individuals with different TNFA genotypes produce different amounts of TNF-alpha? The levels of TNF-alpha protein and mRNA will be assessed in the wound and in stimulated peripheral blood leukocytes of patients with leg ulcers who have been genotyped in a previous study. The working hypothesis is that TNF-alpha protein and mRNA levels will be increased in patients carrying the TNF-308A allele compared to the wild-type TNF-308G allele. Patients homozygous for the A and G alleles will be compared to minimise individual variation.

This project will provide opportunities to interact with patients in a clinical setting, as well a giving a sound grounding in laboratory research techniques. Laboratory techniques for this study will include RNA extraction from cells and tissue, ELISAs and real-time PCR. Students will also have the opportunity to take part in patient assessments, outpatient clinics and observe operating theatre procedures.

References

Dr Robert C Tuckey 6488 3040 Email: robert.tuckey@uwa.edu.au

Cytochrome P-450 and Steroid Hormone Synthesis
Steroid hormone synthesis is dependent upon cytochrome P-450scc which catalyses the three
hydroxylation reactions involved in the conversion of cholesterol into pregnenolone, the precursor of all steroid hormones. We have purified and characterised the human form of this enzyme from 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-450scc catalyses the hydroxylation of cholesterol we will make changes to the primary amino acid sequence of the enzyme by the technique of site-directed mutagenesis. This will enable us to test the role of individual amino acids in the catalytic conversion of cholesterol to pregnenolone. Regulation of progesterone synthesis by the placenta is also being investigated. We are testing the hypothesis that electron supply to cytochrome P-450 scc is the rate-determining step of the progesterone biosynthetic pathway.

References:

**Professor James Whelan**

**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 mendalian 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**

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


Assisting Computer-Based Prediction of Subcellular Localization
Prediction of subcellular localization is a difficult task. The problem can be tackled experimentally, e.g. through the creation fusion proteins. This has been done for a large number of yeast proteins in the Yeast Protein Localization database http://ypl.uni-graz.at/pages/home.html and Yeast GFP Fusion Localization Database http://yeastgfp.ucsf.edu/. Both of these can be accessed via SGD, the yeast genome database http://www.yeastgenome.org/ Similarly, SUBA http://www.plantenergy.uwa.edu.au/applications/suba/index.php has localization information for many Arabidopsis thaliana genes. There is also a considerable amount of information about the locations of many E. coli genes. http://ecoliwiki.net/. However, these databases do not have predictions for all the predicted genes from the respective species, and in general, subcellular localization predictions are not available for most genes from most species, which is understandable given the expense of the process, particularly when attempted on a large scale.
Computer-based predictions therefore offer a cheap source of localization data. For certain compartments, such as mitochondria, chloroplasts and ER, computational localization prediction is effective because localization signals are known (though there is often considerable variation in practice). An example of a prediction system for these compartments is Predotar http://urgi.versailles.inra.fr/predotar/predotar.html. However, for other compartments the situation is much more problematic. (For a review, see Emanuelsson, 2002).

One approach that I have had some success with, in the case predictions of membrane association, is the use of Protein Domain predictions as proxies for protein localization. That is, if all (or at least the overwhelming majority) of proteins known to possess a particular domain are associated with a particular compartment, then one might reasonably assume that any new protein with that domain will also be found in that compartment. A second approach that I would like to try is to see whether there are biases in amino acid composition that are indicative of particular subcellular locations.

Winthrop Professor George C Yeoh

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 and 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 enhance 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 a mouse model of liver disease which induces the appearance of LPCs. The importance of putative cytokines has been confirmed by using transgenic mice which are gene-targeted for the particular cytokine. These studies indicate that IL6, TNF alpha, Interferon gamma and lymphotoxin beta are important LPC regulatory factors. To show that these cytokines directly affect the LPC, we have developed methods to establish primary cultures of LPCs and we have derived immortalised LPC lines. The general thrust of our current research is to characterise the LPC lines and document their response to cytokines we have identified as potentially important in regulating their growth and differentiation.

Specifically, for in vitro experiments we have developed a protocol for inducing, isolating and maintaining primary cultures of LPCs as well as established cell lines from transgenic mice. The transgene comprises the lacZ reporter under the regulation of a hepatocyte specific promoter. This allows us to monitor the differentiation status of the LPC lines as well as to trace them. Our in vivo experiments will evaluate the efficacy of both primary cells and cell lines to correct liver dysfunction in a mouse model of Wilson’s disease which in humans results in copper accumulation leading to metabolic defects in the liver.

Microbiology & Immunology

Chair of Discipline: Assoc/Prof Barbara Chang

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  
The major aims of my research are to  
(a) understand the structure and function of toxins produced by organisms that result in infections that cause septic shock  
(b) study regulatory networks of bacterial pathogens  
(c) understand pathogen and host cell interactions

(A) The endotoxin of *Neisseria meningitidis*  
*Neisseria meningitidis*, the causative agent of epidemic meningitis, is a significant public health burden worldwide causing 1.2 million cases per year globally, with an estimated fatality rate of 10% (WHO). Since the early stages of disease mimic viral infections such as influenza, it is difficult to identify the onset of this disease in hospital clinics. Because of this, it is believed that vaccination is the most relevant option for the control of this disease in the community. Meningococcal infection results in septic shock, an overwhelming immunological response to the release of the bacterial endotoxin. The biosynthesis of meningococcal endotoxin is a complicated process requiring up to 20 proteins in different compartments of the bacterial cell. Because it is expressed by all meningococci this structure is also being examined as a potential vaccine candidate.

(B) Regulatory networks in *Neisseria gonorrhoeae*  
*Neisseria gonorrhoeae* is the causative agent of the sexually transmitted disease (STD) gonorrhoea and globally causes approximately 20-60 million new cases per annum (WHO). Gonococcal infection is the leading cause of pelvic inflammatory disease in women and ~ one third of patients will become infertile. Increased levels of resistance to traditional antibiotics have raised concerns for future treatment options. To date no successful vaccine strategies have been developed for this organism, primarily because the cell surface proteins elicit limited immunological protection against other strains. To enable the development of innovative approaches to the control of gonococcal infections, we propose to investigate the regulatory networks in gonococci that are important for initial colonization and survival in the human host.

(C) Cellular biology of the human nasopharynx  
*Neisseria meningitidis* naturally inhabits the nasopharynx of humans, and in some instances, causes invasive infections culminating in rapidly fatal sepsis. Early studies showed that meningococci bound to non-ciliated epithelial cells in the nasopharyngeal organ culture model (NPOC). Transformed or primary epithelial cell cultures have provided the simplest model to analyze bacterial adherence and invasion, and has allowed the identification of a number of neisserial adhesins (i.e. pili, Opa, Opc) and additional putative virulence determinants which affect bacterial adherence and invasion into host cells (i.e. lipoooligosaccharide [LOS], capsule, PorB). These models have also been used to identify the host cellular receptors for both meningococci and the related pathogen, *N. gonorrhoeae*. To date, this data has been obtained using transformed cell lines growing in vitro, and attempts to translate these observations to the original NPOC model have yet to be attempted. We have access to human
nasopharyngeal tissue and will conduct a series of experiments to assess the validity of the in vitro data on meningococcal pathogenesis.

**Winthrop Professor Barry Marshall**  
9346 4815  Email: barry.marshall@uwa.edu.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.

**Dr Harry Sakellaris**  
9346 2286  Email: harry.sakellaris@uwa.edu.au

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 ie. how these organisms colonise the intestinal tract and (2) identifying new factors that play a role in virulence.

**Immunology**

**Dr Nithiananthan Asokananthan**  
6488 3139  Email: asok.nithi@uwa.edu.au

Characterisation of bacterial exo-products involved in inflammation of epithelial surfaces such as the lung and the prostate. Role of protease activated receptors on epithelial tissues.

**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.

**Dr Thelma Koppi**  
9346 2215  Email: thelma.koppi@uwa.edu.au

The effects of inflammatory mediators on the immunobiology of Dendritic Cells. The biological importance of protease activated receptors in DC function.

**Dr Leslie Mathaba**  
6488 4453  Email: leslie.mathaba@uwa.edu.au

Mites, Bacteria and Asthma. Isolation and characterisation of mite digestive enzymes, with particular reference to bacteriolytic enzymes. Characterisation of bacteria cohabiting within mites. Investigation of the potential of mite enzymes and products of the endosymbiotic bacteria, particularly peptidoglycan, lipoteichoic acid and cholesterol-dependent cytolysins, to modulate cells comprising the mesenchymal trophic unit in the lung. Development of strategies for biological control of medically and economically important mites.

**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.

Professor Geoffrey Shellam) 9346 2050 Email: gshellam@cyllene.uwa.edu.au
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

Chair of Discipline:
Dr Anthony Bakke 6488 7859 Email: ophysiol@cyllene.uwa.edu.au
Research in the discipline of Physiology has four main aims:
- To understand normal life processes with emphasis on humans
- To understand the mechanisms of disease
- To provide a sound scientific basis for new diagnosis and treatment
- To implement physiological genomics

The research activities in the discipline are carried out by groups of academic and research staff. Brief description of the basic aims and areas of investigation of the different research groups are provided below. For more detailed information about possible BMedSci research projects in the department, students are encouraged to talk either to the head of discipline, or to the individual supervisors listed below.

Further information about the Discipline of Physiology can be found under the discipline subheading on the School of Biomedical, Biomolecular and Chemical Sciences website: http://www.biomedchem.uwa.edu.au

Professor Howard Mitchell 6488 3314 Email: howard.mitchell@uwa.edu.au
Dr Peter McFawn 6488 3341 Email: peter.mcfawn@uwa.edu.au
Dr Peter Noble 6488 3310 Email: peter.noble@uwa.edu.au
Foetal and Adult Respiration and Asthma
The major theme for respiratory research is the physiological control of the bronchial tree in diseases such as asthma where airways narrow excessively giving rise to the phenomenon known as bronchial hyper-responsiveness. This is called “twitchy airways” in the general community. The airway is a complex structure and its capacity to regulate the flow of air is determined by interactions between airways smooth muscle, nerves, mucosa and other structural components of the airway wall.

Several new discoveries are providing important clues to the causes of bronchial hyperresponsiveness in asthma. Airways are exquisitely sensitive to the fluctuating pressures in the lung brought about by breathing movements in respiration. It is now clear that the sensitivity of asthmatic airways to pressure differ from normals, and several international laboratories, including our own, are now focusing their research on the regulation of airways in respiration. Many of the changes in the asthmatic airway also appear to start early in life, even before birth – i.e. in the foetus, which provides yet more clues to the basic physiological abnormality in this disease. We and others have already found important differences in the cellular physiology of airway smooth muscle in early life, which might predispose the lung to excessive airway narrowing.

Broad areas from which projects can be formed include:
• which are the most important factors in the airway or the lung determining maximum airway narrowing and which lead to bronchial hyperresponsiveness? How are these controlled by the pressures produced during respiration
• When does airway smooth muscle become functional in the foetus?
• Do newly discovered pathways involving calcium play a role in the development of twitchy airways in the foetus and newborn? (joint projects between this laboratory and Dr. Tony Bakker)
• Does bronchial hyperresponsiveness in asthma occur before birth?

Techniques: Our work has been supported by the National Health and research Council of Australia (NH&MRC) for many years. A wide range of techniques are available to help answer these questions. They include a range of in vitro physiological recordings of airway narrowing, specially some internationally unique methods to simulate breathing movements during respiration, videomicrometry of airway narrowing, immunocytochemistry, western blotting, morphometry and cell culture. We use the pig as experimental animal for studies on airway physiology since the lungs are of an adequate size and we have detailed knowledge of airway physiology based on many years research with this species in the laboratory. Other studies on foetal hyperresponsiveness are carried out in a mouse model of asthma.

Significance of the projects: The Respiratory Laboratory philosophy is to develop new ideas and methodological approaches to study those physiological mechanism which help us understand the abnormality of asthma. Our novel approaches allow us to challenge to existing ‘dogma’, which is an important thing to do in biomedical science. We expect that work from which honours projects are formed will be published in an international journal. Most of the laboratory’s work is published in the US and Europe.

Dr Robert Patuzzi 6488 1422 email: rob.patuzzi@uwa.edu.au
Professor Don Robertson 6488 3291 email: don.robertson@uwa.edu.au

Hearing and Deafness
Deafness is one of the most common forms of sensory impairment, with profound consequences for the individual and society. Our laboratory carries out fundamental research into the basic physiological mechanisms of normal hearing and deafness. The laboratory is funded by grants from the NH&MRC and other agencies and consists of five academic and senior research staff, visiting overseas researchers, postgraduate and honours students.

The research carried out in The Auditory Laboratory is attempting to answer the following broad questions:
• What are the basic mechanisms that determine hearing sensitivity?
• What are the homeostatic mechanisms that regulate inner ear function?
• What molecules and receptors are involved in excitation and inhibition of the auditory nerve
fibres?
• How do the brain and the inner ear interact via descending pathways?
• What are the precise mechanisms of various forms of hearing dysfunction?
• How can events within the inner ear be measured non-invasively and how can this be used for diagnosis in humans?

For information about possible projects, come and talk to the senior academic staff of the lab. Visit the lab’s website for additional information on or research activities. http://www.physiol.biomedchem.uwa.edu.au/index.htm/research/research_activities/hearing_and_deafness_2/about_us

Dr Livia Hool 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 ischemia. Under these conditions there is a reduction in blood flow to the muscle in the heart resulting in a reduction in oxygen. There is an 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.

Honours projects available in the lab include studying the effects of hypoxia on a number of ion channels that affect action potential duration in cardiac tissue. If an alteration in ion channel function is measured, the mechanism by which the alteration occurs will be determined.

The method that will be used to study membrane currents is the whole-cell 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.

In conjunction with local collaborators (Biochemistry, Pharmacology, Physiology, Medicine RPH) and international collaborators (Rome, Italy and Cincinnati, USA) the following questions will be answered:
1. How do cells sense changes in oxygen tension thereby altering ion channel function?
2. Can insulin-like growth factor-1 alter ion channel function and cell calcium handling?
3. Do ion channels in neurons contribute to oxygen conformance?
4. How do ion channels respond to muscarinic receptor stimulation under hypoxic conditions?

Dr Phil Oates 6488 1391 Email: phillip.oates@uwa.edu.au

Iron is essential for life, but too much iron (as in thalassemia and haemochromatosis) or too little (as in iron-deficiency anaemia) can be damaging. One of the principal aims of our research is to characterise iron metabolism in normal, iron-deficient and iron-loaded cells of different lineages and with different functions in iron metabolism. Cell types being studied include enterocytes (intestinal iron absorption), hepatocytes (iron storage), erythroid cells (oxygen transport), macrophages (metabolism and recycling of erythrocyte iron).

We are a diverse group with many different interests in iron. These interests and the relevant people to contact are listed below.

Dr Phil Oates 6488 1391 Email: phillip.oates@uwa.edu.au

Iron is essential for life, but too much iron (as in thalassemia and haemochromatosis) or too little (as in iron-deficiency anaemia) can be damaging. One of the principal aims of our research is to characterise iron metabolism in normal, iron-deficient and iron-loaded cells of different lineages and with different functions in iron metabolism. Cell types being studied include enterocytes (intestinal iron absorption), hepatocytes (iron storage), erythroid cells (oxygen transport), macrophages (metabolism and recycling of erythrocyte iron).

We are a diverse group with many different interests in iron. These interests and the relevant people to contact are listed below.
Intestinal iron transport

The laboratory is interested in the mechanism of iron absorption and how this process is regulated. Throughout the world iron deficiency is a major problem. Affected people can have anaemia, lethargy, poor concentration spans, depressed immune response etc. The major problem is that these people do not receive enough iron in their diet and that the bio-availability of iron is poor. In order to improve this situation it is important that we understand how iron is absorbed by the intestine. Over the last 6 years many new proteins have been identified that are involved in iron absorption but how they function is still very much a puzzle. We are interested in piecing this puzzle together and offer the following projects. Anyone interested in this area and would like to talk about these projects in more details please call by the lab.

Projects
Study 1. Cellular expression and function of IREG1 in Caco-2 cells
Study 2. Ferritin expression in copper deficient IEC-6 cells
Study 3. Characterization of the iron transport properties of IREG1*
Study 4. The interaction of haemochromatosis protein and the transferrin receptor in rats.
*In collaboration with Dr Livia Hool.

Placental iron transport

Iron is an essential nutrient for all growing cells and animals. Hence, it must be transported across the placenta and be utilized by the cells of the fetus if the growing fetus is to survive. The basic physiology of the processes involved is understood. For instance, it is known that iron is transported from maternal plasma transferrin across several cell membrane layers in the placenta to fetal plasma transferrin by processes which are unidirectional, energy dependent and involve receptor-mediated endocytosis of transferrin. Also, the rate of transport increases in parallel with the growth of the fetus as pregnancy progresses. However, details of the molecular mechanisms involved and how they change during development are virtually unknown. Most of the proteins listed above have been detected in the placenta and many have also been found in the fetus. Hence, they almost certainly play a role in placental and fetal iron metabolism. Animal models with mutations of some of the proteins are available. The use of such animals, as well as normal one, will aid in understanding the function of these proteins.

Project: To study the extent and cellular expression of genes and their proteins in the placenta during pregnancy.

Ca²⁺ is a universal second messenger that is essential for the normal function of almost all cells. Changes in intracellular Ca²⁺ can activate a diverse array of processes such as muscle contraction, cell secretion and cell to cell communication. However, if Ca²⁺ levels remain high within a cell for too long, cell death can occur. Loss of control of intracellular Ca²⁺ is a major cause of cell death in many human diseases such as stroke and cardiac infarction. The main interest of this laboratory is the examination of novel pathways responsible for modulation of Ca²⁺ handling and Ca²⁺-mediated effects in mammalian cells under normal conditions and during devastating diseases such as the muscular dystrophies.

Duchenne muscular dystrophy is an inherited muscle wasting disease that results in the death of patients in their early twenties due to respiratory (diaphragm) failure. A pathological rise in intracellular Ca²⁺ is thought to be one of the primary causes of muscle cell death in these patients. The high Ca²⁺ is thought to kill the muscle cells by over-simulating cellular Ca²⁺-activated enzymes such as the calpains and phospholipase A₂ (PLA₂).
Project 1. The role of protease-activated receptors (PARs) in muscle injury

In skeletal muscle, inflammation results from muscle injury. This inflammation is thought to contribute to the skeletal muscle weakness seen in these conditions, although it is unclear how this occurs. PARs are a newly identified family of G protein-coupled receptors that are activated by serine proteases such as thrombin and tryptase. PARs have been shown to mediate an extensive range of cellular activities, particularly during inflammation. In this laboratory, preliminary results in isolated skeletal muscle cells indicate that PAR-1 activation results in a large (≈50%) decrease in sarcoplasmic reticulum Ca²⁺ release, which should induce significant muscle weakness. Therefore, PARs could act as an important link between inflammation and muscle weakness. However, the effect of PAR activation on force production in intact skeletal muscle is unknown.

Aim of study: To investigate the effect of PAR activation on skeletal muscle contractile performance under normal and inflammatory conditions.

The effect of the PAR agonists thrombin and trypsin on contractile measurements made in fast- and slow-twitch skeletal muscle preparations will be undertaken using a recently purchased state of the art force transducer system. The following measurements will be made before and after PAR agonist exposure:

1. Maximal force production (force per cross-sectional area)
2. Tetanic and twitch tension
3. The force-frequency relationship.

These experiments will be performed on muscles from normal mice (a model of normal, pre-injury conditions) and on mice pre-exposed to lipopolysaccharides (IP injection) to induce an inflammatory reaction (a model of inflammatory, post injury conditions). LPS triggers a cascade of inflammatory cytokines (e.g. TNFα, IL-1β & IL-6) in a pattern similar to that seen after damaging strenuous exercise. Experiments will be undertaken using an Aurora 1200A muscle test system.

This study will be the first to determine the effect of PARs on skeletal muscle performance. The results of this study could have important ramifications for the treatment of sports injuries, and diseases where inflammation and skeletal muscle weakness are associated. These include the muscle weakness associated with muscular dystrophy, cancer, chronic heart failure, chronic obstructive pulmonary disease and repetitive strain injury.

Project 2. The role of Phospholipase A2 in skeletal muscle Ca²⁺ homeostasis and fatigue

Phospholipase A2 (PLA₂) is an important enzyme system in all cells. The products PLA₂ activation, arachidonic acid and lysophospholipids, act as second messengers at low concentrations, but are cytotoxic and important mediators of disease and injury at high levels. PLA₂ is highly expressed in skeletal muscle and in this laboratory we have recently published important findings showing that PLA₂ has marked effects on the control of intracellular Ca²⁺ in skeletal muscle cells (Han et al 2003, Am. J. Physiology, 285: C881-890). These findings indicate that PLA₂ could be an important cellular mechanism that contributes to fatigue and exercise-induced muscle damage in skeletal muscle. Furthermore, it has been shown that the skeletal muscle of patients with Duchenne muscular dystrophy exhibit markedly elevated (≈ 600%) PLA₂ activity (Taggesson & Henriksson, 1984; Lindahl et al, 1995), indicating that inhibition of PLA₂ could reduce injury –induced muscle damage in dystrophic muscle.

Aims of the study

1. To investigate the role of PLA₂ in promoting short- and long lasing skeletal muscle fatigue.
2. To determine the effect of PLA₂ inhibitors on eccentric-contraction-induced skeletal muscle damage in normal and dystrophic muscle.
3. To establish the mode of action of PLA₂ on modulation of Ca²⁺ homeostasis in skeletal muscle cells.

We will also investigate the effect of PLA₂ activation and inhibition on rates of fatigue and eccentric contraction-induced muscle damage using an Aurora 1200A muscle test system. The role of PLA₂ in Ca²⁺ homeostasis will be determined using a spectrophotometric Ca²⁺ measurement system (Cairn, UK).

This study will define the role of PLA₂ in fatigue and damage in skeletal muscle. The identification in this study of specific inhibitors of skeletal muscle PLA₂ activity could lead to specific drugs to prevent or ameliorate PLA₂-mediated skeletal muscle disease and fatigue.
Collaboration with Dr Shane Maloney, Physiology.
The tunica dartos muscle is a unique smooth muscle that lines the scrotum and lies in close contact with the scrotal skin. Males born without normal tunica dartos function are infertile, indicating that this muscle plays a pivotal role in the maintenance of testicular temperature and function. We have recently shown in this laboratory that the tunica dartos has unusual properties in that it contracts directly in response to cooling. This occurs independently of neural input, implying a local mechanism of activation. The contractile response is also significantly increased in the presence of the skin, suggesting substances released by the skin may enhance the contraction of the tunica dartos (Maloney, Shepherd & Bakker, 2005, Pflugers Archiv-European Journal of Physiology, 451, 489-497). However, the cellular mechanisms responsible these processes are unknown.

Aims of this study
1. To determine the intracellular signalling mechanism responsible for cooling-induced contractions in the tunica dartos of the rat.
2. To investigate the signalling pathway between the skin and tunica dartos muscle that leads to enhancement of cooling-induced contraction.

Force and intracellular Ca\(^2+\) will be measured simultaneously in tunica dartos preparations using a force transducer and a spectrophotometric Ca\(^2+\) measurement system (Cairn, UK), to determine whether a Ca\(^2+\)-mediated or a Ca\(^2+\) sensitisation process is involved in the cooling-induced contractions. Inhibitors of smooth muscle intracellular signalling pathways will be used to determine the messenger pathway responsible for the cooling effect. Intercellular signalling inhibitors will be used to determine the communication pathway between the skin and the muscle.

Project 4. The ability of antisense oligonucleotides to improve the function of dystrophic skeletal muscle
Collaboration with Prof. Steve Wilton & Dr Sue Fletcher, Australian Neuromuscular Research Institute.
Duchenne muscular dystrophy is a lethal muscle wasting disease that results from a mutation in the gene coding for dystrophin. This protein is important for maintenance of the structural integrity of the cell. Patients with Duchenne muscular dystrophy do not have a functional form of dystrophin, and therefore, they become prone to damage during normal muscle activity. Muscle cells die as a result, and the muscles eventually waste away. Boys with Duchenne muscular dystrophy show signs of muscle weakness as infants, are restricted to a wheelchair by the age of 12 years and 90% will die before their 20th birthday from cardiac and respiratory problems.

In this project a genetic manipulation technique called ‘exon skipping’ will be used to try and restore a functional form of dystrophin in mdx mice (a mouse model of human Duchenne muscular dystrophy, mice that also lack dystrophin). In this technique, antisense oligonucleotides are used to promote exon skipping. This results in the damaged part of the gene being skipped (not read), leading to the expression of a smaller, but still functional form of the protein.

Aim of study: To test whether treatment with antisense oligonucleotides leads to functional improvement in muscle function in dystrophic ‘mdx’ mice.

The best current method for determining whether normal skeletal muscle function has been restored in dystrophic mdx mice is to expose them to ‘eccentric contractions’, where the muscle is lengthened as it is contracting. Dystrophic mdx muscles are much more prone to damage via eccentric contractions than normal muscles. Therefore, if the antisense oligonucleotide treatment works, muscles from mdx mice should exhibit a susceptibility to eccentric contraction-induced damage that is similar to controls. Eccentric contraction-induced muscle damage will be induced, and the effects measured, using an Aurora 1200A muscle test system.

This project will provide important functional evidence about the ability of antisense oligonucleotide treatment to reverse the dystrophic phenotype. A positive outcome in this study could help pave the way for the use of this treatment as a future therapy for human Duchenne muscular dystrophy.

Emeritus Professor Trevor Redgrave 6488 3312 Email: trevor.redgrave@uwa.edu.au

Plasma Cholesterol and Heart Disease
We are investigating some of the basic mechanisms underlying the link between the metabolism of
plasma cholesterol-transporting lipoproteins and the development of atherosclerosis and heart disease.

We use a variety of approaches, including cell culture, measurements in transgenic animals and clinical investigations in patients at the major teaching hospitals.

We can offer projects studying the effects of lipoproteins on segments of arteries in organ baths, and in patients. Arterial function in patients can be studied by measuring flow mediated vasodilation or forearm blood flow during arterial infusions of lipoproteins.

We also offer projects studying the basic cell physiology of receptor-mediated endocytosis of cholesterol-containing lipoproteins. In addition to formal binding studies, uptake of lipoproteins can be observed by fluorescent microscopy. For study of some fundamental problems of lipoproteins at surfaces, we can offer a project using a Langmuir surface balance and a variable angle ellipsometer.

A main thrust of our current research is the development of breath tests for studying cholesterol and lipoprotein metabolism. Several current projects in human subjects are in progress at Royal Perth Hospital and at the Queen Elizabeth II Medical Centre. The work in humans is supported and supplemented by ongoing basic investigations using breath tests in transgenic mice. There are several possibilities for Honours projects within this area.

**Associate Professor Alan Everett**  
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**Synaptic Transmission**

The laboratory is concerned with understanding the mechanisms that determine the strength of a synaptic connection. Experiments are conducted on the neuromuscular junction, and on synapses between hippocampal neurones in culture. Synaptic function is evaluated from both the electrical signs of transmission as well as from novel optical measurements of nerve terminal activity using fluorescent dyes.

Our hypotheses are derived with the view to understanding what determines the probability of release of transmitter. Some neurones nearly always release transmitter when stimulated and therefore have a high probability of secretion; those with low release probability secrete relatively infrequently. Some of our recent research has focused on synaptic plasticity and the behaviour of vesicles in nerve terminals and our main findings from this work can be summarized thus:

1. "Silent" boutons in hippocampal neuronal cultures can be induced to recycle vesicles by activation of protein kinase A.
2. Factors other than simply the number of vesicles available at an active zone in a nerve terminal are important in determining the probability of transmitter release, and
3. The release ready subpool of vesicles at active zones can recycle independently of other vesicles in the terminals at low frequencies of nerve stimulation.

Ongoing questions/project areas of concern by the laboratory include the following:

- What are the roles of calcium and calcium activated second messengers in nerve terminals in the mobilisation of vesicles for exocytosis?
- What role does the cytoskeleton play in regulating vesicle exocytosis?
- What determines the size and distribution of the sub-pools of vesicles at release sites (active zones)?
- What changes occur at synapses when transmission is potentiated or depressed?

This focus should lead to a better understanding of the way signalling is managed in the nervous system and help answer one of the oldest questions in neuroscience: How does the nervous system store information?

**Dr Shane Maloney**  
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**Thermoregulation**

Homeothermic animals (like humans) maintain body temperature within a very narrow range. This feat is achieved by physiological mechanisms adjusting the rate of heat exchange with the environment, even in the face of very large changes in environmental conditions. At the extremes of exposure,
Thermoregulation is insufficient to maintain body temperature and hypo- or hyper-thermia result. This laboratory explores the mechanisms of thermoregulation in humans and other animals along several fronts.

**Thermoregulation of Special Organs**

Countercurrent heat exchange is used to maintain the testes (in scrotal mammals) and the brain (in artiodactyl mammals and carnivores) at a temperature different from the body core. Failure of scrotal thermoregulation leads to infertility. The adaptive advantage of selective brain cooling remains enigmatic. We study the mechanisms of this thermoregulation by investigating the afferent pathways measuring brain and scrotal temperature, and the effectors involved in altering brain and scrotal temperature. Whether humans can selectively cool the brain is widely debated.

**Thermal Strain in Athletes**

Exercise presents a special case of thermoregulation in humans because heat production can increase many fold during strenuous activity. If this activity is undertaken in conditions that limit heat loss (high ambient or radiation temperature, and/or high humidity) hyperthermia and heat stroke can develop. Hyperthermia is known to cause fatigue and so exercise performance is directly related to thermoregulatory ability. The mechanisms that improve thermoregulatory ability offer a means to improve performance.

**Fever**

During fever following infection, the body acts as if an internal thermostat has been turned up; thermoregulation during fever is normal, but defends an elevated temperature. We investigate the mechanisms of this alteration in mammals and birds. Mounting an immune response, including fever, is very expensive energetically and there are times when the immune response is attenuated, such as during malnutrition and in pregnancy pre-term. We are investigating the signals that may be involved in communication between energy balance and immune systems in mammals.

**Heat Stress and Reproductive performance in Livestock**

Reproductive success is seriously impacted in hot weather. Whether the effect of heat is a direct effect of hyperthermia on the hypothalamic – pituitary – gonadal axis, or whether changes in physiology that accompany hyperthermia (such as decreased food intake or acid / base changes) are responsible, is not known. We expose production animals at various stages of the reproductive cycle to elevated temperature and measure aspects of reproductive function (circulating reproductive hormones, sperm production, ovarian dynamics) to elucidate the causes and effects of high temperatures on reproduction.

Some Questions to be addressed:
- Is the physiology of avian fever the same as mammals? Do better acclimated sheep reproduce better during summer than non-acclimated sheep? Is the sweating threshold increased by hypovolemia or is hypertonicity required? Is Leptin involved in the fever-signalling pathway?
- How important is acclimation history to performance of sheep in hot conditions?
- How important is scrotal muscle control in scrotal temperature control and fertility?

**Dr Gavin Pinniger**

The activation of a muscle to produce tension (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 ability of a muscle to lengthen (stretch) while active is just as important as being able to shorten while generating force. However, 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 stretch-induced muscle damage also triggers and inflammatory response that is characterized by the slow development of swelling and stiffness in the days after the initial exercise (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 stretch-induced muscle damage 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 stretch-induced muscle damage 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 stretch-induced muscle damage.

Dr Tony Bakker 6488 7859  Email: tony.bakker@uwa.edu.au

1. **Molecular mechanism of stretch-induced force enhancement**
Experiments on isolated muscle preparations have shown that stretch of an active muscle causes a transient increase in force arising from the strain of both contractile (crossbridges) and non-contractile (structural) components of the sarcomere. The relative contributions of these components can be determined from their force-velocity characteristics and by the use of specific myosin inhibitors. Structural proteins such as titin, act to stabilize the sarcomere allowing the transmission of force within and between muscle fibres and disruption to these proteins is associated with the development of exercise-induced muscle damage. This study aims to determine the contribution of titin filaments to stretch-induced force enhancement and is focused on unravelling the complex molecular mechanisms of tension development during active muscle lengthening. The outcomes of this research will provide valuable insight into the mechanisms of exercise induced muscle damage and help to identify key features of the adaptation process brought about by repeated exposure to eccentric exercise.

Dr Tony Bakker 6488 7859  Email: tony.bakker@uwa.edu.au
And Dr Paul Fournier (Human Movement) 6488 1356  Email: fournier@cyllene.uwa.edu.au

2. **The role of circulating cytokines in skeletal muscle weakness**
Low-level systemic inflammation has been implicated in numerous pathological conditions such as cardiovascular disease, and chronic obstructive pulmonary disease and may contribute to the muscle weakness that is characteristic of Duchenne muscular dystrophy and in the aged population. Acute muscle injury can also trigger an inflammatory response leading to further loss of force and morphological damage. The precise pathways linking inflammation to muscle weakness are unknown. This study will investigate the role of systemic inflammation in muscle weakness by examining the effect of circulating inflammatory cytokines on skeletal muscle function using a hind-limb perfusion system. This system will allow for the administration of precise levels of cytokines into the hind limb circulation of rats or mice while maintaining an intact muscle vasculature. This perfusion system has distinct advantages over isolated muscle systems as the actions of most hormones and cytokines affecting muscle function are mediated to a significant extent by their effects on muscle blood flow. The effects of specific levels of inflammatory cytokines on skeletal muscle function will be determined while recording force output, and other critical variable such as blood pressure, pH, pO2 and temperature.

Dr Tony Bakker 6488 7859  Email: tony.bakker@uwa.edu.au
and Prof. Miranda Grounds 6488 3486  Email: mgrounds@anhb.uwa.edu.au

3. **The role of the inflammatory cytokine TNF-α (Tumour Necrosis Factor-alpha) in muscle damage**
Localised muscle damage and sarcolemmal lesions allow the infiltration of inflammatory cells and key cytokines such as TNF-α which may play a critical role in the development of secondary muscle damage. The cytokine TNF-α promotes an excessive inflammatory response causing direct damage to muscle fibres. This damage may be potentiated in patients with muscular dystrophy as the loss of dystrophin is reasoned to cause sarcolemmal instability through a vulnerability to physical stress. This study aims to determine the role of TNF-α in the secondary decline in muscle force associated with DOMS development after stretch-induced muscle damage. It is hypothesised that blockade of TNF-α activity (using the mouse specific antibody cV1q) will reduce the extent of myofibre necrosis and enhance muscle regeneration following stretch-induced muscle damage. Experiments will be carried out on normal healthy mice and dystrophic, mdx mice using a combination of in vivo eccentric muscle testing as well as isolated, intact muscle fibre experiments.
Drug Delivery
The research focus of this laboratory is on drug delivery. There are two main areas of interest – formulation and evaluation of nanoparticles for drug delivery, and the modulation of drug bioavailability by food components. An appropriate project for the B Med Sci program will be to evaluate the cytotoxicity profile of chitosan nanoparticles. Chitosan nanoparticles are widely studied for the delivery of drugs and genes. In UWA, a spinning disc technology is available for the preparation of monodispersed nanoparticles of a specific size. Nanoparticles of chitosan and chitosan derivatives may be prepared using this technology and the cytotoxicity of the nanoparticles evaluated as a function of their size and chemistry.

Dr Rhonda Clifford
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Complementary Therapies
An increasing number of people take complementary medicines (CMs) and it is evident from pharmacy, health food store and supermarket shelves that CMs have wide availability in the community. Australians spend more than $1.2 billion on CMs annually or almost twice the amount spent on prescription items. CMs range from government “registered” or “listed” products in pharmacies, supermarkets and health food shops to completely uncontrolled “herbal” products produced in-house by Chinese herbalists, homeopaths and naturopaths, and products purchased by mail order or over the internet.

A wide range of complementary treatments are available which claim to assist with weight loss however, in the main, there is a lack of data to prove their efficacy and safety. In 2003, a review of weight-loss supplements and alternative treatments by the National Health & Medical Research Council concluded that no non-prescription supplements (excluding orlistat) demonstrated sufficient evidence of long-term weight loss and lack of significant side effects. It is proposed to do a small scale trial of various complementary therapies in overweight or obese patients.

Dr Danielle Meyrick
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Radiopharmaceutical Science
Our research focuses primarily on the development and application of novel radiopharmaceuticals for imaging, therapy and management of a range of conditions in nuclear medicine. With the installation of a cyclotron for producing radioisotopes at Sir Charles Gairdner Hospital, applications of radioisotopes to medicine for positron emission tomography (PET) and therapy is an area attracting increasing interest locally. It is also a growing field world-wide. Radioisotopes of particular interest to this group are copper-64, useful for PET, and Re-188, a therapeutic beta emitter. The research aims to develop methods for targeted delivery of radioactivity to, for example, neoplasms. The targeting entities may incorporate biomolecules, complexing agents or microsystems.

The laboratory also focuses on elucidating the in vivo physical/solution chemistry of radiopharmaceuticals and other drugs incorporating metals. There is a broad interest in bioinorganic chemistry, including biomineralisation, and metal ions in biological systems.
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

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.

**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

**Winthrop Professor Leon Flicker and A/Prof Christopher Beer (RPH) 9224 2750**
Email: leon.flicker@uwa.edu.au and christopher.beer@uwa.edu.au

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

**Associate Professor S-K Gan (RPH)**
9224 0256/0245  
email: seng.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.leadman@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.

**Research Assistant Professor Anne Barden**  
9224 0272  email: anne.barden@uwa.edu.au

2. Studies of genetic and environmental factors relating to obesity, the metabolic syndrome and cardiovascular risk.
3. Pregnancy diabetes and pre-eclampsia
4. Alcohol and cardiovascular disease.
5. Cytochrome P450 arachidonic acid metabolism.

**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.

**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
3. Dietary antioxidants and blood pressure risk.

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

2. Alcohol and cardiovascular disease.
3. Dietary antioxidants and atherogenesis.

**Professor Kevin D Croft**  
9224 0275  email: kevin.croft@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)**  
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**  
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)**  
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  
  email: ian.lawrance@uwa.edu.au

- **Dr D Nelson (QEII)**  
  9346 4967  
  email: klopcic@cyllene.uwa.edu.au

- **A/Professor R Lake (QEII)**  
  9346 3127  
  email: achew@meddent.uwa.edu.au

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

**Iron Metabolism and Disease**

- **Professor Ian Lawrance**  
  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 Crohn’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 tumours in a mouse model of inflammation-induce colonic carcinogenesis. The inflammatory aspects, roles of Secreted protein acidic and rich in cysteine (SPARC), systemic and oral iron levels, and genetic alterations in the intestinal mucosa are being investigated.

Clinical research investigates the efficacy and tolerability of novel medications in CD. Other clinically based research that has been or is being undertaken includes the cancer risk of small colonic polyps, skin cancer risk in IBD patients on azathioprine, sperm DNA fragmentation and nutritional levels in IBD patients, markers of colon cancer, and the efficacy of rectal tacrolimus in resistant proctitis.

**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**

and **Dr Ross Graham**

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 haemochromatosis type 1 to measure expression of iron transporters and regulators to identify the role of HFE in sensing body iron levels and the regulation of liver iron metabolism and determine how the absence of HFE causes liver iron overload.

**Associate Professor Callum Pearce**

Fremantle Hospital

Gastroenterology

**Medical Oncology**

**Dr Anna Nowak (SCGH)** 9346 3841

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

**Cancer Treatments**

**Professor Michael Millward (QEII)** 9346 3823

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

We cover a very broad range of respiratory research. This includes: air quality and lung health, genetics of airway diseases, studies on airway inflammation and immunology, lung injury and repair – lung fibrosis, clinical trials, physiotherapy and lung vascular diseases and lung transplantation. Our basic laboratory work involves using the following techniques: flow cytometry; eosinophil and neutrophil separation; cell culture; pharmacology; molecular biology and cell biology techniques. We also have staff highly skilled in population health/epidemiology and clinical trial design and application. Some of our current research areas are:

1. Assessment of regulatory systems relating to the airway epithelium and airway smooth muscle control.
3. Dendritic cell biology, airway modulation and allergy
4. Airway inflammation including the role of toll receptors, prostanoids, leukotrienes, kinins and their biochemistry
5. Eosinophils, neutrophils and their relevant mediators and regulation
6. Pharmacogenetics of asthma and COPD
7. Clinical drug trials and their design
8. Air quality and lung health studies
9. Aspirin sensitive asthma
10. The role of exercise training in chronic lung disease
11. Biological markers of bronchiolitis obliterans in lung transplantation
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 to 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: lynette.fernandes@uwa.edu.au
The group is currently interested in novel drug targets for bronchial asthma, with particular reference to
protease-activated receptors and rho kinase. Techniques include cell culture, immunohistochemistry and confocal microscopy, radioligand binding and quantitative autoradiography, together with airway function studies in vitro and in vivo. The effect of important asthma triggers, including respiratory tract viruses and allergens on receptor function and density in the airways and the identification of key cellular pathways in airway neurons is also under investigation.

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
Projects are offered in these areas.

Professor M Martin-Iverson 9346 2812 email: Mathew.martin-iverson@uwa.edu.au

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.

Winthrop Professor Michael J Paech 9340 2222 email: Michael.Paech@health.wa.gov.au
Professor Stephan A Schug 9224 0201 email: stephan.schug@cyllene.uwa.edu.au
Professor Thomas Ledowski 9224 0201 email: Thomas.Ledowski@health.wa.gov.au

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 neuroendocrine 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.

**Dr Fiona Pixley**  
9346 4047  email: fiona.pixley@uwa.edu.au

**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.

**Professor Phil Burcham**  
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**Molecular Toxicology Group**

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

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

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

**Inflammation, senescence, ageing and age-related diseases.** The recent identification of the critical involvement of SirT1 (Silent Information Regulator T1), a protein, NAD dependent, (Lys) deacetylase (leading to protein in/activation and gene silencing) in Alzheimer’s disease, cancer, inflammation and in calorie-restriction induced extension of lifespan has generated a lot of excitement. This project will examine factors which may modulated the de novo synthesis of NAD in specific cells and how this can be manipulated to enhance (or reduce) functional survival of cells when challenges with free radicals and other toxins, delaying senescence (cell death) and the ageing process as well as ageing related diseases.
Pleural Disease Research
Winthrop Professor Y C Gary Lee 93464968  email: gary.lee@uwa.edu.au

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

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

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

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

iii) Mechanism of pleural infection.
   Pleural infection affects 65000 patients in the US and UK each year, and many more in developing countries. Using a new animal model and in vitro techniques, we investigate the pathophysiological effects of common bacteria on the pleura and aim to identify factors governing the migration of bacteria through the mesothelial cell layers.

SCHOOL OF PAEDIATRICS AND CHILD HEALTH

Head of Discipline:
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Professor Peter LeSouef 9340 8173  email: plesouef@meddent.uwa.edu.au
(In collaboration with Clinical Professor Jack Goldblatt)

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 200 children who have presented to the Princess Margaret Hospital Emergency Department with an asthma attack and plan to recruit 200 more. The children are followed up when they have recovered from the attack. Over 70% 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 are also interesting in how genetic and environmental factors (such as tobacco smoke exposure) interact to contribute to the severity of the acute asthma attack. There are several aspects of this exciting study that are suitable for individual projects.

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. **The genetics of vaccine responses in children.** Vaccines have been the major contributing factor to preventing childhood illness in the past century. Considerable differences in responses to vaccines have been noted between individuals and populations. We have a population of children with serum samples taken before and after their measles-mumps-rubella vaccine (MMR). In this and other populations we have found several genetic variations that are associated with altered vaccine responses. In this project we aim to investigate the contribution of innate and adaptive immune genes on the vaccine response in these children.

4. **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 years and 11 years of age. The project aims to examine clinical, physiological, immunological, genetic and environmental factors associated with respiratory disease in adolescence. The project would focus on the effects of puberty and obesity on the development of respiratory disease at this age.

5. **Genetics of asthma** – in cohorts with long-term longitudinal data - (NHMRC project grant)

6. **Immunogenetics of malaria infection in early life** – collaborative study with Barcelona research group of population in Mozambique (EU/NHMRC project)

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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.

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(in collaboration with Assoc Profs Peter Richmond and Dave Burgner)

Potential BMedSc Honours Project

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.

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Primary prevention of asthma in children
Developmental aspects of Childhood asthma
Children’s Environmental Health
Respiratory Physiology
Animal models of asthma
Lung function testing in infants and preschool children
Early detection of lung disease in cystic fibrosis

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Developmental origins of childhood asthma

Associate 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
The immunological effects of *Mycobacterium vaccae* innoculation in children with atopic dermatitis

There is growing evidence that microbial products can inhibit allergic responses. This has lead to the development of these products for the treatment and the prevention of allergic disease.

This unique study will examine the immunological effects of a mycobacterial product in children (aged 5-16 years) with atopic dermatitis. The children completing the study received injections of *Mycobacterium vaccae* or placebo 0, 2 weeks and 4 weeks after commencing the study.

All of the blood samples have been collected and the immune cells cryopreserved. Using cell culture techniques peripheral blood mononuclear cells will be stimulated in vitro with antigens and allergens and the cytokines response will be measured by ELISA and mRNA analysis. The immune response of the 70 children who received the *M. vaccae* will be compared with the 70 who received placebo in this double blind randomised controlled trial.

This is a valuable opportunity for a student to explore immunological responses in allergic children following treatment with mycobacteria.

For further information: Prof Prescott: susanp@ichr.uwa.edu.au or Dr Dunstan: jand@ichr.uwa.edu.au

**Clinical Professor Stephen Stick**
Paediatric Respiratory and Sleep Physiology, Epithelial Cell Biology
Paediatric Respiratory Diseases
Role of indoor air pollution in paediatric respiratory diseases

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1. Epithelial Barrier function in asthma
   **Project outline:**
   The role of the airway epithelium has been well investigated and studies have suggested that intrinsic properties in it contribute to the pathophysiology of asthma. Since current thought places atopy as an initiator of asthma many studies only include subjects with asthma defined by this and other strict phenotypes. Thus, any intrinsic epithelial abnormalities common to the different asthmatic phenotypes are likely to have been overlooked making it impossible to determine to what extent observations are due to primary abnormalities, secondary to chronic inflammation or due to atopy rather than asthma. This project intends to undertake a re-evaluation of the contribution of epithelial function to childhood asthma by first studying a fundamental property of epithelium (barrier function) to determine if there are abnormalities that are common to atopic & non-atopic asthma.

2. 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 focussing 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.
3. 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.

4. 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 dependant 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.

Dr Prue Manners 9340 8174  email: pmanners@meddent.uwa.edu.au
Epidemiology of Paediatric Rheumatological Disorders  
A long-term community survey of musculo-skeletal disorders in the community is being undertaken. Immunological Studies In Juvenile Chronic Arthritis And Other Rheumatological Disorders In Children.

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Aerosols in Pediatric 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  
School/Centre: Paediatrics and Child 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  
School/Centre: Paediatrics and Child Health  
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.
Title: Early life events and markers of adolescent neurocognitive functioning and mental health

Project outline:
Our research (conducted in collaboration with Dr Anke van Eekelen and Dr Eugen Mattes based at the Telethon Institute for Child Health Research) 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. Our objective is to characterise functional polymorphisms for genes related to stress regulation and examine the interactions of these genes with early life events and their neurobiological consequences. We also investigate neurocognitive ability and evaluate brain activity while participants are performing specific cognitive tasks. Students working on this project (which is 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).

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-oxidant 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 up to 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 of Project: 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.

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
- 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.
Students wishing to undertake an Honours project at the Telethon Institute for Child Health Research will be able to do so by enrolling through the School of Paediatrics and Child Health. The Institute’s research programs are available for review via their website (http://www.ichr.uwa.edu.au/research). Opportunities for Honours students are considered under the broader topic of postgraduate student opportunities at the Institute (http://www.ichr.uwa.edu.au/careers/postgrad/becoming). Specific projects (some of which are suitable for an honours year) are listed in a booklet available for the Institute’s web site (http://www.ichr.uwa.edu.au/files/user5/2008_Project_Booklet.pdf).

**Title of Project:** Lung structural changes in response to early life respiratory insults

**Name of Supervisors:** Dr Graeme Zosky, graemez@ichr.uwa.edu.au, 9489 7819
Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia. Clinical Sciences

**Project Outline:** Lung development in early life is a critical period during which susceptibility to respiratory insults is significantly increased. Viral and environmental exposures during this window of susceptibility can have a significant impact on long term lung health.

We have 2 mouse models of early life exposure;
1) Arsenic - human studies suggest that early life arsenic exposure via drinking water increases the risk of obstructive lung disease. We have established a mouse model of *in utero* arsenic exposure that results in altered lung function
2) Flu - severe respiratory viral infection is a known risk factor for chronic lung diseases such as asthma. We have a well established mouse model of early life influenza infection that results in long term changes in lung function

Having fully characterised the changes in lung function associated with these models we can now begin to identify the mechanisms that are involved. The critical first step in this process is to link structure with function i.e. what structural changes have occurred in the lung that would explain the differences we observe in lung function?

We are seeking an enthusiastic student with good attention to detail and a background in anatomy/histology to conduct systematic stereological studies on fixed lung samples obtained from these models. This project will provide an ideal platform for future postgraduate study and will make a significant contribution to our understanding of how early life exposures determine long term lung health.

**Title of Project:** 1. Effect of azithromycin on neutrophil function *in vitro* in cystic fibrosis (CF) 2. Effect of *Bifidobacterium infantis* on *in vitro* lung inflammation in CF.

**Name of Supervisors:** Dr Barbara Sheil, 9489 7817, bsheil@ichr.uwa.edu.au
Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia. Clinical Sciences

**Project Outline No 1:** Infection and inflammation develop early in the lungs of infants and young children with Cystic Fibrosis (CF) and are major factors driving the development of progressive lung damage. Azithromycin is a macrolide antibiotic that has shown some clinical efficacy in CF through immunomodulatory means; however, the exact mechanism is not understood. Clinical and in vitro studies suggest that azithromycin may dampen the immune response seen in CF and protect the lungs from damage by affecting how neutrophils and epithelial cells function.

Neutrophils are the predominating cell in the lungs of patients with CF. Their function is to destroy invading foreign microorganisms through a process called phagocytosis. Epithelial cells release chemotactic factors such which cause neutrophils to move into the lung from the circulatory system. When neutrophils arrive in the airway; they are primed, activated and engage in phagocytosis releasing oxidants and proteases, which kill and digest the foreign material. During sustained infection and
inflammation, such as that seen in CF, the continued migration of neutrophils to the lung and release of oxidants and proteases may contribute to tissue damage. This project will investigate the effect of azithromycin treatment on neutrophil function (migration and phagocytosis) in vitro using healthy and CF samples. The effect of azithromycin on epithelial cell function will also be investigated.

**Project Outline No 2:**  Probiotics are live bacteria that, when given orally, have been shown to reduce severity of inflammation in a number of chronic autoimmune diseases. Some success has also been reported in the prevention and treatment of atopic disorders. Probiotic supplementation reduced the incidence of respiratory infections in children attending day care center. Probiotics work in part, through modifications of immune response which may explain the clinical effects of probiotics observed outside of the gastrointestinal tract. The probiotic Lactobacillus GG has been shown to reduce pulmonary exacerbations, intestinal inflammation and hospital admissions in cystic fibrosis, although the mechanism is not known. This suggests that probiotics may have a role to play in attenuating inflammation in the lung.

Bifidobacterium infantis has previously demonstrated anti-inflammatory effects in the intestine been successfully used to treat irritable bowel syndrome. In this study we will investigate potential in vitro anti-inflammatory effects in cystic fibrosis, a disease associated with repeated cycles of infection and inflammation. We will assess the ability of this bacterium to reduce inflammation in isolated immune cells from healthy subjects and from patients with cystic fibrosis, and in epithelial cell lines. We will also investigate the effects of this bacterium on the immune response to Pseudomonas infection.

**Title of Project:**  Regulation of airway calibre by inspiratory and expiratory breathing manoeuvres in mice

**Name of Supervisors:**  Dr Peter B. Noble, 9489 7818, Peter.Noble@uwa.edu.au  
Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia. Clinical Sciences

**Project Outline:**  In healthy humans a unique phenomenon exists whereby inspiratory breathing manoeuvres such as deep inspiration produce bronchodilation (relaxation or opening) of previously constricted airways. The mechanism(s) of action for the effects produced by inspiration remain unclear, though are likely to involve stretching of the airway wall and ultimately relaxation of airway smooth muscle. The implications of such responses to DI are far reaching. DI represents a potent bronchodilator, rivalling the actions of alternative pharmacological agents, supporting a role of DI as a key physiological mechanism for maintenance of airway calibre (diameter), and therefore the air flow through the tracheobronchial tree i.e., ‘breathing is good for breathing’ (ERJ: 12:1252-1256). Any dysfunction in this mechanism compromises airway calibre. In both asthmatic and COPD (chronic obstructive pulmonary disease) patients, responses to DI are absent or blunted which may be a precursor to airway narrowing, a primary characteristic of obstructive disease.

While the effects of inspiratory manoeuvres have been studied previously, what is unknown is whether expiratory manoeuvres also play a role in the regulation of airway calibre. Evidence from in vitro studies suggest that compressive force such as that which accompanies expiration may also cause relaxation of airway smooth muscle and through this regulate airway calibre. The present project will characterize the effects of both inspiratory and for the first time expiratory manoeuvres on airway calibre in vivo. We will utilize both healthy and diseased mouse models combined with highly sophisticated techniques for assessment of lung function in mice, technology available to few laboratories throughout the world. Results arising from this project will impact on fundamentals of airway physiology and also on practices for assessment of obstructive disease in the clinic in which manoeuvres such as FEV₁ involve both deep inspiratory and expiratory manoeuvres.

**Title of Project:**  Screening of p53 Status in a Panel of Paediatric Leukemic Cell Lines

**Name of Supervisors:**  Prof. Ursula Kees, ursula@ichr.uwa.edu.au, 9489-7777  
Dr. Alex Beesley, alex@ichr.uwa.edu.au, 9489-7777  
Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia.  
Childhood Leukaemia and Cancer
Project Outline: Acute lymphoblastic leukaemia (ALL) is the most common cancer in children and long-term survival has reached 75-90%. However, there are significant side effects associated with chemotherapeutics and it is desirable to refine existing therapies to reduce this patient burden. In addition, a significant number of patients continue to relapse as a result of resistance. To improve our understanding of the development of drug-resistance we have developed a unique and extensive panel of ALL cell lines derived from children at different stages of this disease. We have measured the sensitivity of these cell lines to the most commonly used ALL chemotherapeutic agents and have generated an extensive database of drug-gene signatures that can be interrogated for biological function. However, to assist in the interpretation of this data we require additional information on the genotype of these cell lines, particularly in regard to p53, a tumour suppressor that plays a critical role in the regulation of cell survival. More than 60% of primary human tumours exhibit mutations in this gene but in leukaemia the incidence of such mutations is relatively low. The present study is designed to establish the p53 status of our panel of ALL cell lines as an important contribution to our understanding of their drug-resistance profiles. The study will involve cell culture, DNA extraction, PCR, sequencing and a number of other molecular biology techniques.

Title of Project: Characterisation of the Smo mouse - a murine model of medulloblastoma

Name of Supervisors: Dr Nick Gottardo, nickg@ichr.uwa.edu.au
Dr Peter Dallas, peterd@ichr.uwa.edu.au
Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia.
Childhood Leukaemia and Cancer (Brain Tumour Program)

Project Outline: Medulloblastoma (MB) is the most common type of malignant brain tumour affecting children and is a major cause of childhood cancer related mortality and morbidity. Improvements in treatment options will depend on advances in the understanding of the molecular biology of these tumours. Smoothened (Smo) transgenic mice over-express the sonic-hedgehog (SHH) pathway component Smo, and develop MB via constitutive activation of the SHH pathway. Most Smo mice develop MB within 8 weeks and the tumours have a similar pathology to human MB including the capacity for leptomeningeal spread. These features make this model system particularly attractive for the analysis of MB molecular pathogenesis and for testing new chemotherapeutic intervention strategies. Deregulated cell signaling mediated by the ERBB family of transmembrane receptors has been linked to the development and progression of many cancers including MB, and ERBB family members are established therapeutic targets in multiple tumour types. The aim of this project is to address the activation status of the ERBB signalling pathway in MB that develop in the Smo mouse and interpret these data in the context of the current understanding of MB molecular pathogenesis. The project will involve the quantitative assessment of RNA and protein levels of the four ERBB family members and the analysis of the expression of ERBB alternative transcripts in tumour specimens.


Name of Supervisors: Dr Kim Carter, kcarte@ichr.uwa.edu.au, (08) 9489 7907
Bioinformatics and Biostatistics group
Professor Ursula Kees, Childhood Leukaemia and Cancer
Mr Richard Francis, Bioinformatics and Biostatistics group
Professor Nicholas De Klerk, Bioinformatics and Biostatistics group
Dr Peter Dallas, Brain Tumour Program
Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia.

Project Outline No 1: Bioinformatics is an exciting new research field that involves the use of techniques including informatics, mathematics and statistics, computer science, and genetics to solve biological problems.
Over the last few years, scientists have discovered an important new class of small RNA molecules, which are involved in fundamental cellular processes. These microRNAs (miRNAs) have been demonstrated to play a role in a variety of human diseases including diabetes, cardiovascular diseases, psychological disorders and particularly cancers. Recent studies have highlighted a link between regulation of miRNAs and solid tumours, such as primitive neuroectodermal tumours of the central nervous system (PNETs) - the most common type of brain tumour affecting children. This research project involves the development of novel Bioinformatics methodologies, algorithms and software for identifying, analysing, and visualising the role that microRNAs play in the development and progression of PNETs. The knowledge and resources developed as part of this project will greatly enhance the body of knowledge of microRNAs, and will be of great benefit to researchers in a wide range of areas.

Project Outline No 2: Bioinformatics is an emerging research field involving the use of computing technology to answer biological questions. The field pulls together expertise from informatics, mathematics and statistics, computer science, genetics and other related fields. DNA microarray technology allows researchers to rapidly assess which genes are being expressed in a particular tissue in a highly automated way. Expression patterns can then be compared between healthy and diseased tissues samples, providing clues to understanding the genetic causes of diseases such as cancer.

Although DNA microarray technology is still in its infancy, a plethora of data already exists. Large-scale gene expression technologies enable scientists to rapidly generate gene expression profiles with thousands of data points on many individuals. Advanced Bioinformatics techniques are required to manage, manipulate, analyse and visualise these data, to help to transform the raw data gathered into information and knowledge about biological patterns and profiles. This research project involves the development of novel Bioinformatics methodologies, algorithms and software for identifying, analysing, and visualising data from gene expression studies. These Bioinformatics techniques will be applied to aid with our understanding of the genetic causes of childhood cancers, such as leukaemia, by identifying genes and genetic pathways linked with these diseases.

Title of Project: 1. Does UV irradiation of neonatal skin affect asthma development in adult mice? 2. Does UV irradiation or vitamin D3 application affect outcomes of skin vaccination?

Name of Supervisors: Professor Prue Hart, prueh@ichr.uwa.edu.au, 08-94897887 Dr Shelley Gorman, shelleyg@ichr.uwa.edu.au, 08-94897884 Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia Molecular Biotechnology (Inflammation)

Project Outline No 1: Asthma development is determined by the genes you inherit and your environment, particularly during childhood. We have shown that UV irradiation of skin can suppress the induction of allergic airways inflammation in mice. However adult mice were used for both the UV irradiation of skin and the sensitisation to allergens associated with the experimental asthma models. In this project, neonatal mice will be UV irradiated and its effect on asthma induction in adult mice (>8 weeks) investigated. The effect of both UV irradiation and allergen sensitisation of young mice will also be examined and compared with responses by adult mice. The induction of regulatory immune cells by UV irradiation in the mice of different ages will be investigated.

Project Outline No 2: The laboratory is interested in the immunosuppressive properties of UV irradiation of skin. The effects may be due in part to UV-induced vitamin D3 synthesis. The effect of antigen sensitisation via UV-irradiated or vitamin D3 treated skin is not known. These studies are relevant to the success or otherwise to vaccination through the skin in winter vs summer.

Title of Project: 1. Determining the importance of vitamin D deficiency in the development of asthma. 2. Understanding mechanisms by which vitamin D modulates immune responses.
Name of Supervisors: Professor Prue Hart, prueh@ichr.uwa.edu.au, 08-94897887
Dr Shelley Gorman, shelleyg@ichr.uwa.edu.au, 08-94897884
Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia
Molecular Biotechnology (Inflammation)

Project Outline No 1: Vitamin D is produced in skin following its exposure to the UV component of sunlight. UV also suppresses immune responses including allergen specific responses in a mouse model of asthma. Vitamin D is an important molecule that could be responsible for this suppression. By establishing a vitamin D deficient colony of mice, this project aims to determine the importance of vitamin D in modulating various aspects of allergic airways disease in utero and/or early childhood. Responses in various immune compartments will be analyzed.

Project Outline No 2: Vitamin D is produced in skin following its exposure to the UV component of sunlight. Vitamin D can modulate immune responses by altering immune cells such as dendritic cells. We have been investigating the effects of skin-applied (topical) vitamin D on the function of dendritic cells located in the skin, and also skin-draining lymphoid tissue. Topical vitamin D is currently used to treat immune-driven skin conditions such as psoriasis. This project aims to gain a better understanding of the immune mechanisms by which vitamin D acts to curb inappropriate immune responses.

Title of Project: Genetics and epigenetics in the development of hypospadias

Name of Supervisors: Dr Sarra Jamieson: sjamieson@ichr.uwa.edu.au 9489 7912
Genetics and Health
Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia
Dr Natasha Nassar
Population Sciences and Kolling Institute of Medical Research, University of Sydney (Perinatal Research Group)
Mr Richard Francis, Bioinformatics and Biostatistics group rfrancis@ichr.uwa.edu.au, 9489 7930

Project Outline: Hypospadias is a congenital malformation of the male reproductive organs characterised by incomplete development of the urethra. In Western Australia hypospadias is the second most common birth defect affecting, on average, 1 in every 130 male infants with rates doubling over the last 25 years. The aetiology of hypospadias is largely unknown but a lapse or disturbance in endogenous hormone production, principally androgen production, or exposure to exogenous oestrogenic hormones in pregnancy, has been identified as a key causal mechanism. Evidence from small scale candidate gene studies and animal models point to the involvement of both genetic and epigenetic mechanisms in such hormone disturbances.

The aims of this study are two-fold and include the investigation of both the genetic and epigenetic mechanisms in the development of hypospadias.

1. For the genetic analyses 400 children diagnosed with hypospadias at birth plus their parents (i.e. trios) will be recruited. DNA will be extracted from saliva samples for allelic association analysis of plausible candidate genes involved in hormone synthesis, signaling and response.
2. For the epigenetic analyses an appropriate tissue sample will be obtained from infants with hypospadias and will be compared to tissue from healthy boys undergoing circumcision.

For both components of the study brief information on parental in utero exposure to environmental anti-androgens or oestrogens will also be collected for analysis. This project will be undertaken within the Division of Genetics and Health and will provide experience in a broad range of molecular genetic methodologies. This includes DNA extraction, high-throughput genotyping technologies and genetic statistical methods for the genetic component as well as bioinformatic identification of CpG islands, RNA & protein extractions, gene expression analysis using RT-PCR and DNA and bisulfite sequencing for the epigenetic component.
**Title of Project:** Comparative genomics of *Leishmania* species to understand the parasite genetic determinants of human disease

**Name of Supervisors:** Dr Christopher Peacock, cpeacock@ichr.uwa.edu.au, 9489 7915  
Professor Jennie Blackwell, Genetics and Health  
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**Project Outline:** Leishmaniasis is a neglected disease that afflicts millions of people each year with a broad spectrum of disease ranging from self healing cutaneous lesions to fatal systemic infection. The *Leishmania* species involved is the main factor that determines what form of the disease the patient gets. To date, three species of leishmania (*L. major, L. braziliensis and L. infantum*) have been completely sequenced, representing the most diverse disease phenotypes. Comparative analysis of the genome data from these sequencing projects revealed a surprisingly small number of genes restricted to each of the different species. This project will examine the parasite factors involved in human disease with the aim of utilizing the findings to develop potential disease interventions. Two specific areas of interest will form the basis of this study. Sequencing and comparative analysis of clinical isolates from Brazil that cause well defined phenotypes in humans will identify specific parasite factors involved in modulating the host's immune response. In addition, the recent identification of an indigenous Australian *Leishmania* species, that has the capacity to cause leishmaniasis in macropods but not in humans, has provided an opportunity to improve our understanding of factors critical for establishing human infections. It is the closest relative to the human pathogens and as such will represent an ideal comparison to help identify parasite genes responsible for the adaptation to human parasitism. In addition, modified with the insertion of immunogenic genes, it will provide a possible attenuated vaccine candidate.

The project will involve the use of bioinformatic tools to visualize, annotate and compare the assembled sequences. *In silico* analysis will provide the framework for functional studies to knock out and knock in these genes, assessing their impact on infectivity *in vitro* and *in vivo* models of infection.

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**Title of Project:** Fructose intake and food sources in adolescents

**Name of Supervisors:** Dr Wendy Oddy, wendyo@ichr.uwa.edu.au, 9489 7879  
Dr Therese O’Sullivan, tosullivan@ichr.uwa.edu.au, 9489 7924  
Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia  
Population Sciences (Nutrition and Development)

**Project Outline:** While most dietary carbohydrate is digested into glucose in the gastrointestinal tract and enters the bloodstream directly, fructose is processed through the liver. Excess fructose entering the liver results in increased triglyceride production in the liver, and may contribute to hypertension, dyslipidemia, and non-alcoholic fatty liver disease. Some dietary fructose comes from natural sources, such as fruit and vegetables, however use of fructose as a sweetener is increasing in processed foods, particularly in the form of sucrose. There has been very limited research on intake of fructose, particularly in adolescents. This study will utilise three day food records from the 14-year follow-up of the Western Australian Pregnancy Cohort (Raine) Study to investigate fructose intake in adolescents.

The aims of this study will be to:

1) Conduct a comprehensive review of the literature investigating the role and effects of fructose in the diet  
2) Link existing fructose composition data to individual foods and beverages consumed in the Raine Study population identified using food record data  
3) Assess intake of fructose in the Raine population  
4) Identify food/beverage sources contributing to fructose intake in the Raine population
Title of Project: 1. Pubertal development and menstrual management in girls and young women with Rett syndrome

2. Comparison of Parent-report and Medicare data in a longitudinal study

Name of Supervisors: Dr Helen Leonard, hleonard@ichr.uwa.edu.au, 9489 7790

Ami Bebbington, Population Sciences
Telethon Institute for Child Health Research, Centre for Child Health Research,
The University of Western Australia

Dr Helen Woodhead, Endocrinologist at Sydney Children’s Hospital

Project Outline No 1: Rett syndrome is a neurodevelopmental disorder mainly affecting females. Those affected have varying degrees of physical and intellectual disability. We are undertaking a five-year study designed to examine various aspects of Rett syndrome, including clinical, psychosocial, and genetic aspects and the economic and social burden on the family and society. Part of this information is being gathered through video footage and questionnaires completed by the families. The study is based at ICHR and has national and international collaborators. There are isolated reports of early pubarche and we previously showed that bone age was comparatively advanced in younger girls whilst growth retardation is often a later feature of Rett syndrome. However it still remains unclear whether or not pubertal development is normal. This project will focus on a descriptive analysis of the pubertal development and menstrual management in girls and young women with Rett syndrome using data collected in the 2000, 2002, 2004 and 2006 Follow-up Questionnaires.

Project Outline No 2: This project will compare data from Medicare to data submitted by parents and carers of people with Rett syndrome to the Australian Rett syndrome Database. The Australian Rett syndrome database is a database of initial and followup questionnaires from a population-based study of people with Rett syndrome in Australia born since 1976. In these questionnaires parents and carers were asked to provide details on the health service use and medication used by their child (person in care) during the study period. We have Medicare data from the corresponding time frame. This could be expanded to a Masters by including a comparison with similar data on Down syndrome.


2. Description of the pre- and post-operative experiences of parents of girls and women with Rett syndrome who have undergone spinal surgery for scoliosis.

Name of Supervisors: Dr Helen Leonard, hleonard@ichr.uwa.edu.au, 9489 7790

Dr Jenny Downs, Population Sciences (Epidemiology)
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Project Outline No 1: Rett syndrome is a neurodevelopmental disorder mainly affecting females and those with the disorder have varying degrees of physical and intellectual disability. We are conducting a longitudinal study that aims to describe detail of the phenotype of Rett syndrome and its relationship with genotype. As a part of this study, we have developed a video protocol and demonstration video for families to systematically collect video data. Families who participated where asked to film their daughter in her natural setting of home and school whilst performing various tasks in the oral motor, mobility, hand function, communication and personal care domains. Videotapes showing functional abilities have been collected from families in both 2004 and 2007, and some families have participated on both occasions providing longitudinal data. This project will focus on the coding of the communication data, describing the range of communication abilities and analysing relationships with other relevant variables.

Project Outline No 2: Rett syndrome is a neurodevelopmental disorder mainly affecting females and associated with physical and intellectual disability. Scoliosis is a common orthopaedic complication of Rett syndrome and surgery is commonly used to reduce asymmetry in severe cases of scoliosis. The decision to proceed with spinal surgery can be difficult for many parents because of the potential for adverse medical outcomes and anxiety about their daughter experiencing complex and sometimes
painful procedures. Systematically collected information could usefully inform peri-operative procedures. This project aims to collect and analyse qualitative data that describes parents’ experiences, thoughts and feelings before and after their daughter’s spinal surgery.

Title of Project: 1. Trends in prevalence of intellectual disability in the Aboriginal population in WA.
2. Validating intellectual disability status from hospital morbidity records.

Name of Supervisors: Dr Helen Leonard, hleonard@ichr.uwa.edu.au, 9489 7790
Jenny Bourke, Population Sciences
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Project Outline No 1: The appropriateness of standard IQ tests for measuring the IQ in culturally and linguistically diverse (CALD) populations has been questioned. These tests, along with measures of adaptive behaviour, are used as a means of determining whether an individual meets criteria for intellectual disability (ID) in order to access services within the disability and education sectors. This project will investigate the prevalence of ID in Aboriginal and non Aboriginal populations in WA over the past 20 years and describe any changes in prevalence, particularly over the more recent years when more appropriate tests have been applied.

Project Outline No 2: The IDEA database collects population-based information on people identified with an intellectual disability (ID) through notifications to the Disability Services Commission and the Department of Education. It is unknown whether more complete ascertainment may be possible through linkage to the hospital morbidity system. Using a linked dataset including all children born over the period 1983-1999, we wish to investigate
• how many of those already known to IDEA are identified as having an ID from hospital morbidity codes
• whether any individuals identified with an ID from hospital morbidity codes are not in the IDEA database
• describe the pattern of coding for hospital admissions in those with an ID

Title of Project: How does having a child with Rett syndrome impact on parent work practices?

Name of Supervisors: Dr Helen Leonard, hleonard@ichr.uwa.edu.au, 9489 7790
Paula Dyke, Population Sciences
Telethon Institute for Child Health Research, Centre for Child Health Research,
The University of Western Australia

Project Outline: Rett syndrome is a neurodevelopmental disorder mainly affecting females. The disorder is characterised by a short period of normal development followed by a regression of function, the development of symptoms such as hand stereotypies and mental retardation. Affected individuals require a great deal of care and support which can impact substantially on family life. In 2007 the Australian research team received a UWA small grant to investigate the impact of having a child with Rett syndrome on the work practices of parents. 185 English speaking families, who were participants in the ongoing international project InterRett, were invited to participate. 172 of these consented and subsequently completed a short online survey. This project will focus on the analysis and of these data and information previously collected as part of the InterRett project with a view to publication in a peer reviewed journal. With additional qualitative work this could be a Masters project.

Title of Project: Examining the relationship between infectious disease exposures during childhood and incidence of atherosclerosis in later life

Name of Supervisors: Dr Kim Carter, kcarter@ichr.uwa.edu.au, 9489 7907
Associate Professor David Burgner, SPACH
Professor Nicholas de Klerk, Bioinformatics and Biostatistics group
Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia

**Project Outline:** Cardiovascular disease is a major worldwide health and economic burden. The Australian Institute of Health and Welfare estimates that heart disease will become the single leading public health problem for the world by 2020. Within Australia, heart disease and stroke are the first and second biggest killers, with 90% of Australian adults having one (modifiable) risk factor for heart, stroke and vascular disease and 25% having three or more.

Atherosclerosis, hardening and narrowing of the arteries, is the usual cause of heart attacks, strokes, and peripheral vascular disease. Atherosclerosis is an inflammatory process, with low level chronic inflammation leading to vascular damage. There is mounting evidence that multiple exposures to infections during childhood may play a key role in the development of atherosclerosis in later life.

This research project involves the investigation of the relationship between hospitalisation for infection in childhood and atherosclerosis in later life using the internationally unique population-level health database available in Western Australia. Our ultimate aim is to further the body of knowledge of the pathogenesis of atherosclerosis, and to enable better identification of higher risk individuals.

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**SCHOOL OF DENTISTRY**

**Contact person**

Associate Professor Linda Slack-Smith 9346 7874 email: Linda.Slack-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 Paul Waring 9346 2739 email: paul.waring@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.
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

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.

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Dr Campbell Witt  9224 2899  email: campbell.witt@health.wa.gov.au
Dr Wai Lim

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

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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?

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

Medical Genetics
The focus of this group is molecular mechanisms behind the genetic control of inflammation and immunity. Molecular and cell biology have been used to investigate these areas in autoimmune diseases including type 1 diabetes and inclusion body myositis, as well as the outcome of infectious diseases such as HIV/AIDS and non tuberculous mycobacteria. Specific interests include cytokines, chemokines and genes within the major histocompatibility complex (MHC).

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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.
The following members of the academic staff of the School are able to supervise BMedSc projects in 2009.

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).

Dr 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, biostatistical models applied to complex data, and statistical consulting.

Dr Tom Briffa (6488 1292)
Secondary Prevention and Translational Cardiovascular Disease Research
Dr Briffa is a Research Fellow and a member of 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, in particular the benefits physical activity and exercise therapy.

Dr Angus Cook (6488 7804)
Environmental Epidemiology; Water Borne Disease from Pathogens and Pollutants; Mosquito Borne Disease; Medical Geology
Dr Cook is a Research Fellow 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, 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 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.

**Dr Elizabeth Geelhoed** (6488 7129)

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

Dr Geelhoed is Senior Lecturer in Health Economics and Policy. Her 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 Billie 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 NO$_2$, NO$_x$, SO$_2$ 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.
Dr 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.

Ms Helena Iredell (6488 1274)

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

Ms 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.

Dr Keith Lui (6488 1296)

Health Informatics; Evaluation and Clinical Trial Assessment of Health Informatics Technologies

Dr Lui is a medical graduate with postgraduate qualifications in computer science and health informatics. His PhD research involved developing a tool for measuring experimental quality in health informatics and computer science. His current research interests include health informatics education and accreditation, clinical decision support and clinical informatics evaluation.

Associate Professor Rachael Moorin (6488 1416)

Health Economics; Health Services Research (utilisation and outcomes); Equity in Healthcare

A/Prof Moorin is the Director of the UWA node of the Australian Centre for Economic Research on Health (ACERH) - UWA Node – having previously been a member of Professor D’Arcy Holman’s research team at the Centre for Health Services Research, UWA. Rachael is also the Director of Health Science Studies.
and teaches within the school of population health. Rachael is currently undertaking research with ACERH in three program areas: health insurance; ageing; and the economic burden of illness and injury. Rachael’s research interests include: The health effects of social inequality; provision of health services; health care financing and the impact of health care policies on utilisation and outcomes.

**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.

**Dr 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.

**Dr 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).

SCHOOL OF PRIMARY, ABORIGINAL AND RURAL HEALTH CARE (SPARHC)

Head of School:
Professor Jon Emery         9346 7502 or 9346 7504
Email: jon.emery@uwa.edu.au

http://www.sparhc.uwa.edu.au/
http://www.emergmed.uwa.edu.au/
http://www.cucrh.uwa.edu.au
http://www.rcs.uwa.edu.au
http://www.crroh.uwa.edu.au
http://www.camdh.uwa.edu.au

SPARHC collectively contributes to quality primary health care outcomes for the Western Australian community with particular emphasis on rural and Indigenous health. The School has a role in facilitating and developing strategies for collaboration within the School and its key stakeholders to maximise the benefits that flow from such collaborations. Research activities in SPARHC are carried out by groups of academic and research staff. For more detailed information about possible BMedSci research projects in the School, students are encouraged to talk 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:**
**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:

**Winthrop Professor George Jelinek**
9346 4354  
Email: George.Jelinek@health.wa.gov.au

Venom research  
Emergency Medical Systems  
Triage and Casemix  
Emergency Health Care Outcomes

**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 diastolic heart failure and sepsis.

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

**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.

**Anaphylaxis and immunotherapy**

We have identified potential roles for IL10, IL6 and TNF in human anaphylaxis. Ongoing studies will
examine the role of a number of receptor gene polymorphisms for these cytokines in the clinical manifestation (severity) of anaphylactic episodes. Our group also oversees a large randomised controlled trial of venom immunotherapy in Tasmania in which a high rate of occurrence of anaphylaxis is being observed. A BMedSci project would explore whether these receptor gene polymorphisms are predictive of adverse reactions during immunotherapy and sting challenge result after immunotherapy. This project would suit students interested in the mechanisms of critical illness as well as life-threatening allergy and immunotherapy.

**Allergy**

CCREM holds a large bank of native Australian ant venoms and allergic sera from patients who have experienced anaphylaxis. A BMedSci project is available to explore the identities of the allergens within these venoms and allergenic cross-reactivity between species. Using a variety of immunologic and proteomic techniques. This project would suit a student with a particular interest in allergy and/or proteomics.

**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.

**Associate Professor Glenn Arendts**  9224 0363  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**

Research projects examining a variety of problems around acute diastolic heart failure in the elderly patient are available as BMedSci projects. These include

- Identifying clinical and laboratory (vasoactive, neurohumoral and inflammatory) markers that are most important in the genesis of decompensated diastolic heart failure
- Development of clinical decision rules, using a combination of clinical, laboratory and echocardiograph data, to aid 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, in particular exploring the hypothesis that acute diastolic dysfunction can be identified and is important in the progression of shock in elderly sepsis

**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.

**Facilitated discharge of the frail elderly**

Several BMedSci projects are available for students with an interest in improving the provision of care for the chronically ill frail elderly patient that presents to ED. These include examining the efficacy of multidisciplinary intervention pre discharge, and alternate care plans or ED avoidance strategies for people living in aged care facilities.

**Centre for Aboriginal Medical and Dental Health (CAMDH)**

**Director:**
**Professor Helen Milroy**  6488 2038  Email: helen.milroy@uwa.edu.au

CAMDH’s principle roles within Medicine and Dentistry are to recruit and support Indigenous students in the courses offered by the faculty; develop, teach and coordinate the Aboriginal Health curriculum throughout the faculty; and to provide a resource for community organisations in relation to Aboriginal health. CAMDH staff members are actively involved in all aspects of these roles, including research and
would be interested in supervising BMedSci projects within their areas of interest. Students may choose a topic solely within the Centre or may undertake the degree in another school in the Faculty with a joint supervisor from CAMDH.

**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 the Centre or may undertake the degree in another school in the Faculty with a joint supervisor from CAMDH.

**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.

**Assistant Professor Paula Edgill**  6488 8140  Email: paula.edgill@uwa.edu.au
Dr 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.

**Ms Adele Cox**  6488 1411  Email: adele.cox@uwa.edu.au
Ms Cox has a joint appointment with CAMDH and the Rural Clinical School of Western Australia. She helps co-ordinate the teaching of Indigenous Health within the RCSWA and her research interests are child and adolescent health and Indigenous health.

**Combined Universities Centre for Rural Health (CUCRH)**

**Director:**
**TBA**  9956 0200  Email:
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.

**Associate Professor Juli Coffin**  9956 0247  Email: julicoff@cucrh.uwa.edu.au
Juli 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.

**Professor Isabelle Ellis**  9158 9900  Email: iellis@cucrh.uwa.edu.au
Isabelle Ellis is located at CUCRH’s Pilbara office in South Hedland. She is involved with state and national e-health and tele-health initiatives, Indigenous health, health economics, and practice innovation. A/Prof Ellis is available to co-supervise Honours, Masters and PhD students.

**Associate Professor Marisa Gilles**  9956 0232  Email: mgilles@cucrh.uwa.edu.au
Marissa 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.

**Assistant Professor Ivan Lin**  9956 0204  Email: ivanl@cucrh.uwa.edu.au
Ivan 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.

**Research Associate Lecturer Sylvia Lockyer**  9158 9900  Email:  sylvial@cucrh.uwa.edu.au
Ms Lockyer is a Registered Nurse in Aboriginal Health Education currently a Research Associate located at CUCRH’s Pilbara office in South Hedland. Interests include research in indigenous maternal and child health, indigenous tobacco related projects and indigenous health workforce.

**Professor Timothy Skinner**  9956 0232  Email:  timskinner@cucrh.uwa.edu.au
Tim Skinner was trained as a health psychologist in the UK. His main area of research and clinical practice is in chronic disease care, especially diabetes and more recently sleep apnoea. However, his work is varied, covering all areas of health behaviour including sun protection behaviours, smoking cessation and meditation. As a psychologist, he also conducts work in the promotion of social and emotional well-being with a particular focus on adolescent health.

**Assistant Professor Jan Hall**  9956 0247  Email:  janh@cucrh.uwa.edu.au
Jan 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.

**Research Assistant Professor Melissa Barrett**  99560226  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.

**Research Associate Lecturer Hamish Morgan**  9956 0292  Email:  hamishm@cucrh.uwa.edu.au
Hamish Morgan recently completed an anthropological PhD that reconsidered the notion of ‘community’ in terms of Aboriginal social practices. His research was based in a little Aboriginal community near Wiluna called Ululla, where he lived for two years. Hamish is interested in experiential, peer based learning, intercultural exchange and the power of stories, ‘country’ and cultural awareness to change professional and personal trajectories. He is project officer for the Healthy Murchison Kids Project, a project that promotes healthy eating and lifestyle in Murchison schools. His research interest centers on Aboriginal practices of community, storytelling and practices of mobility.

**Assistant Professor Simon Forrest**  9956 0207  Email:  simonf@cucrh.uwa.edu.au
Simon Forrest is an Assistant Professor in Aboriginal Health. Simon is an educator as a primary teacher and tertiary lecturer having been in the field for over 30 years. He brings this expertise to CUCRH to assist in the development of various teaching programs in the areas of Aboriginal cultural awareness, competency and security. His research interests include Indigenous history and Indigenous knowledge and its representation in the academy.

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**The Rural Clinical School of Western Australia**

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

**Chair of Research Steering Committee:**
*Professor Kirsten Auret*  9842 5555  Email:  kirsten.auret@uwa.edu.au

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 12 sites around the state and an intake of 79 students in 2010. 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:

**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.

**Winthrop Professor Campbell Murdoch** 9722 1883 Email: campbell.murdoch@uwa.edu.au  
Professor Murdoch is the Chair of Rural and Remote Medicine. His research interests are in rural and remote medicine, rural and remote medical education, care of the elderly in the community, care of the intellectually disabled and chronic fatigue syndrome.

**Associate Professor David Atkinson** 0438 380 209 or 9193 6043 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 2 PhD projects and 2 honours or BMedSci type studies at present. 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.

Dr Atkinson, Dr Julia Marley the RCSWA research fellow, Dr Carmel Nelson the Medical Director of KAMSC, staff of the Kimberley Population Health Unit and other practitioners in the region can support a range of practical research projects. Broome provides a supportive research environment and we are looking for people with an interest in Aboriginal health and enthusiasm who would like to be part of our team.

**Research Associate Professor Harriet Denz-Penhey** 9346 7361 Email: harriet.penhey@uwa.edu.au  
Dr Denz-Penhey is the Senior Research Fellow whose research interests are in using qualitative methods and patient-centred clinical care research. Much of her current research is focussed on the educational evaluation of the RCSWA programme. Her personal research has included using grounded theory and action research methods in the exploration of patient self care in serious illness.

**Associate Professor Andrew Kirke** 9722 0500 Email: andrew.kirke@uwa.edu.au  
Dr Kirke is a Medical Coordinator with the RCSWA in Kalgoorlie. 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.
**Associate Professor Helen Wright**  
Email: helen.wright@uwa.edu.au  
Dr 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 videoconferences 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.

**SCHOOL OF SURGERY**

**Head of School:**  
Winthrop Professor Paul Norman  
Email: paul.norman@uwa.edu.au  
9346 2150

**Bowel Cancer: Causes and Treatment**

**Professor Barry Iacopetta**  
Email: barry.iacopetta@uwa.edu.au  
9346 2085

Professor Iacopetta’s molecular-based research on bowel cancer includes genetic, epidemiology, pathology and oncology studies.

**Projects:**
1. Improving the identification of individuals in the population with the familial bowel cancer syndrome HNPCC
2. Low risk genetic factors for bowel cancer: are they different between proximal and distal colon?
3. Evaluation of molecular and pathological markers of prognosis in early stage bowel cancer
4. Using genetic markers to predict toxicity and response to chemotherapy

**Breast Cancer: Causes and Treatment**

**Winthrop Professor Christobel Saunders**  
Email: christobel.saunders@uwa.edu.au  
9346 2146  
Dr Toni Musiello  
Email: toni.musiello@uwa.edu.au  
9346 4174

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.

Professor Saunders is currently involved in the following research projects and trials:
1. International clinical trials of breast cancer preventions and treatment such as IBIS II Prevention study
2. Gestational Breast Cancer Studies
3. Evaluation of MRI (Magnetic Resonance Imaging) in imaging breast cancer
4. TARGIT (Targeted Intraoperative radiotherapy) in early breast cancer
5. OCT (Optical coherence tomography) pilot study to detect cancerous lymph nodes
6. Western Australian Breast Cancer in Young Women Database Project
7. Menopause after Breast Cancer Research Clinic (including ovarian function and chemotherapy)
8. A randomised controlled trial of a cancer shared care model
9. The Fertility – Decision Aid study for young women with early breast cancer
10. Health outcomes of rural breast cancer patients
11. WA Cancer and Palliative Care Network Research and Evaluation Unit - various studies
12. Angiogenesis and Gestational Breast Cancer
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 Prof Hilary Wallace 6488 7514 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 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.

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 Dicken Hayne, Fremantle Hospital)
7. General practitioners’ preferences for managing the care of people with cancer (in collaboration with 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)**

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<tr>
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<tr>
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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 four 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

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 soon to be completed dedicated research facility at 1 Salvado Rd, 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**

The tympanic membrane and its biology: Our research on the tympanic membrane includes early development, pathology, wound healing and artificial replacement of the chronically perforated membranes.

Projects:
1. Study of early cellular and molecular development including keratinocyte maturation and the mapping of the cell-cell and cell to matrix adhesion machinery
2. Study of wound healing events in perforated tympanic membranes
3. Cholesteatoma: understanding the molecular and cellular origin
4. In vitro culture and characterisation of primary tympanic membrane and cochlea cells

Other research includes regeneration of auditory hair cells; in addition to examining the genes involved in the processes of age-related hearing loss and noise-induced hearing loss

Cells involved in the detection and coding of sounds are highly differentiated and are particularly susceptible, as the mechanics of hearing are never “switched off” even during periods of sleep. It is thought that this constant stimulus results in a gradual decline in the health of the cells and eventually leads to cell death. Processes occur within the cell to guard against damage; however, little research has been done to unravel these protective processes and the genes that control them.
Projects:
1. Genetics of Age-Related Hearing Loss
2. Genetics of Noise-Induced Hearing Loss
3. Hair cell protection in Organ of Corti-Cultures

Information and Computer Science
This research group has developed a successful tele-otology system which is in use at a number of sites in Australasia. The group continues to develop ways to improve the access of people in rural and remote areas to ear and hearing services.

Projects:
1. Assessment of clinical outcomes related to chronic ear disease when utilising tele-otology in remote sites
2. Validation of a clinical decision support system for otology
3. Validation of automated audiometry
4. The role of tele-otology in the treatment pathway of Otitis Media in metropolitan indigenous children
5. Validation of telehealth for nose, throat and head & neck disorders
6. Electronic medical records

Audiology
The dedicated team of research audiologists provide specialist hearing care in assessment, diagnosis and rehabilitation, particularly for patients requiring cochlear implants or other implantable devices, patients with complex hearing losses, and patients with balance disorders. Projects are available in the assessment of outcomes following rehabilitation, the interaction between audiology and other medical services, noise exposure and hearing protection.

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 programmes. The fellowship programmes 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.

ESC is also involved in the Busselton Healthy Ageing Study (BHAS), an epidemiology project that is exploring the genetic and environmental influences on health. ESC is focussing 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.

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

Orthopaedics & Related Biomedical Research

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

Disciplines of Research
- Pathology of Bone, Cartilage and tendon
- Orthobiologics and Tissue Engineering
- Molecular biology of bone cells (osteoclast and osteoblast)
- Intracellular vesicle trafficking of osteoclast
- Intracellular signaling of bone cells
- Matrix induced autologous chondrocytes implantation
- Bone allograft and related clinical and laboratory research
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, 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 Centre for Orthopaedic Research 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 biocompatibility studies in vivo.

The Role of p62 in Pathological Bone Loss
Approximately 30% of patients are admitted to public hospitals in Australia for reasons related to skeletal disorders, including trauma, osteoarthritis, osteoporosis, primary and secondary bone tumours, genetic and metabolic disorders. Abnormal bone resorption contributes to most of these diseases and conditions. Based on the clinical evidence of p62 mutation in patients with Paget's Disease of bone, and our observation of the involvement of p62 in RANKL-induced NF-Kb signaling, we propose that intracellular molecule p62/A172 may play an important role in the switch off/on signals necessary for bone resorbing cells to resorb bone. To this end, we will study the molecular mechanism of p62 in action, and the interaction with its possible partners for the facilitation of abnormal bone resorption. The clinical significance of this project is to:

1. enhance understanding of abnormal bone resorption in Orthopaedic related diseases and conditions.
2. provide a strategy of drug development for the treatment of these diseases and conditions.

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.

Professor Jiake Xu 9346 4051 Email: jiake.xu@uwa.edu.au

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
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

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
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.

**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.

**Biological, Social and Epidemiological Studies of Schizophrenia**
Professor Jablensky has been involved for many years in epidemiological research into schizophrenia and affective disorders conducted by the World Health Organisation. Assen has played a central role in the development of the ICD-10 classification of mental and behavioural disorders. Since 1994 his research in Australia has involved conducting studies on the genetic epidemiology of schizophrenia; the neurodevelopment of children born to mothers suffering from psychotic illness; and criminal offending.
by persons with psychoses. In 1996-99 he was the Chief Investigator of a major national study on the prevalence of psychotic disorders in urban areas.

**Professor Dieter Wildenauer** 9347 6782 email: Dieter.Wildenauer@uwa.edu.au

**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. We are following up the linked areas on chromosome 6p and 10p and 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 a large family sample from Indonesia for linkage studies in schizophrenia. A genome wide linkage scan revealed evidence for a gene locus on chromosome 3, which will be investigated further for presence of schizophrenia susceptibility genes. In addition, a sample of 1000 individuals with schizophrenia in the Indonesian population will be collected for association studies.
- In collaboration with Prof. Gary Hulse we are collecting currently a large sample of individuals with heroin dependence for genome-wide association studies with DNA sequence variants.

**Associate Professor Kellie Bennett** 9346 2251 email: Kellie.Bennett@uwa.edu.au

Dr Bennett’s main research interests involve child psychological health and wellbeing 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.

**Professor Hans Stampfer** 9346 2394 email: Hans.Stampfer@uwa.edu.au

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

**Wellbeing and Depression**
Dr Street is involved in a number of studies exploring the role of social cognitive factors in the aetiology and maintenance of both wellbeing and depression. She is particularly interested in the role of goals and goal setting in childhood and adult wellbeing and the importance of an ongoing nurturing environment. Her recent research also considers the role of motivation and 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

Associate Professor Roland Kaiser has a broad interest in medical ethics, including ethical aspects in 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 is conducting several research projects in the area memory performance in the elderly in relation to oestrogen, testosterone, homocysteine, vitamins, cardiac and cerebro vascular disease and diabetes. He also investigates treatment options for chronic schizophrenic patients with memory problems.

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

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

Professor Mohan Isaac  9433 0322  email: Mohan.Isaac@uwa.edu.au
Dr Isaac has been involved in organization of mental health services in resource poor settings and training of primary health care personnel in basics of mental health care, in developing countries for over two decades. His current research interests consist of community mental health, public health aspects of psychiatric disorders including suicides and primary care mental health.

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

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

SCHOOL OF WOMEN’S AND INFANTS’ HEALTH

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

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

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

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

GYNAEOLOGY
– 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 lifelong 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**  
Email: karen.simmer@uwa.edu.au  
Neonatal Intensive Care; Lactation and Infant Nutrition; and Factors Involved in Infant Growth and Development.

**Title: The influence of human milk on commensal and pathogen recognition**
**Project outline:**
The protection of breastfeeding has been ascribed to milk components such as maternal immunocompetent cells, immunoglobulins, antimicrobials peptides, oligosaccharides, growth factors, cytokines, lysozyme, lactoferrin, complement, and nutrients. We now also know that early human milk has the capacity to influence neonatal anti-microbial responses by specifically and differentially modulating the innate immune receptors (Toll-like receptors) that recognize bacteria by producing soluble forms of these receptors. In this project, the candidate will examine several of the soluble immunomodulatory factors present in human milk, over the first few weeks of an infants life, and explore their impact on commensal and pathogen recognition and control. This will be done in conjunction with an ongoing clinical study examining development of infection in infants from the same mothers providing the milk samples. This study will enhance our understanding of how breastfeeding contributes to prevention of infection while allowing normal microbial colonization of the newborn. There is potential to develop the project into a higher degree.

**Associate Professor Roger Hart**  
Email: roger.hart@uwa.edu.au  
Fertility; Reproductive Endocrinology; Polycystic Ovarian Syndrome

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

**Clinical Professor Ian Hammond**  
Email: ian.hammond@uwa.edu.au  
Gynaecological oncology; Colposcopy: Laparoscopic and Complex Pelvic Surgery

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

**Clinical Associate Professor Ronald Hagan**  
Email: ronnie.hagan@uwa.edu.au  
Neonatal Intensive Care; Long-Term Follow-Up of Children Following Preterm Birth; Postnatal Depression.
Title: Activation of the placental innate immune system by oxidised lipids  
Project outline:  
The innate immune system consists of a number of extra- and intra-cellular receptors that are activated by various microbial cell wall products, triggering a cellular inflammatory response. It has recently been discovered that the activity of these receptors can be modified by oxidised lipids and fatty acid metabolites. Placental inflammation and oxidative stress play key roles in several major pregnancy disorders; the effects of lipid oxidation on placental inflammation has not been investigated, however. This project will explore the effects of various lipid metabolites on the innate immune response of human placental tissues, employing a number of different biomedical research techniques to elucidate the mechanisms through which these effects are manifested. This information will help further our understanding of the interaction between oxidative stress, inflammation and pregnancy disorders such as preeclampsia, intrauterine growth restriction and premature birth.

Title: Lysophospholipids: Novel initiators of uterine contractility?  
Project outline:  
The pregnant uterus is usually held in a state of quiescence until factors that cause uterine contractility increase in concentration and trigger labour and delivery. Uterine muscle cells express receptors for a group of common lipid molecules called lysophospholipids. This project will explore the hypothesis that lysophospholipids, which are produced in large amounts by platelets during clotting, can act upon uterine muscle cells to induce the expression of contractile-associated proteins that convert the uterus into a contractile organ. This finding would explain the mechanism underlying uterine haemorrhage-triggered preterm labour and could lead to development of novel treatment and prevention strategies.

Title: Inhibition of inflammatory signalling pathways in placental tissues  
Project outline:  
Inflammation is a major cause of preterm labour and birth prior to 32 weeks gestation. Using a human fetal membrane perfusion model, a number of novel anti-inflammatory drugs will be tested in this project to explore their effects on inflammatory gene expression and cytokine production from intrauterine tissues. Protein microarrays will be employed to elucidate intracellular signaling pathways affected by these agents in the presence of an inflammatory stimulus. These studies are aimed at identifying a non-toxic, selective inhibitor of placental inflammation that can be taken to clinical trials with the objective of decreasing the rates of preterm birth in high-risk women.

Title: Ventilation induced dysfunction in the premature diaphragm  
Project outline:  
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: Ventilation induced dysfunction in 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). Mechanical ventilation unloads the diaphragm which becomes inactive leading to the development of VIDD. In adult models of prolonged ventilation VIDD is characterized by loss of diaphragmatic force-generating capacity and endurance with evidence of muscle fibre atrophy, structural injury and myofibre cellular dysfunction. Experiments have shown that the preservation of spontaneous breathing activity may blunt the severity of VIDD. Whilst VIDD has been well characterized in the adult, there is very little information about the relevance of this disorder in the immature newborn infant. The extremely premature neonate may be at increased risk of developing VIDD due to the need for extended periods of ventilation, immature myofibre composition, rapid respiratory rates, high mechanical loads, and exposure to steroids, infection, poor nutrition and sedation. Pilot studies in the preterm lamb suggest that the onset of VIDD in the newborn may be more rapid than in the more mature adult model, with reduction of force generating capacity, myofibre atrophy and impaired signalling of muscle protein synthesis. Potential projects suitable for B Med Sci students in 2010 could utilize existing samples to define the impact of antenatal exposures (steroids, endotoxin) on protein synthesis and degradation in the diaphragm using Western Blotting, Immunohistochemistry and quantitative PCR techniques. We will also do some extended ventilation studies (24 hour) on near term lambs, and will assess the difference in oxidative stress and protein synthesis in ventilated lambs compared to those that breathe spontaneously without assistance.

Alternatively, a B Med Sci in 2010 could use physiological techniques to assess the force-generating capacity and fatigability of diaphragm muscle in preterm lambs. Physiological studies would utilize fresh specimens to be collected in 2010 that will aim to define the timecourse of the development of VIDD in the preterm lamb, and compare this to that observed in the fully matured newborn lamb, or the preterm lamb exposed to maternally administered antenatal steroids.

The projects will be undertaken within the School of Women’s and Infants’ Health, with co-supervision from Dr Thea Shavlakadze and Prof Miranda Grounds from the School of Anatomy and Human Biology (for protein signalling project) or by Dr Gavin Pinniger and Dr Tony Bakker from the Department of Physiology (School of Biomedical Biomolecular and Chemical Sciences)

**Title: Effect of Heliox during High Frequency Jet Ventilation** (suitable for a student with medical, physiology or engineering background)

*Project outline:*
High frequency jet 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 (240-660 breaths/min) to remove carbon dioxide, whilst a constant, high distending pressure facilitates oxygenation. Although HFJV has been in clinical use for over 25 years, there is still much to be learned about its optimal delivery. This project will look at how the density of the inspired gas may influence the distribution of gas, and the ventilation requirements using a model of neonatal meconium aspiration.

**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 look at 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 lung injury or gas exchange.

**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 are keen to see if using variable ventilation enhances surfactant pool size and production in a near term lamb model, ventilated for 24 hours. By undertaking this project, 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 (in lambs). You will also be responsible for analysing the physiological data and the surfactant pool analysis (which may involve a trip to our collaborator’s laboratory in USA).

**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 on-going 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 beast 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**

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*Supervisor:*  
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**1. MLF1 PROJECT**

Myeloid leukemia Factor 1 (Mlf1) was identified as a gene that caused some forms of acute leukaemia. This laboratory independently described Mlf1 as Hls7, a gene isolated when leukemic cells underwent a hemopoietic lineage switch (Hls) ie displayed different features from the original leukaemia. Our work investigating the function of Mlf1 suggests that its leukemic action may
be caused by preventing cell cycle arrest when cells attempt to terminally differentiate. 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 early developmental processes and lineage fate determination in the haemopoietic system. We have developed transgenic mouse lines that express Mlf1 in different haemopoietic compartments as well as mice deficient in Mlf1. Available research projects include:

1 **Role of Mlf1 in hemopoiesis.** This project will use our mouse model over-expressing Mlf1 in the haemopoietic compartment to investigate the role of Mlf1 in development of various haemopoietic lineages.

2 **Investigating the role of Mlf1 in stem cells.** This project will use the mouse model over-expressing Mlf1 in the stem cell compartment to determine what effect Mlf1 has on haemopoietic stem cell development. This research will contribute to our understanding of the role of Mlf1 in blood cell differentiation and leukaemia.

2 **HLS5 PROJECT**
This laboratory isolated Hls5 as a gene that was expressed when leukemic cells underwent a haemopoietic lineage switch (Hls) and displayed different features. Hls5 is a novel member of the RBCC family of molecules, which includes a number of genes involved in cancer/leukaemia eg Pml, Rfp and Tif1α. Family member Pml is considered to be a classic tumour suppressor gene. Hls5 maps to chromosome 8p21, a region frequently deleted in a number of tumours, and it is thought that tumour suppressor genes reside at this locus. When introduced into cancerous or leukemic cells, Hls5 slows their growth and induces cell death. Yeast 2-hybrid screens have identified a number of very interesting partner proteins including FOG, Ubc9 and PIAS1. Our recent biochemical data confirmed these interactions, which indicate that Hls5 is involved in regulating the key transcription factor GATA-1. Microarray data have demonstrated that Hls5 influences expression of genes in several important signalling pathways involved in immune regulation and blood cell maturation. Available research projects include:

1 **Identification / characterisation of genes associated with Hls5 down regulation.** We have an in vitro model of Hls5 knock down in haemopoietic cells using RNAi. Microarray will be used to identify genes differentially regulated following down regulation of Hls5. Detailed analysis will then be carried out on selected candidate genes.

2 **Identification of new Sumo target molecules.** Post-translational modification by Sumo has been associated with transcriptional regulation and nuclear assembly and represents an important regulatory component of gene expression. Hls5 has been implicated in sumoylation and nuclear domain assembly. This project will use cellular and biochemical techniques to investigate the role of Hls5 in key regulatory processes.

3 **Analysis of Hls5 gene expression in Melanoma patient samples (honours).** Hls5 interacts with a number of molecules involved in TGFβ signalling. This pathway has been identified as playing a role in Melanoma. This project will look at expression of Hls5 in melanoma samples as well as key genes affected by TGFβ signalling that could play a role in the development / progression of melanoma.

**Hormone Dependent Cancers**

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**Dr Keith Giles** 9224.0327  email: kgiles@waimr.uwa.edu.au  
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**Project title:**
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 co-regulators that regulate a range of NR signalling pathways. These
molecules include SLIRP, a NR repressor of estrogen action in breast cancer. SLIRP also represses PPAR signalling, 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 signalling 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 co-regulators in the metabolism of microRNA processing, regulators of hormone action, and investigating the intersection between miRNA biology and NR signalling.

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

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

Project aims:
1. Determine the effects of altered SLIRP expression on PPAR reporters in liver and macrophage cell lines.
2. Assess the impact of changes to SLIRP levels on endogenous gene expression.

Angiogenesis and Tumour Immunology

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Topic/research focus title:
Research focus: angiogenesis; multistage tumorigenesis; tumour immunology; transgenic mice

Project title: Regulation of the ‘Blood-Tumour’ Barrier

Topic/research focus overview:
Cancer is one of the major causes of mortality and its incidence continues to increase. Remodelling of blood vessels during tumour growth, a process termed angiogenesis, appears to control the movement of immune cells into solid tumours. Our research program aims to identify mechanisms which control neovascularization in cancer, to develop "angio-immuno" therapies which alter the tumour vasculature
and promote immune cell entry and to study the role of vessel-specific genes which may control the barrier function of solid tumours.

**Cell Signalling**

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One of the hallmarks of many cell signalling processes involved in proliferation/differentiation, as well as leukaemia and cancer development, is the activation of tyrosine kinases. We have focused on the signalling cascades within red blood cell precursors that are activated by the hormone erythropoietin (Epo) and involve tyrosine kinases. Further, we have shown that a member of the Src family of intracellular tyrosine kinases, Lyn, is activated through the Epo-receptor, and is important for the differentiation of red blood cell progenitors into mature erythrocytes (Figure-1). Lyn is also involved in the regulation of certain types of leukaemia and cancer cells. Consequently, our group is interested in investigating the signalling events pertinent to this molecule (Lyn) (Ref 1, 2, 3).

Through our expertise in protein-protein interaction, in particular via the yeast two-hybrid system, and our development of a phosphotyrosine specific version of this interaction assay, we have identified novel signalling pathways involving Lyn, that lead to changes in diverse cellular responses. We also utilize mice with genetically altered Lyn levels/activity to help study Lyn and its binding partners involvement in signalling processes. Projects available in our group are directed at analysing the signalling pathways of the Lyn interacting molecules within the context of erythroid cell development, as well as regulating leukaemic and cancer cells, utilizing animal models, and cell and molecular biology techniques.

**Figure-1 Erythroblastic Island showing different stages of erythroid cell differentiation.** Neutral benzidine and Wright’s stain of erythroblasts at different stages of development isolated from an erythroblastic island. Hemoglobin is stained yellow/orange. Cells present are proerythroblast (Pr), basophilic erythroblast (B), polychromatic erythroblast (Po), orthochromatic erythroblast (Or), and enucleated reticulocyte (R).

Specific project outlines

1) **Using novel fusion proteins (Cbp/SOCS1) to down-regulate kinases in cancer/leukaemia**

This project involves generating expression vectors and make small proteins corresponding to the interaction motifs and functional elements of two signalling molecules Cbp and SOCS1. We will use the high affinity Lyn binding sites of Cbp and the ubiquitination mediating region (socs box) of SOCS1 to generate an inhibition/knockdown of active Lyn kinase and other Src family kinases in leukaemia and cancer cells. The fusion protein will be expressed and purified from bacteria/eukaryotic cells and then tested on model cancer/leukaemia cell lines for its ability to turn off the activity/level of Lyn and other tyrosine kinases. Then it will be tested for its ability to alter/inhibit the growth/spread of cancer/leukaemia cells in animal models.

2) **Effects of altering the tyrosine kinase modulating molecule, Cbp, on mice erythropoiesis and its intersection of new pathways (PI3K/Akt) regulated through**

We have Cbp−/− mice and will be characterizing the erythroid compartment of these animals in detail and assessing the different signalling pathways (PI3K/Akt anti-apoptosis pathway, PLC and fes oncogenic pathways) that we have identified as potentially intersected by this signalling intermediate. This project will involve assessing the different stages of erythroid cells, from early progenitors to fully differentiated red blood cells, comparing them to wild-type counterparts to see if deleting the Cbp gene inhibits/enhances their proliferatin/differentiation. We will also look at the erythropoietin induced signalling within the Cbp−/- erythroid cells and see how this affects their signalling networks.

3) **Effect of keeping a kinase active (Lynup/up) on mice erythropoiesis and signalling pathways**

These animals have a constitutively active form of Lyn (Lynup) and this project will characterize the erythroid compartment of these animals and look at the alteration of signalling pathways down stream of this molecule. We will look at the signalling events within erythroid cells isolated from these mice and compare them to wild-type as well as cells with the Lyn gene deleted (Lyn−/- mice), looking at the erythropoietin signalling pathways, the timing and kinetics of the activation of these pathways.
4) A new oncogenic pathway in cancer/leukaemia controlling cell shape (Lyn-LACM)

The Lyn-LACM pathway (Figure-2) has significant effects on cell shape and this project will continue current efforts to detail the ability of this pathway cytoskeletal aspects (shape, movement, different cancer and leukaemia cells. When we pathway through tyrosine we cause the F-actin to instigating cell rounding which would significantly cancer/leukaemia cells ability to migrate/interact cells/the extracellular matrix. Such pathways are for controlling metastasis – a process that is the cancer to produce deaths.

**Figure-2 Model of Lyn-LACM pathway.** The region of LACM promotes multimerization and filamentous actin. The SH3 domain can bind a LACM (1), promoting Lyn phosphorylation of LACM (2). This then leads to association of Vav2 and Nck2 (3) through SH2-pY motif binding. Combined, these interactions lead to changes in the cells cytoskeleton (4).

**References**


**Cancer Gene Regulation**

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**Project outline:**

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. Ultimately these types of investigations will lead to insights into diseases of the brain such as brain tumors and dementia.

**Mitochondrial Medicine and Biology**

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Mitochondria play a fundamental role in cell and energy metabolism and consequently mitochondrial
dysfunction can lead to severe multi-system disorders with wide range of clinical presentations that commonly include neurodegeneration, muscle defects and exercise intolerance. To understand these conditions better and identify therapeutic targets it is necessary to understand how gene expression is regulated within mitochondria as some of the most significant gaps in our knowledge of mitochondrial function and disease are in the regulation of mitochondrial gene expression. Links between transcription and translation in mammalian mitochondria are not known. Mitochondrial mRNAs are transcribed as part of long primary transcripts that generally encompass the entire mtDNA, therefore the ratios of the 13 mammalian mitochondrial mRNAs and their proteins must be controlled at a post-transcriptional level. Little is known about how these 13 mRNAs are regulated in mammalian mitochondria. This is particularly important since tissue-, cell- and disease-specific variations in expression of the 13 different mtRNAs has been observed, but cannot be explained at present. The basic components and mechanisms of transcription have recently been discovered, however the control of mRNA processing, translation and stability remains unknown.

Mitochondrial RNA-binding proteins

We are interested in identifying mammalian mitochondrial RNA-binding proteins and investigating their role in RNA metabolism in cells. Discovery of proteins and the RNAs they bind may shed light on the regulation of gene expression in mammalian mitochondria. In addition, we are developing new methods for the identification of mitochondrial RNAs bound by the mitochondrial RNA-binding proteins that may regulate their expression in health and in disease.

Mitochondria as targets for chemotherapeutics

Recent developments in understanding the central place of mitochondria as a regulator of cell death have stimulated enormous interest in targeting mitochondria in new approaches to cancer chemotherapy. A major aim for this research is to overcome the two problems in cancer chemotherapy, drug resistance and the lack of selectivity of cancer drugs in differentiating between normal and tumour cells. A number of therapeutic strategies targeting mitochondria for cancer therapy have been described which include a variety of gold compounds. We are investigating the mechanism of selective antitumour activity of gold lipophilic compounds in cancer cells, which will enable us to identify gold compounds with optimal properties that selectively target mitochondrial antioxidant proteins in cancer cells. The aim is to develop novel and unique probes for the study of mitochondrial redox regulation in cells and aid the development of new chemotherapeutics.

Synthetic Biology and Drug Discovery

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Engineering synthetic proteins, RNAs and cells

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:
Re-engineering the genetic code of cells.
Development of **synthetic proteins for gene therapy** of neurodegenerative diseases.
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).

Selected reading:

Liver Diseases and Carcinogenesis

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**Towards liver cell therapy (Project 1)**

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 differentiated hepatocyte or stem cells such as 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. Accordingly, one of the objectives of our research is to identify cytokines that regulate LPCs and to understand their mechanism of action. This will underlie strategies to increase the contribution LPCs make to liver repair in vivo as well as to grow large numbers of functional liver cells; hepatocytes or cholangiocytes in culture for cell therapy applications.

To accomplish this, we are assessing the ability of different transgenic mice to respond to a model of liver injury induced by subjecting them to a choline deficient, ethionine supplemented diet. We are also generating LPC lines from mice in which specific cytokine mediated cell signalling pathways are ablated. Collectively these studies are providing important information relating to the growth and differentiation of LPCs.
Understanding the basis of liver cancer (Project 2)
The LPC is also of considerable interest to cancer researchers for it has been proposed as a target cell for transformation leading to the development of hepatocellular carcinoma (HCC). Our laboratory has established LPC lines from mice which have the p53 gene deleted. These are called p53 immortalised liver (PIL) cells. Interestingly we have PIL cell lines which are transformed and tumorigenic while others are normal (Ref 1). We are adopting the approach that by comparing these cell lines, we will identify important genes which are responsible for transformation of liver cells to hepatocellular carcinoma (HCC).

PROJECTS
1. Documenting the effect of cytokines on proliferation and differentiation of LPCs and determining their mechanism of action
This project takes advantage of three resources available in our laboratory. First we have established a LPC line (BMOL TAT) which expresses beta-galactosidase when it differentiates into a hepatocyte (Fig 1).

Second we have an instrument which measures cell growth continuously in cultured LPCs maintained in a 96-well format which allows for testing of many replicates under a variety of culture conditions such as the exposure to a variety of cytokines. We have published the application of this instrument called the Cellscreen to monitor growth of LPCs (Ref 1). Third we have identified several cytokines which are associated with liver inflammation induced by a choline deficient ethionine supplemented diet which are associated with the induction of LPCs in mice following liver damage (Ref 2 & 3). This project will focus on the role of TNF alpha, IL6 and IFN alpha in cultured BMOL TAT cells in terms of their respective effects on cell proliferation (using the Cellscreen instrument) and differentiation by quantifying the expression of beta-galactosidase. To confirm the effects of each cytokine on proliferation and/or differentiation, their ability to induce cyclin D (proliferation) and/or HNF4 alpha (differentiation) will be determined by qPCR and Western blotting.

Fig 1. BMOL TAT cell line in growth conditions (top left) in which cells do not express beta-galactosidase (top right). Following differentiation induced by high density culture (bottom left) clusters of cells express beta-galactosidase (bottom right).

References

2. Identifying genes that are responsible for the transformation of liver progenitor cells into hepatocellular carcinoma.

This project will exploit differences between a non-tumorigenic PIL4 cell line which does not grow in semi-solid medium in contrast to the tumorigenic PIL2 line which odes (see Fig 2). To identify genes that may be causal in the transformation of LPCs we have profiled the pattern of gene expression of PIL2 (transformed) and PIL4 (normal) cells. The list of genes which have been up-regulated (potential oncogenes) and down-regulated (potential tumour
suppressor genes) is extensive. This project will adopt two approaches to identify which are important genes. One is a bioinformatics approach to highlight genes which i) are associated with HCC and ii) are altered in LPCs as a result of deleting p53 (by comparison with wild type LPCs). The other approach is to follow up on recent findings which indicate that the lack of p53 in liver cells leads to up-regulation of two intracellular molecules IAP and Yap which cooperate to induce tumorigenesis (Ref 2). Our array data indicates that expression of these genes is increased in PIL2 cells. This needs to be confirmed by qPCR, which can also be used to investigate other genes highlighted by the first approach. Finally the differential expression of IAP and Yap needs to be confirmed at the protein level. Confirmation that these gene products are causative would be obtained by their ability to transform normal PIL4 cells by their over-expression.

References

LABORATORY FOR MOLECULAR GENETICS

Neuromuscular Disease

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

Project title: Developing gene upregulation therapy for genetic disorders

Project background:
The last 20 years has seen the dawning of the golden age of human genetics with the identification of the genes responsible for a large number of inherited or genetic disorders. The success of the Human Genome Project has greatly facilitated this process. Now that many of the disease genes have been identified the focus is moving to successfully developing therapies for these disorders. The Molecular Neurogenetics Laboratory within WAIMR has identified the genes responsible for genetic muscle diseases, notably that mutations in the skeletal muscle actin gene cause a significant percentage of all congenital myopathy cases in the world, severely affecting newborn children (Nowak et al. 1999). Since we identified mutations in skeletal muscle alpha actin we have believed that it should be possible to use cardiac actin, the actin we have in our hearts to treat the skeletal muscle actin diseases. Cardiac actin is also present in our skeletal muscle before we are born but is, for unknown reasons, switched off before we are born (Ilkovski et al. 2005). This year we published proof that cardiac actin could replace skeletal actin in mouse muscle (Nowak et al. 2009). This demonstrates that indeed cardiac actin is a route to therapy for the skeletal actin diseases. What we need to do now is find a way to upregulate cardiac actin in patient skeletal muscle. Upregulation therapy has had some success for the haemoglobinopathies in clinical practice (Vadolas et al. 2004). The skeletal actin diseases offer an excellent model to perfect gene upregulation therapy, which may then be applicable to many other genetic disorders.

Project aims:
The project aims are to participate in drug screens trying to find a pharmaceutical that causes upregulation of cardiac actin in skeletal muscle.
Techniques involved:
Muscle dissection, muscle culture, drug screen, immunohistochemistry, analysis of muscle culture results. Ultimately expansion from any positive hits and application in first our mouse models of these diseases, then in human patients. We will not get this far in one year, but will in time.

Key references

Medical Genetics

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

Genetics and cell biology of autism and Rett syndrome

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.

Neuropsychiatric Genetics

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

Project title: Microdeletions or duplications in schizophrenia: a focus on chromosome 1q, 15q and 22q
**Project description**

**Background**
Schizophrenia is a devastating mental disorder affecting approximately 1% of the population worldwide. Evidence for participation of genetic factors has been obtained by family-, twin-, and adoption studies. Our goal is the identification and characterization of genes conferring risk to schizophrenia. Knowledge of the genes and the gene defect will aid in elucidation of the pathophysiology of schizophrenia. There is now increasing evidence that microdeletions and duplications could play a major role in some cases of schizophrenia.

**Aims and experimental design**
The aim of the current project will be to establish a screening protocol for small deletions using quantitative real time PCR technology (qRT-PCR). Using this protocol, screening for possible deletions in three different chromosomal areas will be performed. These areas have been reported being important to schizophrenia.

**Significance**
Studying genetic variation is an important first step for the identification of susceptibility genes contributing to the development of schizophrenia. Identification of the molecular causes of schizophrenia would provide new targets for the development of novel pharmacological treatments.

**Genetics of Schizophrenia**

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**Discovering a novel gene for primary congenital glaucoma**
Mendelian disorders in a genetically isolated population (the Roma/Gypsies) is a major field of research that our team is involved in. We are currently working on primary congenital glaucoma (PCG), an autosomal recessive condition, which is an important cause of childhood blindness. PCG is rare worldwide, but has a higher incidence in the Gypsies, suggesting ancestral mutations that have spread by founder effect. The two PCG genes known to-date, *CYP1B1* and *LTBP2*, account for about 60% of the affected children of Gypsy ethnicity. This project will aim at the identification of the third gene involved in the pathogenesis of congenital glaucoma. A high-density genome-wide scan of single nucleotide polymorphisms (SNPs) will be performed in the coming months on a sample set of affected patients and families, where *CYP1B1* and *LTBP2* mutations have been excluded. The genotyping data will be analysed for region(s) of homozygosity shared by affected subjects from multiple apparently unrelated families, which harbours a mutation inherited from a distant common ancestor. Bioinformatics analysis to identify candidate genes in such region(s) will be followed by sequencing analysis, in search of the pathogenic mutation. Thanks to its specific biological history, the Gypsy population can assist in the identification of this disease gene, to the benefit of affected families from all ethnic backgrounds across the world.

**References:**

**Cancer Epidemiology**

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**Supervisor/s:**
**Professor Lin Fritschi**, Western Australian Institute for Medical Research  
Associate Professor Jane Heyworth, School of Population Health  
Professor Barry Iacopetta, School of Surgery
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 MOLECULAR ENDOCRINOLOGY
Cell Growth

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Location: CMR/WAIMR, C Block, QEII Medical Centre

Our research program involves 3 different research areas: the role of immunophilins in 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).

Background:
Immunophilins and steroid hormone action: For optimal signaling, 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 PP5, a protein phosphatase with weak FK506-binding affinity. These immunophilins are associated with preferred receptors in steroid receptor-Hsp90 complexes to mediate distinct influences on receptor function. CyP40 predominates over other immunophilins in estrogen receptor (ER)-Hsp90 complexes from uterus, suggesting that CyP40 has a specific role in ER function in this tissue. We have generated a CyP40 knockout mouse to define CyP40 control over estrogen signaling and steroid hormone action. In addition, collaborative groups have successfully generated FKBP51 and FKBP52 knockout mice.

Regulation of CaR activity through its binding partners: Some years ago we performed a yeast two hybrid screen of the CaR intracellular tail in order to identify accessory proteins that might influence CaR signaling and/or expression. A number of partner binding proteins were identified including one currently under study, the endoplasmic reticulum-associated protein, OS-9, which we propose has a profound influence on receptor maturation and expression.

Paget’s disease genetics: Paget’s disease of bone is characterized by focal lesions where an initial increase in bone resorption leads to excessive and disordered bone formation. 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 RANKL during osteoclastogenesis. Our laboratory has screened the C-terminal region of SQSTM1 for mutations associated with both sporadic and familial PDB and have 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.
Honours projects

1. The influence of CYP40 and cyclosporin A (CsA) on the expression of estrogen receptor (ER)-regulated genes in MCF-7 breast cancer cells. Using Northern analysis we have previously shown that CsA is able to enhance estrogen-stimulated expression of the estrogen receptor-regulated gene, cathepsin D, in the MCF-7 cell line. The aim of this project is to use real-time PCR (RT-PCR) to examine the upregulating effect of CsA on cathepsin D expression in wild type MCF-7 cells and in cells depleted in CYP40 by siRNA and to extend the study to additional ER-regulated genes, including PR and GREB1. Our laboratory has developed an MCF-7 CYP40 tet-off stable cell line which overexpresses CYP40 in the absence of doxycycline. This cell line will allow us to test the effect of overexpressed CYP40 on the expression of ER-regulated genes, with and without CsA. **Methods/techniques:** 1) cloning of cathepsin D, PR, GREB1 and GAPDH into appropriate bacterial plasmids, 2) maintenance, treatment and RNA extraction of tissue culture cell lines, 3) siRNA methodology, 4) optimisation and running of RT-PCR, and 5) statistical analysis of results.

2. Steroid receptor- and tissue-specific actions of Hsp90 immunophilin cochaperones. This study will determine the effects on estrogen receptor beta (ERβ), progesterone receptor (PRA, PRB) and glucocorticoid receptor (GR) mediated responses of immunophilin loss in mouse embryo fibroblasts (MEFs) derived from FKBP51, FKBP52 and CYP40 knockout mice or immunophilin siRNA knockdown in human cancer cell lines from different tissues: HeLa – cervix; ECC-1 – endometrium; ZR-75-1 – breast. **Methods/techniques:** 1) tissue culture, 2) siRNA methodology, 3) Western blotting, 4) luciferase reporter assays to determine receptor transcriptional activity, 5) confocal microscopy to determine changes to receptor localization within the cell.

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

**DIABETES RESEARCH**

Centre for Diabetes Research

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The Centre for Diabetes Research, within WAIMR, is one of Australia’s leading research groups studying the causes and cure of diabetes. Our activities are focussed on identifying genes which cause susceptibility to diabetes (type 1 and type 2) and its complications, and on developing a cure for type 1 diabetes. We examine genetics in both mouse models and in humans. We are also investigating ways of restoring the ability to produce insulin by developing stem cell treatments. In addition, we are establishing state-of-the-art “systems genetics” technologies to allow integration of multiple levels of data with underlying genetic information, allowing the definition of networks of interacting genes. Suitable projects within the study areas outlined below can be designed following discussion with the Centre’s Director, Professor Grant Morahan.
Projects:

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 in rates of both diabetes susceptibility and insulin resistance (a feature shared by people at risk for either T1D or T2D). This project will test candidate genes in this region to identify which one causes susceptibility.

c) Testing genes in human type 2 diabetes (T2D).
We have identified two genes causing T2D related traits in mouse models. We will now 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 other 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) Genetics of diabetic kidney disease.
We have developed a new mouse model for analysing genes that control the kidney’s response to increased blood glucose levels. Diabetic kidney disease (nephropathy) is a major life-threatening complication. This project involves the genetic analysis of approximately 600 mice derived from this new mouse model, for which the traits and phenotypes have been measured. Techniques used will include: PCR, genotyping, DNA sequencing, basic molecular biology, linkage analysis, bioinformatics, comparative genomics. This project should yield novel findings with clinical relevance because very few experiments have investigated genetic contributions to diabetic nephropathy

f) Regulation of pancreatic islet development and function by bone morphogenetic protein receptor IA
The best prospect for a cure of T1D and some T2D is to regenerate new β cells in situ. We discovered that certain bone morphogenetic proteins (BMPs), members of transforming growth factor superfamily, potently stimulate the proliferation of pancreatic cells and subsequent development of β cells. This suggests that BMPs play a key role in pancreas development and function. Recently, we have generated a mouse with a pancreas-specific knockout (cKO) of the BMP receptor type IA (Bmpr1a) gene. The homozygous cKO mice are viable, but develop some interesting phenotypes. We will examine how BMPRIA-mediated signalling regulates pancreas development, islet formation and pathogenic processes.

g) Are insulin-secreting β cells in the adult pancreas derived from self-duplication or from differentiation of progenitor/stem cells?
Studies have shown that insulin-independence can be achieved for up to seven years in some patients after pancreatic islet transplantation. Because the life span of β cells is about 30-60 days, new insulin-secreting β cells must come from either self-duplication or differentiation of islet progenitor/stem cells within the transplanted islets. This fundamental but highly challenging question has profound clinical significance. Along with transplantation biology, we will use strategies including gene-tracing.

h) Identification of molecules/drugs that stimulate maturation of pancreatic β cells.
T1D results from the destruction of pancreatic islet β cells by autoreactive T lymphocytes. However, exogenous insulin therapy is not a cure and does not prevent the development of complications. Transplantation of islets offers potential treatment, but has been restricted by poor availability of islets. Currently, insulin-positive cells can be generated from a variety of cell sources, but they are not completely glucose responsive. Foetal β cells are immature in terms of response to glucose stimulus, suggesting that they could be used to identify mechanisms of β-cell maturation. Foetal β cells from mice
will be purified from neonatal pancreas after enzymatic dissociation by a fluorescence activated cell sorter. The effects of various molecules/drugs on their function will be tested using technologies such as microarray analysis.

i) 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 suit someone wishing to undertake a career in bioinformatics, and will combine molecular biology techniques with extended microarray analyses.

j) 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.

CLINICAL RESEARCH IN EMERGENCY MEDICINE (CCREM)

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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 or immunology are invited to contact one of the researchers to discuss potential projects, according to the main fields of interest as outlined below.

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.

Neutralisation of Dugite and Gwardar (Western Brown Snake) venom toxins.
Preliminary evidence suggests that the brown snake antivenom used clinically in Australia may not fully neutralise the procoagulant toxins in the venoms of the two brown snake species found in Western Australia (Gwardar, Dugite). This study will be in three parts. First, the procoagulant effects of the three venoms (common brown, Dugite and Gwardar) will be characterised using human plasma. Secondly the ability of different antivenoms (CSL brown snake antivenom and polyclonal antivenoms raised against each species) to prevent these in vitro venom effects (simple clotting/turbidity, thrombinoscope, thromboelastograph) and to bind the procoagulant toxins (western blot) will be assessed. Finally, samples from human cases pre and post antivenom treatment will be examined by specific ELISA for evidence of unbound procoagulant toxin post treatment.

Emergency Department Anaphylaxis (EDA) Project: Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. The most common causes of anaphylaxis are food (nuts,
legumes, seafood), insect venom (bee/wasp/ant stings) and medication (antibiotics). The principal aim of this project is to improve our understanding of the pathophysiology of human anaphylaxis by examining mediators and their relationships to reaction sub-types and outcomes. Patients presenting to ED with symptoms of anaphylaxis have serum and plasma collected at three timepoints: \( T_0 \) – arrival at ED, \( T_1 \) – one hour after arrival and \( T_2 \) – pre-discharge from hospital (between 2-12 hours after arrival). We have identified IL-10 and IL-6 as potential mediators of anaphylaxis. The student choosing this project will develop a method for culturing mast cells from human peripheral blood mononuclear cells and use these cells to examine the effects of IL-10 and IL-6 on mast cell mediator release and IgE receptor expression.

**Venom Anaphylaxis and Immunotherapy:** Life-threatening allergy to stings from native ants constitutes an important clinical problem in Australia. Our group has made significant progress by proving the efficacy of venom immunotherapy (VIT) for allergy to the most common of these ants, the jack jumper ant (JJA). VIT desensitises individuals to specific venoms through the subcutaneous injection of gradually increasing doses of venom extract over time until a target maintenance dose is achieved. We are now undertaking a laboratory-based immunology study linked to a large clinical trial of JJA VIT (a prospective multi-centre randomised 2x2 comparison of ultra-rush (rapid increase in venom dose over 1 week) versus semi-rush (gradual increase in venom dose over 3 months) initiation and 50µg versus 100µg target maintenance dose). Serum and heparin-treated blood for PBMC isolation and cryopreservation are collected prior to receiving a first dose of VIT on Day 1 and at various time points up to 5 years after commencing VIT.

Linked to this project we have also just completed a national study of venom allergy and have a large bank of sera from patients allergic to a range of other native Australian ant species. Students interested in our venom allergy research have two options to consider:

(i) Investigating changes in venom-specific immunoglobulins (IgE, IgG1, IgG4), other serum factors and leukocyte cytokine production (IL-10, IL-4, IFN\( \gamma \)) over the course of JJA VIT and correlate results with clinical outcome and adverse events during therapy.

(ii) Defining the allergens responsible for anaphylaxis to native Australian ants. This would have a significant proteomics focus in collaboration with Proteomics International.

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

**Acute cardiac failure and sepsis**
Research projects examining a variety of problems around acute diastolic heart failure in the elderly patient are available as BMedSci projects. These include

- Identifying clinical and laboratory (vasoactive, neurohumoral and inflammatory) markers that are most important in the genesis of decompensated diastolic heart failure
- Development of clinical decision rules, using a combination of clinical, laboratory and echocardiograph data, to aid 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, in particular exploring the hypothesis that acute diastolic dysfunction can be identified and is important in the progression of shock in elderly sepsis

**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.

**Facilitated discharge of the frail elderly**
Several BMedSci projects are available for students with an interest in improving the provision of care for the chronically ill frail elderly patient that presents to ED. These include examining the efficacy of
multidisciplinary intervention pre discharge, and alternate care plans or ED avoidance strategies for people living in aged care facilities.

CENTRE FOR IRON METABOLISM AND LIVER DISEASE

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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 whether 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 manifold. 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).

The role of iron and Hfe in the development of colorectal cancer. We have shown that iron promotes tumourigenesis in colorectal carcinogenesis when inflammation is present. This project will determine how iron deprivation (use of iron chelators and dietary iron depletion) affects tumourigenesis using mouse models of HH and colorectal cancer. Alterations in cellular iron metabolism and carcinogenesis 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.
How individuals age will continue to be greatly impacted by the health research being conducted today. While living well and exercising is important, many people are also counting on research to find new and better ways to treat, diagnose, prevent, and cure a number of diseases and disorders that present themselves as a person ages. This is main focus of research at the WA Centre for Health and Ageing.

Our Centre has a multidisciplinary approach to disease prevention, delay and cure. We are currently offering Honours projects in the following areas;

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

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

- **QUALITY OF LIFE IN PEOPLE WITH DEMENTIA**
  WACHA is participating in several ground breaking projects to understand and enhance the quality life of people with dementia in community and residential settings. Two ongoing projects are underway to investigate the association of quality of life with cognition, and to examine the effect of an educational intervention to improve the quality of life of people with dementia living in residential care. Studentships and Honors projects, are envisaged collecting, managing and organising portions of data from these ongoing studies. Supervision by both medical specialists and neuropsychology staff is possible, making these programs suitable for students form a range of disciplines.

- **NEUROIMAGING AND STRUCTURAL BRAIN DISEASE**
  WACHA has a strong track record in use of neuroimaging to understand the pathogenesis of cognitive decline in various settings, such as people with heart failure. WACHA also has an interest in CT perfusion imaging and is establishing collaborations to develop mathematical models to facilitate automated processing of CT perfusion maps. Several projects are being offered in processing and analysing imaging data from these various cohorts.

- **LICIT DRUGS FOR OLDER PEOPLE**
  WACHA has successfully completed work to understand the health effects of licit drug use on older people. Current work builds on this foundation to examine the effects of polypharmacy in large cohorts and initiate intervention trials to examine the effect of reducing drug burden in older people. Honours projects are being offered in each of these areas.
PREVENTING FRAILITY

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.

CENTRE FOR ASTHMA, ALLERGY AND RESPIRATORY RESEARCH (CAARR)

Director: Professor Philip Thompson 9346 3198/9346 3822
Email: pjthomps@liwa.uwa.edu.au

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 $2.7million.

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.

There are currently seven research Units within CAARR. They are;

Inflammation & Immunology: Head - Professor Kanti Bhoola
9346 3703/9346 3198 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 B1 and B2 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 in vivo.

1c. Role of the ECM and transforming growth factor beta (TGF-β) in mesothelioma growth. Studies using the proline analogue thiaprolone 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.

Molecular Genetics:  Head – Dr Carolyn Williams
9346 7948/9346 3198  Email: carolynw@liwa.uwa.edu.au
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 remodeling 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.

Epidemiology:  Head - Prof Philip Weinstein
6488 8108/ 9346 3198  Email: philip.weinstein@uwa.edu.au

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
Enquiries 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
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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 $\beta_1$-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 Rakocy 9381 0726 Email: rakoczy@cyllene.uwa.edu.au

Dr May Lai 9381 0729 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 9381 0808 Email: mariapia@cyllene.uwa.edu.au

The Experimental Immunology group studies the immune system and concentrates on defining the interactions that occur between viral pathogens and components of the host immune system with the aim of determining how these interactions contribute to anti-viral immunity. It is expected that the knowledge generated by such studies will be of relevance not only to controlling infection, but also to 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 9381 0754 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.

Telemedicine / e-Health
Head of Department
Prof Yogesan Kanagasingam 9381 0817 Email: yogesan@cyllene.uwa.edu.au

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.

Dr Fred Reinholz 9381 0756  Email: reinholz@cyllene.uwa.edu.au
Biomedical Photonics conducts research into the use of **Light and Lasers for Diagnostic and Therapeutic Procedures in Ophthalmology.**

The main areas of research focus around a unique Scanning Laser Ophthalmoscope (SLO) which is capable of multi-spectral and stereo imaging. Investigative applications of this SLO include imaging of glaucomatous optical nerve heads in both animals and humans and screening for diabetic retinopathy. Further developments of the system are directed towards miniaturization, increased sensitivity, automatic control of imaging parameters and computerized image analysis.

Experiments to study the feasibility and characteristics of high resolution ocular imaging in five dimensions ($x,y,z$, time, wavelength) are in progress. They are based on modern microscopic techniques such as two-photon fluorescence, short coherence tomography, active adaptive optics, and time resolved fluorescence decay.

Other major research topics include the generation of narrow band, high energetic light (violet and ultraviolet) and of short (nanoseconds) and ultra-short (pico- and femtoseconds) emission pulses using solid state lasers. Utilizing appropriate delivery systems the laser light is used for corneal shaping or selective deactivation of retinal enzymes. Attenuated mode locked and tuneable lasers are also used as light sources in SLO imaging.

**Clinical Ophthalmology & Research**

Dr Ian McAllister 9381 0870  Email: ianmca@cyllene.uwa.edu.au

Dr Graham Barrett 9381 0872  Email: barrett@cyllene.uwa.edu.au

**Areas of Clinical Interest**
- Cornea and corneal surgery;
- Refractive surgery; and
- Cataract Surgery.

**Areas of Research Interest**
- Development of Intraocular Lenses & Materials;
- Development of formulae for lens calculation;
- Small incision surgery;

Dr Geoffrey Crawford 9381 0871  Email: gic@cyllene.uwa.edu.au

**Areas of Clinical Interest**
- Cornea and corneal surgery;
- Refractive surgery; and
- Cataract Surgery.

**Areas of Research Interest**
- Development of an artificial Cornea, AlphaCor;
- Uses for the Femtosecond laser in corneal surgery;
- Development of an integrated orbital implant, AlphaSphere;
- Lamellar surgery for corneal disease; and
• Corneal Cross linking for keratoconus

Dr W Morgan 9381 0873 Email: whmorgan@cyllene.uwa.edu.au
Glaucome 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 database 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

Centre for Neuromuscular and Neurological Disorders (CNND)

Primary supervisor: 
Adjunct A/Professor Bruno Meloni  
9346 3535  email: meloni@cyllene.uwa.edu
Other supervisor:  Professor Neville Knuckey  
9346 7206  email: Neville.Knuckey@health.wa.gov.au
Location: Centre for Neuromuscular and Neurological Disorders (CNND)

Project title:  
Establishment of RNA interference (RNAi) to down-regulate proteins in neuronal cultures in order to study protein function

Project Background: Our research is focussed on identifying and characterising neuroprotective and neurodamaging proteins in order to develop therapeutic agents for the treatment of acute (stroke, traumatic brain injury) and chronic neurodamaging (Alzheimer’s, Parkinson’s disease) disorders.

Project aims: This project aims to establish the RNAi technique to down-regulate specific proteins in neuronal cultures. Once the technique is established, several proteins we have previously identified to have neuroprotective or neurodamaging activity will be assessed when down-regulated in our in vitro stroke-like models.

Techniques involved: Cell culture, RNA isolation, PCR, Western blotting
Key references: