BSc Honours 2011

CHEMISTRY PROJECTS

Artwork by Dr. J. Stok, BSc Hons (Chemistry) 1996

School of Chemistry & Molecular Biosciences
Faculty of Science

THE UNIVERSITY
OF QUEENSLAND
AUSTRALIA
CHEMISTRY HONOURS PROGRAM
2011

The School of Chemistry & Molecular Biosciences offers the Bachelor of Science with Honours, BSc(Hons). It is undertaken full-time. The Program can be commenced in either first or second semester.

The Importance of an Honours year

The BSc(Hons) Program provides training well beyond that provided by the basic BSc degree, particularly in the area of research methods and in problem solving. The extra training equips students for a wider range of positions in industry and in government laboratories than is available from the BSc degree. The positions generally have a greater involvement in research and development; responsibility levels are higher and there are better financial rewards.

The Honours degree may lead directly into the higher research degrees, MPhil and PhD. Class I performance is required for entry to the PhD. Often a class IIA grading will allow admission also. The advantages of higher degree studies are an extension of those for Honours; enhanced academic maturity and superior skills can lead to positions of even greater responsibility, usually with predominant involvement in research.

Although parallel BSc/BEd degrees, or a three-year BSc, followed by a BEd, give the necessary professional qualification for students planning to be secondary school teachers, the Honours degree in Science together with the BEd, provides a better preparation, by virtue of a deeper and broader appreciation of chemistry and advanced practical skills. Particularly for those aiming to become specialist teachers of chemistry, this can lead to greater career satisfaction and to better opportunities for promotion. The extra year also enables students to consider whether their teaching vocation may lie in the tertiary education sector, where teaching can be combined with research activities; in this case, further training in the form of PhD study, followed by postdoctoral experience, generally overseas, is then undertaken.

Students who have gained a place in the Graduate Medical Program are permitted to defer entry into that program for one year to pursue an Honours degree.

The Chemistry BSc(Hons) Program

The BSc(Hons) program in Chemistry may lead to an Honours degree in one of these Fields: Chemistry, Biological Chemistry, Nanotechnology, Drug Design & Development, Computational Science. You need to indicate the desired Field when applying for Honours. If you do not indicate a desire for another Field, the Field will be “Chemistry”, by default. The Fields other than Chemistry may also be accessed through programs offered by other Schools. The Honours program can be entered from the BSc degree at this university. For students in the Field of Chemistry, normally 8 units of third level chemistry should have been completed, at a Grade Point Average of 4.5 or above. In some cases for the Chemistry Field, and for the other Fields mentioned other relevant disciplines may be included in the #8. For the Field of Biological Chemistry, #8 from a mix of Chemistry, Biochemistry, and Microbiology courses would be appropriate. The School of Chemistry and Molecular Biosciences has some discretion in the application of the entry rules, and may, on the recommendation of the Honours Director, allow entry from students who fall slightly below this cut-off. Students with a good academic record may also be accepted with a BSc qualification from another university. An original or certified copy of your final academic transcript must be submitted with your application form. International students must submit an application form through the International Office. Visit their web site on http://www.uq.edu.au/international/ or contact any IDP Education Australia office or Australian Diplomatic Mission in your capital city.

The 16 units of credit associated with the Honours program is a mixture of research and course work. It comprises four components:
Honours Research Project #10
This is a year-long component and culminates in the submission of a research report. The research project is carried out under the supervision of a member (or members) of the academic staff. The research topic is assigned by the supervisor after consultation with the student.

Honours Research Proposal #2
The research proposal outlines the work that the student will undertake and why they are doing it. The research proposal will consist of a literature review and will state the aims and significance of the proposed research. The research proposal must be completed in the semester that they begin work as it is intended to provide an early focus for the student on their project work. It may also form the basis of the introductory chapter for the student’s research report.

Honours Seminars #2
The research proposal is also presented as an introductory seminar to be held at the end of the first semester of the program.
A research symposium will be held after submission of the final research report in late October. Each student will give a research seminar outlining their achievements and they will be awarded a consensus mark from academic staff members present.
Furthermore, attendance at the weekly Chemistry & Biological Chemistry Seminar series is compulsory. Although occasional absences may be unavoidable, they must be accompanied by an apology sent to the Seminar Convenor and a valid reason for your inability to attend. Chronic absences will result in a failing mark for this course. You are expected to maintain a seminar notebook which must be available for scrutiny.

Coursework #2
Each student shall choose one of the following modules. More details (course profiles, timetabling etc.) will follow later.

Module 1       Organic Chemistry
Module 2       Inorganic Chemistry
Module 3       Physical Chemistry

The selection of course work by Honours students should be discussed with the student's supervisor. The final choice is subject to approval by the Honours Director.

Administration of the Honours Program
The Honours program in 2010 is coordinated by Dr Ross McGeary (r.mcgeary@uq.edu.au) and enquiries regarding the program may be directed to him in the first instance. Administrative assistance is provided by Jennifer Falknau, Room 68-316 (j.falknau@uq.edu.au), Elizabeth Do, Room 302 (e.do@uq.edu.au) or Academic Coursework & eLearning Manager, Athol Reid, Room 68-313 (areid@uq.edu.au).

Research Projects
Students are invited to discuss the projects listed in this booklet with the staff members concerned and to submit, to the Office of the School of Chemistry & Molecular Biosciences (Third Floor, Chemistry Building) on the form inserted into this booklet, their first three preferences for supervisor(s). Failure to abide by this ruling (e.g. nominating only a first preference of supervisor) will not constitute a valid application.
The Honours Director will make recommendations on assignment of supervisors, taking into account:

- the student’s preferences
- the academic background of the student
- the total number of students supervised by each staff member
- resource implications
- planned extended absences of the staff member from the School
- other factors that may affect the staff member’s ability to supervise effectively a particular student’s research project.

For students starting in February, it is highly recommended to express your preferences before Christmas. If you do this, you will be notified of your supervisor by mid-January. Students who lodge their applications later may have less chance of obtaining their first preference. Mid-year starting students should similarly lodge their application during Semester 1 in anticipation of a successful mid-year completion of their BSc.

**Enrolment Procedures, Fees and Charges**

Apply to enrol in the honours program by completing the form enclosed in this book and submitting to Jennifer Falknau in Room 316 of the Chemistry Building. Forms can also be downloaded from the School website [www.scmb.uq.edu.au](http://www.scmb.uq.edu.au).

Successful applicants will be sent an offer letter from the School. On acceptance their enrolment in the program will be activated. Additionally, honours students must enrol themselves via mySI-net in the courses for each semester. Any queries related to enrolment may be directed to Jennifer Falknau (j.falknau@uq.edu.au).

Full time domestic Honours students study as undergraduate Commonwealth supported students and are required to pay a Student Contribution Amount in both semesters of their honours program. It is the student’s responsibility to ensure they educate themselves on their individual requirement with regard to their Student Contribution Amount. As a first step you may consult [http://www.uq.edu.au/study/](http://www.uq.edu.au/study/)

Further details can be obtained from the Student Centre, level 1 JD Story building. Please note that administration charges apply for late enrolment.

**Financial Support**

Up to six hours per week of teaching duties, in the form of demonstrating to students in the First Year laboratory may be available. All Honours students (depending on past experience) are eligible to seek employment as part-time tutors for laboratory classes within the School of Chemistry & Molecular Biosciences.

Please indicate your interest in undertake tutoring on the Honours Application Form.

**Commencement Date**

The commencing dates for Honours students will be Monday 7 February or Monday 25 July 2011.

A number of introductory programs for Honours students are run early in the semester. Attendance is mandatory at all of these sessions. These comprise:

- School Safety Induction, where School procedures are explained, particularly safety and waste disposal methods.
- Tutor Training, where an introduction to laboratory teaching methods is given for students participating in 1st year laboratory demonstrating.
- A library course, where use of electronic databases and referencing software (e.g. Endnote) are described.
SUMMARY FOR BSc(Honours)

- If you wish to commence a BSc(Honours) in 2011 you should address any general enquiries to either:
  - Chemistry Honours Director: Dr Ross McGeary (r.mcgeary@uq.edu.au), phone: 3365-3955; or administrative contacts: Jennifer Falknau (j.falknau@uq.edu.au), phone 3365-3509, Room 68-316 (Chemistry Building) or Athol Reid (areid@uq.edu.au), phone 3365-7976, Room 68-313.

- If you already have a firm idea about the supervisor you are likely to nominate as your first preference, consult widely with members of the academic staff to find out more about the projects being offered and the style of work involved. Remember, your first preference may not ultimately be your allocated supervisor, so it is important to be aware of alternative projects. Be aware that some details of projects being offered may change between the time when this booklet was prepared (July 2010) and your commencement time.

- For students commencing in February, lodge an application form, including your list of project preferences at Room 316, (third floor of Chemistry Building) before Christmas, if at all possible. Indicate on the form your preferred Honours Field if other than “Chemistry” (otherwise your field will be “Chemistry”, by default). You do not have to wait for your examination results to be released before submitting the form. Preferences should indicate three different supervisors or combinations of supervisors in the case of joint projects. For students commencing in July, indicate your likely mid-year enrolment to the Honours Director during Semester 1, 2011. Lodge your application before or during your mid-year examinations.

- Please provide a contact phone number, address and email address.

Dr Ross McGeary (Chemistry Honours Director)
August 2010
PROFESSOR PAUL BERNHARDT

Phone: 3365-4266
Email: p.bernhardt@uq.edu.au

Our research efforts are concerned with coordination chemistry of relevance to biology, analytical science and technology. The current research interests of the group are summarised below and projects in all of these areas are available. Students interested in any of these areas of research should contact Prof. Bernhardt for a more detailed project description.

**Iron as a Therapeutic Target in Cancer Treatment and Iron Overload Disorders (synthetic and biological coordination chemistry)**

**Cancer:** Iron plays a crucial role in cancer cellular proliferation as Fe-containing proteins are involved in key reactions concerning oxygen transport, energy metabolism and respiration. These characteristics render Fe a potential therapeutic target for preventing the growth of tumour cells. Recently we have investigated the coordination chemistry of a series of heterocyclic chelators, some of which exhibit extremely high activity against cancer cells (see below).1-3

![Chemical structures](image)

The mechanism of action of these chelators is not fully understood, although chelation of intracellular Fe appears to be a common theme. This project will investigate the coordination chemistry of some of these chelators with Fe and other biologically important metal ions in an effort to understand the complex mechanisms by which they exert their biological activity. Compounds synthesised during the course of this project will be screened for anti-cancer activity at the Pathology Department, University of Sydney.

**Fe overload:** Iron overload is a potentially fatal condition which requires continual chelation therapy for patients to survive. The approved drug DFO must be administered by subcutaneous infusion (~16h/day, 5-7 days/week). In recent years we have been studying the biological coordination chemistry of a number of hydrazone (HPCIH) and hydrazine ligands (H2IPH) and their complexes (see below). The structure of the chelators is related to their efficacy in lowering cellular Fe level. The reason for this remains unclear and the coordination chemistry of these chelators with iron and other essential metals is needed in order to better understand the mode of action of these promising potential drugs.


Fluorescent Chelators for Cellular Imaging of Ferric and Ferrous Ions (coordination chemistry and spectroscopy)

Cellular imaging of metal ions is a rapidly growing field and careful design of ligands has enabled the mapping of cellular concentrations of many different metal ions, both endogenous and exogenous. More conventionally it has been used in a passive way where a fluorescent chelator binds to metal ions in all accessible regions of the cell.

In our own work we have a longstanding interest in Fe as a novel biological target for the treatment of diseases such as cancer and Fe overload. Fe chelators have emerged as a novel approach to halting cancer cell proliferation but little is known about the biological targets of these chelators or the cellular regions where the chelators concentrate and bind to Fe.

This project will aim to graft known fluorophores onto chelators derived from Fe chelators with known biological activity to spotlight Fe within the cell using fluorescence techniques. The ‘R’ groups shown in the scheme above shown the possible position where the fluorophore will be attached whilst not disturbing the Fe binding capability of the ligand.

Furthermore based on our earlier work in unearthing compounds that can select Fe in either its divalent or trivalent oxidation state, we may speciate Fe within the cell and reveal any differences in location of these compounds in complex with Fe. The ability to speciate different oxidation states of Fe within a cell is novel; all known fluorescent probes for Fe are either unselective or only bind to Fe. These experiments will provide, for the first time, a link between biological activity and cellular localization that until now has not been possible. The project will involve a mix of synthetic chemistry and spectroscopy.

Enzyme Electrochemistry (research area: biosensors/bioelectrochemistry)

Enzyme electrode biosensors are devices that comprise a redox active enzyme integrated with electronic circuitry to give real-time quantitative analysis of chemical compounds in biological fluids or the environment. The current that is generated by the oxidation or reduction of the substrate provides a quantitative measure of the substrate concentration (see below).

The great advantage of enzyme based biosensors is that they exploit the intrinsic selectivity of the protein for a particular substrate, and thus do not suffer from interference effects from other compounds present in the sample and are portable, which enables rapid analysis in the field, clinic or in the home. The most successful example is the glucose biosensor. This sensor, which utilises the enzyme glucose oxidase, is sold in pharmacies worldwide and used by diabetics to monitor blood glucose levels.

This project will involve the electrochemical investigation of sulfite oxidising metalloenzymes currently available within in our group. Various methods of electrode preparation will be investigated with the aim of enabling quantitative analysis of sulfite, an important antioxidant and antimicrobial agent (preservative 220) used in beverages such as beer and wine. This may provide a useful alternative approach to current wet chemical methods of sulfite analysis currently used in beer and wine production.

Relevant Recent Publications

DR JOANNE BLANCHFIELD

Phone: 3365-3622
Email: j.blanchfield@uq.edu.au

Dr Blanchfield is not offering projects in 2011.
The Centre for Organic Photonics and Electronics is located on floor 9 of the Chemistry Building. The Centre contains state-of-the-art synthesis laboratories, a Class 1000 clean room and a suite of instrument rooms for the characterization of materials and opto-electronic devices. The mission of the Centre is to develop ‘organic materials’ that can be used in high performance cutting edge technologies including solar cells, flat panel displays, plastic electronics, explosives sensors, and fuel cells. Honours students working in these areas will learn the key skills of synthetic chemistry and characterization of small and macromolecules, the latter including dendrimers (branched macromolecules) and polymers. In addition, the Honours student will have the opportunity to learn how to fabricate devices in a clean room environment and work with physics colleagues in interpreting device performance to lead the design of the next generation of materials. For a full picture of COPE please look at our website: http://www.physics.uq.edu.au/cope/. We are currently offering projects in the following areas:

**Project 1: Solar Cells**

Man-made global warming is a scientific fact creating arguably our biggest challenge now and in the coming decades. A key component of slowing and ultimately halting climate change is the provision of clean (non-fossil fuel) energy. The conversion of solar energy directly into electricity [photovoltaics (PV)] will play a major role in the future energy mix. On average 1 kJ of solar energy falls on each square metre of the Earth’s surface per second of every daylight hour. Capturing a proportion of this massive and reliable resource would make a dramatic effect on the world’s energy use and supply. However, to realize this goal it will be necessary to produce large area, efficient solar cells cheaply. Solution processing techniques are ideal for manufacturing large area PV devices (see Siemens plastic solar cell above) and this gives critical momentum to the development of solar cells based on solution processible ‘organic’ semiconducting materials. This proposal aims to developing new materials for solution processed, efficient, stable, large area solar cells. The materials will be based on macromolecular materials (e.g., 1) with the main objectives being to make materials that absorb the solar spectrum well and are stable to long-term light exposure.
Project 2: Flat panel displays

The two main flat panel display technologies are based on liquid crystal (LC) and plasma displays. However, there is an exciting new flat panel display technology based on organic light-emitting diodes (OLEDs) (e.g., the 11” Sony television in the figure). OLED flat panel displays have the potential advantages of cheap manufacturing, better power consumption, better colours, and ultimately being flexible. Imagine a TV screen that could roll up into your mobile developing solution processible phosphorescent dendrimers (e.g. 2) to form highly efficient OLEDs, amongst the most efficient in the world. However, there are challenges remaining and these form the basis of the projects in this area. Projects will involve developing materials to get all the colours for a display, methodologies for processing to form pixels, and the development of charge transport materials.

Project 3: Explosives sensors

Recent global events have raised concerns over national security and counter-terrorism measures in civilian areas. In particular, the deployment of hidden explosives over large populated areas requires creative and feasible preventative measures. Currently the most sensitive detectors for explosives are canines. A technology based on a chemical sensor that gives accurate, real-time, and remote sensing would be a powerful tool in preventing these modern-day disasters. For example, imagine the importance of strategically placed sensors inside train stations, at airports, or at sporting venues that could detect explosives, while the monitoring is done remotely. Most current methods for detecting explosives are slow and the equipment cumbersome. We are developing an explosives sensor based on semiconducting organic materials that will be portable, selective and fast. These materials rely on electron-deficient analytes (explosives) to quench their luminescence, giving a reduction of the normal signal upon binding. For example, dendrimer 3 can detect 1,4-dinitrobenzene, which is found in TNT, and we will be synthesizing and testing new materials to improve the performance.

Project 4: Plastic electronics

Transistors drive a broad range of electronic devices from LCD displays in our mobile phones and TVs to computers. Transistors are traditionally manufactured from silicon, but it is possible to build organic (plastic) transistors. Organic field effect transistors (OFETs) consist of source, drain, and gate electrodes [S, D, and G in figure (a)], and insulating (I) and active layers. When the gate electrode is switched on, charge accumulates at the interface of the active material and the insulating layer, allowing current to flow between the source and drain. The two key requirements for the active layer are that it must have a high on-off ratio (low leakage current) and high charge mobility. Silicon based field-effect transistors (FETs) have these characteristics but they are not processed under ambient conditions and they are not flexible, placing a limit on their applications. OFETs can be prepared on flexible substrates and if the organic material is solution processible, there is the exciting prospect of simple, low temperature and low cost methods for forming transistors over large areas. We will be designing and synthesizing new dendritic materials [(b) in the figure] that will enable the optimization of the processing and charge transporting properties.
Organic or plastic optoelectronics is one of the fastest growing fields in chemistry and physics. The Centre for Organic Photonics & Electronics (COPE) based in the chemistry building brings together chemists and physicists to develop exciting new technologies such as organic light-emitting diodes for displays and lighting, and plastic solar cells. COPE has extensive programs in these areas (see Paul Burn's and Shih-Chun (Lawrence) Lo’s pages in this prospectus) in compound development and device fabrication and testing. An additional and important question that we ask is whether we can model the properties of the materials and then use those models to predict the properties of new compounds before they are made – this would be an extraordinary and major breakthrough in the field of plastic optoelectronics. We therefore offer the two following cutting edge projects.

Relativistic effects in organic solar cells and organic light emitting diodes

Purely organic molecules usually absorb or emit (fluorescence) light only via their singlet states because transitions to the triplet state are ‘forbidden’. However, in organometallic complexes with heavy metals such as iridium or platinum strong relativistic effects (such as spin-orbit coupling) mean that transitions to and from triplet states are allowed. However, at this stage it is not possible to predict or even explain why some complexes perform very well, e.g., are highly luminescent while others with only slight structural changes are not. We have been working on a method that will allow this to be done for the first time. The projects in this area will compare the solutions of the Schrodinger and Dirac equations to study the role of relativistic quantum-mechanical effects in the materials to explain the properties of known material. We will then use this new understanding to design and predict the properties of new materials, which will then be prepared and tested leading to a process that may allow the faster development of more efficient organic solar cells and light emitting diodes.

Charge transport in organic solar cells

There are two key elements that control the efficiency of a solar cell. How many electrons can we generate for a given illumination level (sunlight) and how much useful work can we get out of those electrons. In this project we study the transport of electrons through organic solar cells using a mixture of mathematical and computational modelling. We will seek to answer questions such as do the electrons hop or tunnel through the active layers, what is the energy costs associated with such transport, and are there molecular designs that can optimise the processes. This will allow us understand the limitations of the current generation of solar cells and design improved devices.
My research group focuses on the detection, isolation, characterisation, identification and evaluation of novel bioactive metabolites from Australian marine and terrestrial biodiversity. These metabolites span all known biosynthetic structure classes including many molecules new to science, and their study requires the use of sophisticated chromatographic, spectroscopic and chemical technologies. Natural products uncovered during our investigations represent valuable new leads in the search for drugs with application in the fields of human and animal health and crop protection, have potential as molecular probes to better interrogate and understand living systems, and could find application as biological control agents.

Potential Chemistry Honours Projects for 2011 include:

**Project 1: Synthesis of Aplysinopsins and Tubastrindoles**

Methylaplysinopsin (1) was first described in 1981 as a serotonergic agent and potential antidepressant from a Great Barrier Reef sponge *Aplysinopsis reticulata*. Since that time many metabolites of the alysinopsin structure class have been reported from a variety of marine organisms, including the dimeric tubastrindoles (i.e. tubastrindole B (2)). The tubastrindoles are believed to be biosynthetically derived from the alysinopsins by the action of a Diels-Alderase. Our recent investigations (unpublished) have revealed selected tubastrindoles as potent and selective modulators of important ion channels – with possible application in the treatment of pain and epilepsy. To advance these investigations requires assembly of a library of synthetic alysinopsins, tubastrindoles and related analogues. This project will explore the application of Diels-Alder chemistry to assemble such a library. All synthetic compounds will be subject to chromatographic and spectroscopic analysis, and will be screened in specialist ion channel assays.

**Project 2: Synthesis of Cytotoxic Phosphodiesters**

During recent investigations we discovered (unpublished) a series of novel phosphodiester polyketides, franklinolides A-C, from an Australian marine sponge. While the phosphodiesters functionality forms the backbone of DNA and RNA, and can be found in phospholipids that make up cell walls, this functionality is rare among secondary metabolites. The discovery of the franklinolides was all the more challenging given their propensity for hydrolysis of the phosphodiester. Indeed, closely related polyketides lacking the phosphodiester, the bitungolides, have been reported from an Indonesian
sponge. Of particular note, when compared to the bitungolides, the franklinolides displayed a 30-50 fold increased cytotoxicity against an array of human cancer cell lines. Chemical modification (glycosidation etc…) of anticancer agents is common practice, to enhance bioavailability and improve therapeutic properties. To the best of our knowledge, such modifications have not extended to glyceric acid phosphodiester. This project seeks to take inspiration from the franklinolides, to develop synthetic strategies for the modification of cytotoxic agents (i.e. taxol, podophyllotxin) as glyceric acid phosphodiester. All synthetic compounds will be subjected to detailed chromatographic and spectroscopic analysis, and will be assessed for cytotoxicity (potency and selectivity) against mammalian cancer cell lines.

Project 3: Synthesis of Trachycladazine A

During our investigations into bioactive metabolites from Australian marine sponges we discovered (unpublished) a new cytotoxic diketopiperazine, trachycladazine A (1), that is a structure analogue of the anticancer agent NPI-2358 (2). The diketopiperazine 2 is a promising new vascular/tubulin modifying agent developed from a marine fungal isolate that is undergoing commercial development as an anticancer therapeutic. To better explore the anticancer potential of 1 we require a convenient, short and efficient synthesis capable of delivering the natural product and an array of analogues. This project will investigate a selection of synthetic approaches to diketopiperazines. All synthetic compounds will be subjected to detailed chromatographic and spectroscopic analysis, and will be assessed to assess cytotoxicity (potency and selectivity) against mammalian cancer cell lines.
My group is concerned with biological and synthetic chemistry and in particular with the application of chemical principles to the understanding of biological processes. While some projects involve purely synthetic organic chemistry, most are a blend of the range of disciplines that make up modern bio-organic chemistry: synthesis and structure determination, molecular biology, protein purification. A wide range of techniques are employed in these projects, ranging from the more biochemical (e.g. PCR, gel electrophoresis etc) to the more traditionally chemical (e.g. NMR, HPLC, GC, GC/MS etc). The following project areas illustrate the types of research carried out in my laboratory but the exact nature of the work e.g. more chemical or more biological will be determined by the interests of the student.

**Project 1: Cytochromes P450**

The cytochrome P450s are a superfamily of oxidative haemoproteins that catalyse an amazing variety of oxidative transformations, ranging from simple alkene epoxidation all the way through to oxidative carbon carbon bond cleavage. P450s are of interest as they (i) are often unique enzymes in a biosynthetic pathway and as such represent new targets for chemotherapeutic agents or (ii) are extremely efficient catalysts that offer the potential of developing tailored oxidative catalysts for synthetic transformations. We are interested in understanding the mechanism of action of a number of P450s.

CYP61 is a unique P450 involved in steroid biosynthesis in fungi and other pathogenic organisms. As such it represents a potential target for novel chemotherapeutics. CYP61 catalyses an unusual reaction for a P450, namely the dehydrogenation of an alkane to an alkene. However, essentially nothing is known about the exact structure of the substrate, the stereochemistry of the reaction or its mechanism. Projects in this area will involve the synthesis of potential substrates and mechanistic probes, the analysis of the products of enzyme catalysed reactions, production and characterisation of enzyme mutants and design and synthesis of inhibitors based upon our understanding of the mechanism of the enzyme.

P450cin is a unique biodegradative bacterial P450 that we have isolated that initiates a cascade of reactions allowing a bacterium to live on cineole (eucalyptol) as its sole source of carbon and energy. The protein has been cloned and over-expressed and basic characterisation has revealed several novel features, such as the absence of conserved amino acids thought to be important in its mechanism of action. Projects in this area will range from construction and characterisation of site-directed mutants, structural identification and stereochemical analysis of oxidation products, synthesis of alternative substrates as mechanistic probes and utilisation of oxidation products in enantiospecific syntheses.

P450Biol is a carbon carbon bond cleaving enzyme that is involved in biotin biosynthesis. We have broadly defined the pathway of bond cleavage but the detailed mechanism is poorly understood. The reaction is similar to one that occurs in steroid hormone formation and thus we wish to investigate the mechanism more fully. Projects in this area will include stereospecific synthesis of modified substrates, structural analysis and synthesis of enzyme oxidation products and characterisation of stiochiometry of enzyme turnovers.

**Project 2: Constituents of Medicinally Used Herbs**

Whilst herbal medicines are widely used within the general community and have a long history of such use, their chemical constituents are often poorly characterised. This makes assessment of the true biological activity of many of these preparations extremely difficult to determine. In collaboration with a local herbal medicine company (MediHerb) we have embarked upon a program of phytochemical characterisation of a number of therapeutically prescribes herbs. The results have been surprising with a number of previously unknown compounds isolated from
supposedly well characterised species as well as significant variation in the constituent profile varying with both harvest time and processing methods. This project would involve the isolation, chromatographic purification and structure determination (especially employing 1D and 2D nmr spectroscopy) of the chemical constituents of selected herbs. The structures of some recently isolated compounds are given below.

Project 3: Fruit-Fly Pheromones

Tephritid fruit flies are of great economic importance as a number are destructive pests of many forms of horticulture in the tropical and temperate world. Consequently, considerable effort is now directed world-wide towards monitoring and control methods of pestiferous species. However, environmentally friendly methods of control must be based on detailed knowledge of the chemistry and biology of individual species. This project will seek to provide fundamental information on sex-pheremone biosynthesis in selected fruit fly species. Basic information about the steps involved in biosynthesis will be gathered as a prelude to isolation of the enzymes involved in catalysing these reactions and the design and synthesis of inhibitors of these enzymes.

Specifically, *B. oleae* (olive fruit fly) utilises 1,7-dioxaspiro-[5,5]-undecane 1 as an almost single component pheremone. We have shown that compounds such as 2 and 3 are direct precursors of the spiroactal 1 by a combination of labelled synthesis and GCMS analysis. More recently, we have shown that the precursor/product relationship between hemiketals and the corresponding spiroketals such as 3 and 1 appears to be general. Thus, the dimethylspiroketal 4 of *B. cucumis* was demonstrated to be formed from the hemiketal 5. This project will involve the further characterisation of the biosynthesis of spiroketals such as 1, and may involve the synthesis of labelled biosynthetic precursors and products and the characterisation of metabolites by GCMS, NMR etc. It may also include the isolation and characterisation of one of the enzymes involved in the biosynthesis of 1.

Relevant Recent Publications


Our research programs (http://fairlie.imb.uq.edu.au/) link chemistry to biologically important problems related to pathogenesis and treatment of disease. Chemistry students develop expertise in organic, medicinal or biological chemistry; learning principles of molecular design, synthesis (solid and solution phase, combinatorial chemistry, microwave-assisted), structure determination (2D NMR spectroscopy), or biological properties originating from interactions between small molecules and proteins. Outcomes are new compounds, structures, reactions, mechanisms, enzyme inhibitors, protein agonists/antagonists, and new drug leads.

In 2009 each Honours student (http://fairlie.imb.uq.edu.au/researchers.php?id=24; id=22; id=25; id=26) produced significant publishable results from their project (Synthesis of agonists and antagonists for an inflammatory GPCR; Design and Synthesis of anti-inflammatory phospholipase inhibitors; Evaluation of nociceptin analogues as potent agonists and antagonists of Opioid Receptor Like receptor; Metal clips for fixing peptides in alpha helical structures). Similar projects are available in 2010-2011.

In 2010-11, among Honours chemistry projects available in our group are:

1. **Antagonists of human G protein coupled receptors.** We are interested in these proteins which exist on the surfaces of human cells and are important in most human diseases. We wish to synthesize small nonpeptidic organic compounds that can bind with high affinity to these proteins on cell surfaces and regulate intracellular signaling pathways associated with cancer, inflammatory conditions, cardiovascular and Alzheimer's diseases. The project involves 90% organic synthesis (using solution and solid phase techniques, NMR spectroscopy, combinatorial and microwave synthesis methods) and collaboration with other members of the group who will undertake most of the biology, unless the student also wishes to learn principles of antagonist characterization. For background see: Blakeney JS; Reid RC; Le GT; Fairlie DP. Nonpeptidic Ligands For Peptide-Activated GPCRs. Chemical Reviews 2007, 107, 2960-3041.

2. **Inhibitors of Proteases.** Proteolytic enzymes are involved in the synthesis, turnover and degradation of all proteins and are validated therapeutic targets in human diseases. We are interested in designing potent and selective nonpeptidic inhibitors of proteases associated with inflammatory diseases. Either a metalloproteinase, a cysteine protease or a serine protease will be the enzyme target for this project which will involve design, synthesis and evaluation of small organic compounds as specific inhibitors. The project involves synthetic chemistry (using solution and solid phase techniques, NMR spectroscopy, combinatorial and microwave synthesis methods), collaboration with a computer modeller, and willingness to screen compounds every 3-4 weeks in a 2 hour bioassay. Resulting compounds will be anti-inflammatory agents. Background reading: Leung D et al; Protease Inhibitors : Current Status and Future Prospects, J. Med. Chem. 2000, 43, 305-341.

**For more information:** contact David or visit [http://fairlie.imb.uq.edu.au/](http://fairlie.imb.uq.edu.au/)
My research interests encompass carbohydrate chemistry and biochemistry, and medicinal chemistry, with a focus on the synthesis of compounds to probe and/or inhibit carbohydrate-protein interactions involved in disease processes. Of particular interest is heparan sulfate (HS; shown below) and the development of HS-mimetics as potential drugs for cancer and infectious diseases. Previous work in this area resulted in the discovery of PG545, an anticancer drug candidate expected to enter Phase I clinical trials in 2010.

1. Synthesis of heparanase inhibitors with improved specificity

Heparanase is an endo--glucuronidase that cleaves HS in the extracellular matrix (ECM) and thus facilitates metastasis of tumour cells and vascular remodelling associated with angiogenesis. Heparanase is an attractive target for the development of cancer drugs with antimetastatic and antiangiogenic activity. Muparfostat (PI-88) and PG545 are examples of heparanase inhibitors that have shown potent in vivo activity in metastasis models. Despite the advancement to clinical trials of inhibitors, there is a need to develop new heparanase inhibitors with greater specificity and the potential for oral delivery.


2. Probing the function of the human endosulfatases in carcinogenesis

Two recently identified HS-degrading endosulfatases, SULF1 and SULF2, have been implicated in carcinogenesis. SULF1 and SULF2 desulfate HS on the cell surface and in the ECM and modulate HS-binding growth factor signalling in multiple cancers. SULF1 appears to have a tumour suppressor effect, whilst SULF2 promotes tumour cell growth in vitro and in vivo. Targeting SULF2 or the interaction between SULF2 and SULF1 may lead to novel therapeutics for the treatment of cancer. Current SULF assays are either non-specific, cumbersome or both. There is a need to synthesize appropriate probes to establish the substrate specificity of the two SULFs and to design inhibitors which can in turn help to elucidate the complex interplay between the SULFs.
3. Synthesis of inhibitors of virus-cell attachment

Herpes simplex virus (HSV) has been shown to play an important role in the spread of HIV AIDS by enhancing the transmission of HIV between individuals. The development of microbicides fully active against both HIV and HSV is thus of some urgency. Many viruses, including HSV, use HS as an entry receptor or co-receptor. Various HS mimetics inhibit the attachment of viruses to cells. However, they mostly do not inactivate the virus particle and so the inhibitory effects are reversible. Recently, we have developed a series of HS mimetics that not only inhibited attachment of virus to cells, but also inactivated the virus particles.\(^3\) Such compounds have potential as treatments for established infections or as topical microbicides for prophylaxis. This project will focus on the synthesis of novel HS mimetics that inhibit HSV cell attachment and possess virucidal activity.

\(^{3}\)Ekblad et al., Antiviral Res, 86:2, 196-203 (2010)

4. Synthesis of designer substrate molecules to probe the function of a unique glycosyltransferase from \textit{Moraxella catarrhalis}

\textbf{Collaboration with Dr Jennifer Wilson and Dr Darren Grice (Institute for Glycomics, Griffith University)}

In Australia, otitis media (middle ear infection) is particularly prevalent in Aboriginal children and results in significant incidences of hearing loss. \textit{Moraxella catarrhalis} is a Gram-negative bacterium that is a major cause of otitis media in children. Gram-negative bacteria are characterized by the presence of lipooligosaccharides (LOSs) on the cell surface which play important roles in pathogenesis. In recent studies of \textit{M. catarrhalis} LOS biosynthesis,\(^4\) an unusual glycosyltransferase enzyme has been identified that appears to be responsible for the addition of three glucose residues to a central core glucose – typically, the addition of each sugar would require a separate enzyme and it is twice the length of a “normal” glycosyltransferase. To understand how this enzyme operates in this unique way we need specific “designer” substrate molecules to be synthesised so that we can probe its biological function. This work will inform the design and synthesis of enzyme inhibitors targeted against \textit{M. catarrhalis} and could ultimately lead to new treatments for otitis media.

\(^{4}\)Peak et al., FEBS J. 274, 2024-37 (2007)
Glycerophosphodiesterase from *Enterobacter aerogenes* (GpdQ) is an enzyme that displays remarkable activity toward all classes of phosphate ester substrates. Notably, GpdQ is capable of degrading EA 2192, a toxic product formed by the hydrolysis of VX (one of the most powerful nerve agents), as well as a number of agricultural pesticides. For this reason, GpdQ is of great interest for its application as a versatile enzymatic bioremediator. Its active site contains room for two metal ions. The metal ion in one site is coordinated by four amino acid residues, a terminal water ligand, and a hydr(oxide) molecule that bridges the two metal ions; in the second site, the metal ion may also be coordinated by four amino acid residues but, based on spectroscopic and kinetic data, is predicted to be less tightly bound (*see our recent publications in J. Am. Chem. Soc.*). The physiologically relevant metal-ion composition is unclear; however, the recombinantly expressed, purified enzyme appears to contain at least one Fe(II) ion. Metal-ion replacement studies indicate that GpdQ can operate using a range of divalent transition metal ions, including Zn(II), Cd(II), and Co(II). This project will have two major aspects to it. In one apo-GpdQ will be isolated, and metal ion studies will be undertaken with Fe(II) in the tight binding site and other divalent metal ions (e.g. Zn(II), Co(II), Mn(II)) will be incorporated into the less tightly bound site in order to explore the reactivity of the enzyme. The second goal will be to prepare a synthetic analogue of the enzyme (a catalyst model) and attempt to prepare a mixed metal ion (e.g. Fe(II)/Zn(II)) analogue). The active site of GpdQ and the proposed model are shown below.
Gallium(III) Analogues of Phosphomonoesterases

The ligand, 2-((2-hydroxy-5-methyl-3-((pyridin-2-ylmethylamino)methyl) benzyl)(2-hydroxybenzyl)amino)acetic acid (H$_3$HPBA), contains a donor atom set that mimics that of the active site of the enzyme purple acid phosphatase. Reaction of H$_3$HPBA with iron(III) or iron(II) salts results in formation of the tetranuclear complex, [Fe$_4$(HPBA)$_2$(OAc)$_2$(μ-O)(μ-OH)(OH$_2$)$_2$]ClO$_4$.5H$_2$O. X-Ray structural analysis reveals the cation consists of four iron(III) ions, two HPBA$_3^-$ ligands, two bridging acetate ligands, a bridging oxide ion and a bridging hydroxide ion. Each binucleating HPBA$_3^-$ ligand coordinates two structurally distinct hexacoordinate iron(III) ions. The two metal ions coordinated to a HPBA$_3^-$ ligand are linked to the two iron(III) metal ions of a second, similar binuclear unit by intramolecular oxide and hydroxide bridging moieties to form a tetramer.

Surprisingly, the tetrameric complex is catalytically active towards phosphomonoesters but it is not clear the form in which it is active. An excellent probe for Fe(III) is Ga(III) which is of about the same size and Lewis acidity but has the advantage of being diamagnetic and NMR active (Sarah JBIC 2007). In this project we will probe the reactivity and mechanism of the phosphomonoesterase activity of the gallium(III) complex of H$_3$HPBA. Thus the gallium(III) complex will be synthesised, the structure resolved using X-ray crystallography and NMR ($^{13}$C, $^1$H, $^{71}$Ga) and the esterase activity of the complex will be probed. The relationship between the esterase activity of the iron(III) complex will be compared with the gallium(III) analogue.


ASSOC PROF GARY SCHENK & PROF LAWRIE GAHAN

How does a Bioremediator work?

Organophosphates (OPs) are used as pesticides and agents of mass destruction (e.g., sarin, VX), and they lead to considerable environmental damage. In the developing world each year 100s of thousand of people die of OP-related poisoning. A powerful new method to remove OPs from the environment, but also treat poisoned patients in hospitals, involves an OP-degrading enzyme extracted from the soil-dwelling bacterium Agrobacterium radiobacter (OPDA).1,2 In order to exploit the full potential of OPDA as a bioremediator it is essential to understand its function. In recent research the crystal structure of this enzyme has been solved, and methods to study its function have been established in our group in collaboration with Prof. David Ollis from the Research School of Chemistry at the Australian National University, Canberra. In this project, the student will characterise mutant forms of OPDA that have improved catalytic properties towards the degradation of some OPs, and which may also be more stable when applied in Nature. This is a project at the interface between biophysical chemistry and biotechnology and involves techniques such as protein expression and purification, mutagenesis, kinetics and spectroscopy.

Figure 1: Overall fold (left; metal ions shown as green spheres) and active site structure (right) of OPDA. The metal ions play an essential role in binding the reactants and initiating catalysis.


The tyrosine phosphatase CpsB from *Streptococcus pneumonia*: are three metal ions better than two?

The glycerophosphodiesterase from *Enterobacter aerogenes* (GpdQ) is an enzyme that we have been studying for a number of years. It is one of a group of metalloenzymes which display remarkable activity toward all classes of phosphate ester substrates. Most of the metalloenzymes we have studied are bimetallic systems, either homodivalent (Co(II)Co(II); Zn(II)Zn(II), Mn(II)Mn(II)). In recent years a new group of phosphatase enzymes has been studied. Of interest is the tyrosine phosphatase CpsB from *Streptococcus pneumonia* which is in fact a trimetallic system (structure shown below).\(^1\)

The Mn(II)\(_3\) form has been isolated and characterised crystallographically and there is some doubt as to the identity of the native from of this enzyme. There are other examples of trimetallic enzyme systems but they are not common. A significant aspect of our work is to model the active site of a metalloenzyme using relatively simple “biomimetics”. We have had considerable success with both structural and functional models of a number of bimetallic metalloenzyme systems (GpdQ, OpdA, PAP) and we would now like to investigate structural and functional models of CpsB.

In this project a model ligand will be synthesised and metal complexes prepared. The structure, spectroscopy and hydrolase activity of the model will be studied. It is anticipated that parallel studies with the metalloenzyme itself will be undertaken.

PROF LAWRIE GAHAN and PROF PAUL BERNHARDT

Preparation of New Agents for Molecular Imaging with Copper-64

This project is in association with Dr Suzanne Smith, Radiopharmaceuticals R & D Division, ANSTO, Lucas Heights, Sydney.

Macrocyclic ligands such as DOTA (1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid) and TETA (1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid) have found application for 64-copper labelling of antibodies which show excellent targeting of tumours. 64-Copper has a half life of 12.7 hours and is a positron and \( \beta^- \) emitter and the decay characteristics of 64-copper make it suitable for positron emission tomography (PET) imaging and radiotherapy. Of recent interest has been the application of hexaazamacroyclic cage ligands for the delivery of 64Cu. Dr Smith and her colleagues at ANSTO have patented a cage ligand, abbreviated SarAr. We have expanded the study of these bifunctional macrobicyclic ligands to include a mixed thioether/amine donor ligand (N3S3sar). There have been no indications that in the case of the N6 cage the copper(II) ion resides anywhere but wholly within the cage (coordinated by all 6 N atoms); however, in the presence of high concentrations of halide ion (specifically bromide) in DMSO the N3S3sar complex displays complicated behaviour indicative of the metal ion being partially removed from the cage. These findings have important implications in terms of the clinical applications of SarAr where it would be utilised in the presence of high halide concentrations.

The project will involve, initially, the synthesis of the encapsulating ligands using well-described synthetic strategies. Once the ligands have been prepared the copper(II) complexes will be isolated and characterised. Using a combination of Electron Paramagentic Resonance (EPR), visible spectroscopy, kinetic analysis and X-ray crystallography we will investigate the chemistry of the copper(II) complexes with a view to understanding the processes involved in the mobility of the copper(II) ions. If the project progresses well, time will be spent at ANSTO investigating these systems using 64Cu.
The research in my group focuses on the biological chemistry of natural products from marine and terrestrial sources. One quarter of the world’s drugs come from Nature, primarily from microorganisms and from rainforest plants. As terrestrial resources become overexploited, attention has turned to the marine environment as an alternative source of novel bioactive metabolites. A number of different Honours and PhD projects are available which provide experience of (i) isolation and structure elucidation (ii) biosynthesis (iii) synthetic organic chemistry (iv) chemical ecology.

**Project area 1: Biologically-Active, Nitrogenous Terpene Metabolites - Structure Elucidation and Biosynthesis**

The sponge *Amphimedon terpenensis* contains cytotoxic and antimalarial diterpene isocyanides exemplified by disocyanoadociane (1a) and the isothiocyanate analogue (1b), while *Acanthella cavernosa* produces volatile antimalarial sesquiterpenes such as (2a) and (2b). Other sponges of current interest include *Axinyssa* n.sp. which contains the thiocyanate (3a) and *Stylotella aurantium* which exhibits the unusual dichloroimine (= carbonimidic dichloride) functionality, e.g. in (4a) and (5). Recent work by our group has shown that cyanide or thiocyanate can act as biosynthetic precursors for all four functional groups (-NC, -NCS, -SCN, -N=CCl₂).

All four sponges contain additional metabolites of biosynthetic and pharmacological interest which require detailed structural and stereochemical investigation. The next phase of our biosynthetic work is advanced precursor incorporation studies using labelled forms of the above terpenes. Immediate synthetic targets are (1b), (2b), (3b) and (3c). The role of isonitrile and isothiocyanate precursors in dichloroimine biosynthesis can be tested by incorporation of labelled (4b) and (4c). The synthetic approaches we have selected start from amines such as (1c) or from bromo compounds (eg. (4d)).

The four sponges are also of biological interest. For example, samples of *Stylotella aurantium* inhibit metamorphosis of ascidian larvae, but the chemical basis of this inhibition has not yet been tested (collaboration with Prof. B. Degnan, Zoology).
Project area 2: Structure Elucidation of Bioactive Australian Marine Natural Products

Samples are analysed by TLC, 2D NMR techniques and biological screening to identify organisms of interest. Modern techniques of organic chemistry are then applied to work out the structures of the isolated metabolites. Organisms currently under study include the sponges *Haliclona* and *Xestospongia* spp. which contains structurally-complex cytotoxic and antifungal alkaloids such as \((6)\) and \((7)\) and *Dactylospongia* spp. which contain cyclopropyl-substituted terpenes that are cytotoxic, eg. \((8)\). Candidates for study also include metabolites (eg. \((9)\)) from marine molluscs that feed on sponges.

![Haliclonacyclamine A (7)](image1)

![Xestospongin A (6)](image2)

![Dictyoceratidiquinone (8)](image3)

![Spongiadiol (9)](image4)

Project area 3: Structure Elucidation of Bioactive Natural Products from SE Asia

Through collaborations with colleagues from Indonesia and Thailand, we have access to a range of extracts of medicinal plants for chemical study. Recent work has included plants from West Timor (*Pandanus, Ochrosia* spp) and from Kalimantan (*Durio* spp.), leading to the isolation of compounds such as \((10)\) and \((11)\). Current work also focuses on bacteria isolated from Thai marine sponges, from which cyclic peptides (eg. \((12)\), whose synthesis and spectroscopic properties are of current interest, have been isolated.

![Pandanus extract](image5)

![Durio extract](image6)

![Cyclic peptide](image7)

Recent Publications


Biopolymers: Starch Structure, Biosynthesis and Human Health

Food with certain digestibility characteristics, such as a low glycemic index and high in resistant starch, has major health benefits. Starch, a complex branched polymer of glucose, is the main energy component of food. It has a wide range of molecular weights (up to $10^8$) and a complex branched structure. Its structure is controlled by a complex set of enzymes. This structure affects digestibility, particularly the avoidable diseases of obesity, diabetes and colorectal cancers, which are reaching epidemic proportions in both advanced and developing countries. Mitigating this health problem requires collaborative work in physics, chemistry and the biological sciences. This involves establishing biosynthesis-structure-property relations between the very complex structure of starch and digestibility. The most sensitive structure characterization technique is our multi-detector size-exclusion chromatography (SEC) system, plus fluorophore-assisted capillary electrophoresis, together with new high-level theory. Data from these new techniques provide a powerful new set of tools to provide a mechanistic basis for linking molecular architecture, the biosynthetic processes controlling this structure, and material behaviour for starches. Establishing this basis will allow rational selection of plant molecular breeding targets, crop growth and food processing conditions for desired nutritional properties.

There is a host of both experimental and theoretical projects in this field, including the following. (1) New insight into plant biosynthesis from novel experimental and theoretical procedures for size distributions; (2) Genetic sequences, SNPs and starch structure; (3) Kinetics of homogeneous and heterogeneous digestion; starch as a branched polymer: characterization and properties.

Relevant recent publications:

Using molecular size distributions to understand the nature of $\alpha$ and $\beta$ particles in glycogen. MA Sullivan, F Vilaplana, RA Cave, DI Stapleton, A Gray-Weale, RG Gilbert. Biomacromolecules, 11 1094 (2010)
Extracting physically useful information from multiple-detection size-separation data for starch. A Gray-Weale, RA Cave, RG Gilbert, Biomacromolecules, 10 2708 (2009)
The primary research area of the Grondahl Group is in biomaterials design and evaluation. All projects builds on Physical Chemistry and Materials Chemistry fundamentals. Collaborations with chemists and biologists at UQ enable the tailoring of projects to specific interests of students. The projects listed below are examples of what could constitute an Honours project in the Grondahl Group.

**Protein Adsorption to Well-Defined Surfaces**

Many biomaterials possess suitable bulk properties; however, their surface properties are not ideal. The material surface characteristics influence the final type, orientation and conformation of adsorbed proteins and hence the subsequent cell-surface interactions. Biomaterials with non-ideal surface properties therefore frequently fail to perform appropriately in vivo leading to an extensive prolonged inflammation, fibrous capsule formation and implant rejection. Investigating the protein adsorption to surfaces with controlled surface features will advance the knowledge needed to design future generation biomaterials with optimal properties. This project involves collaboration with Dr Justine Hill (SCMB).


**In Vitro Mineralisation in the Presence of Macromolecules**

Hydroxyapatite (HAP) is the main mineral phase of bone and teeth. In vivo the biomineralisation process occurs in the presence of biological macromolecules where the ion concentrations are too low for spontaneous nucleation and growth of crystals to occur. In addition, the morphology of the HAP crystal is affected by the presence of these macromolecules. In order to produce HAP nanoparticles suitable for composite bone biomaterials a better understanding of how to control size and shape is required. This study will investigate the nucleation and growth of HAP in the presence of macromolecules. It involves collaboration with Dr Kevin Jack (CMM).
Tailoring scaffolds for Tissue Engineering applications

Tissue engineering (TE) is a vibrant field of research at the interface between biology, chemistry and engineering. In many TE applications, biodegradable polymers are favoured as the materials of choice due to their inherent capability to degrade in vivo post or during tissue development, leaving a fully functional regenerated tissue in its place, avoiding the need for further extractive surgery or long-term implantation. This project will focus on making hydrogel based scaffolds incorporating chemical and biological signalling molecules and studying cell growth. The main goal of this project is to produce a 3D biomimetic scaffold. This project involves collaboration with Prof Justin Cooper-White (AIBN).


See also projects listed for Dr Lisbeth Grondahl and Dr Gwen Lawrie.
DR LISBETH GRONDAHL and DR GWEN LAWRIE

Self-assembled polysaccharide matrices for cartilage repair
A novel strategy has been implemented to develop a composite graded hydrogel material designed for articular cartilage repair with the specific aim of alleviating pain for patients experiencing osteoarthritis in the knee joint. This material comprises a carefully constructed matrix reflecting the variable structure of articular cartilage. This project involves the preparation of hydrogels of variable composition and cross-linking density from the natural biopolymers alginate and chitosan and will involve the study of physico-chemical properties of their polyelectrolyte complexes. Advanced instrumental techniques such as NMR, FTIR, AFM and XPS as well as various microscopic techniques (optical, fluorescence, and cryo-EM) will be used in these studies.

Tailored matrices for temporal delivery of drugs in bone repair
Non-union and delayed union fractures are unable to heal by themselves and therapeutic options would therefore greatly benefit from delivery of bone-growth inducing factors. Successful delivery of factors requires the development of drug delivery systems optimised for these molecules. Biodegradable gels can be used to encapsulate these bone-inducing factors. Specifically, one project will investigate functionalisation of alginate with amino acids for tailoring the gel matrix and another project involves investigation of using LbL assemblies to control the drug release rate. The drug delivery systems will be characterised using a combination of microscopic techniques (optical, fluorescence, and cryo-EM) and spectroscopic techniques (Fluorescence, FTIR) and their stability in a simulated body environment will be assessed. In addition, drug encapsulation efficiency and the drug release rate from the system will be optimised. This project involves collaboration with Dr Justine Hill (SCMB).

Our research links chemistry with biophysics and cell biology to characterise the structure and function of complex protein machines involved in apoptosis and innate immunity. We apply a multidisciplinary approach, combining a wide range of experimental methods to answer the questions that we’re interested in. Honours students can gain expertise in biological chemistry and structure determination using multidimensional NMR spectroscopy. NMR is a powerful technique not only for structure determination, but for studying interactions in solution, enabling us to understand how proteins interact to form complexes and larger assemblies.

We are particularly interested in the assembly of complexes that regulate caspase activation such as the death-inducing signalling complex (DISC) and inflammasome. Our goal is to better understand how molecular interactions within these multiprotein complexes regulates their biological activity with remarkable specificity. This knowledge will pave the way for medicinal chemistry efforts to develop new therapies to combat diseases such as immune disorders and cancer.
Honours research projects are available in the following areas.

(1) **Death receptor-mediated apoptosis**

Apoptosis, the major form of cellular suicide, is crucial for numerous physiological processes including normal development, tissue homeostasis and immune system function. Consequently, defects in apoptosis contribute to the pathogenesis of a wide variety of human diseases including neurodegenerative disorders, autoimmune syndromes and several forms of cancer. Death receptors such as cell-surface sensors that trigger apoptosis in response to specific extracellular death signals. Activation of a death receptor facilitates the recruitment of an adaptor protein FADD and procaspase-8, leading to the formation of the ‘death-inducing signalling complex’ (DISC). Several endogenous and viral proteins known as FLIPs have also been identified as inhibitors of procaspase-8 recruitment and activation. We are studying the molecular basis of DISC assembly and its regulation by FLIPs using high resolution NMR spectroscopy in combination with biochemical and functional analysis.

This project will involve:
- Protein chemistry (incorporation of $^{15}$N and $^{13}$C labels into proteins to aid their characterisation using NMR spectroscopy).
- Multidimensional NMR spectroscopy using high resolution 750 MHz and 900 MHz instruments to analyse protein structure and protein interactions.

(2) **Inflammasome assembly and regulation**

The inflammasome is a multiprotein complex that mediates caspase-1 activation and inflammation in response to a number of stress and pathogen danger signals. While initially protective, prolonged inflammation is damaging to the body as observed in inflammatory diseases such as rheumatoid arthritis. Assembly of the inflammasome is mediated by interactions between pyrin domains (PYDs) and caspase recruitment domains (CARDs), members of the death domain superfamily. Several PYD- and CARD-containing proteins have also been identified as endogenous regulators of caspase-1 activation and IL-1β secretion. Despite a key role for these proteins in the regulation of inflammation, little is known about their molecular mechanisms of interaction. We are investigating the molecular basis of interactions between several PYD- and CARD-containing proteins.

This project will involve:
- Protein chemistry (incorporation of $^{15}$N and $^{13}$C labels into proteins to aid their characterisation using NMR spectroscopy).
- Protein structure determination using multidimensional NMR spectroscopy.
- Characterisation of protein interactions using biophysical methods, isothermal titration calorimetry (ITC) and surface plasmon resonance (Biacore).
Learning in chemistry requires the recognition and application of concepts across multiple contexts supported by multimodal experiences to enable students to construct their understanding. The development of innovative learning activities to promote complex reasoning and higher order thinking skills is based on research to understand the processes of knowledge construction. My research focuses on concept construction through active learning experiences and the integration of mental models to create new ideas and understanding. Two projects currently available are:

1. **The sustainability of mental models developed through dynamic molecular representations in chemistry.**

Students are expected to gain fluency in multiple representations of molecules (symbols, line structures, ball and stick models and space filling models) while learning chemistry. Dynamic molecular animations and simulations are often used to support visualisation of concepts within learning environments (lecture or laboratory). Dynamic visualisation of chemical processes at a molecular level to support the construction of mental models has been widely established as having a positive impact on learning. However, students frequently demonstrate poor ability to translate or apply these conceptual models in new contexts which involves higher order thinking. This project investigates the factors which influence the application of concepts gained through virtual representations of chemical processes to new contexts (eg unfamiliar laboratory experiments). The factors that will be explored include visuospatial thinking, metacognition, and misinterpretation of images. Student conceptual understanding, perceptions and learning strategies will be evaluated through analysis of interviews, artifacts (qualitative data) and questionnaires (quantitative data).

2. **Modification of alginites for microencapsulation applications and translation into undergraduate research experiences.**

Dr Gwen Lawrie & Dr Lisbeth Grøndahl

Joint Chemistry Research & Chemical Education Project

Alginate is a versatile polysaccharide used widely in biomaterials research particularly in the microencapsulation of biomolecules or of cells for therapeutic purposes. Modification of this polymer molecule via the carboxyl moiety offers many options for tailoring its functional and structural properties. The modified polymer can be applied to prepare hydrogel matrices for drug delivery applications imparting enhanced immunogenicity and specific targeting properties. This project involves two components:
A. Core Chemistry Research Component (80%)
This project involves the modification of alginate molecules (Fig 1.) with amino acids and/or small peptide molecules. These modified alginates will be blended to generate multifunctional membranes which can be used to prepare microcapsules. The modification of alginate will be achieved through carbodiimide coupling and the product will be assembled on a number of matrices which will require structural and chemical characterisation prior to and post-assembly. A number of advanced instrumental techniques including FTIR and XPS will be applied during characterisation of these matrices.

B. Chemical Education Research Component (20%)
The synthetic procedure and characterisation tools used in the core research in part A will be modified and re-presented in a format to be achievable by undergraduate students within a practical course. This will form a self-contained undergraduate research module which will replace traditional laboratory experiments in a practical course (following the model of the existing CASPIE undergraduate research modules developed at Purdue University and implemented in 1st year chemistry at UQ). A learning goal of an undergraduate research experience is to increase the opportunities for students to develop skills including: critical appraisal of their observations; solving problems and data processing. This is a core component in learning chemistry and as part of this educational research; the project will involve development of an evaluation instrument to assess critical skill acquisition gains by students.

3. The impact of context on student engagement and outcomes in scientific inquiry.
Dr Gwen Lawrie & Dr Tony Wright (School of Education)

Student engagement in undergraduate research and scientific inquiry practices are becoming widespread at the tertiary level. Students arriving at university typically have been exposed scientific inquiry as a learning environment in their secondary education. However this context represents a well established and secure learning community where the judgement of peers and instructors is predictable. The role of these prior learning experiences on the ability of a student to develop new research questions that they perceive as scientifically relevant at the tertiary level has not been explored to date. This is an important issue for the implementation of inquiry in university courses where students are often placed in unfamiliar learning communities and then are expected to rapidly synthesise research questions and outcomes. In this project, a comparison between students participating in extended experimental investigations in secondary chemistry classrooms and participating in undergraduate research in 1st year chemistry will form the basis of a study exploring transitional issues in inquiry skills. Student attitudes, perceptions and strategies will be evaluated using both established and new instruments developed for this study. Qualitative and quantitative data will be collected through interviews, questionnaires and learning outcomes.
Design and Synthesis of Organic/Organometallic Nanomolecules

Within the new research Centre, Centre for Organic Photonics and Electronics, we are focusing on developing new classes of quantum nano-materials for opto-electronic application, such as flat-panel light emitting displays (Adv. Mater. 2007, 19, 1675), solid-state lighting, and solar cells (Chem. Rev. 2007, 107, 1097), clean-energy (hydrogen generation) (Angew. Chem. Inter. Ed. 2009, 48, 2842), and health-care applications (Nature Mater. 2005, 4, 435). Honours students will involve and learn how to design, synthesise and characterise these nano-materials for the exciting/critical applications.

Quantum dots (QDs)—exhibit a vast array of interesting size-dependent electronic, magnetic, optical and catalytic properties—have been heralded as the next generation building blocks for opto-electronic and bio-applications. However, for the utilisation of QDs in any nanotechnological applications, the colloidal nano-crystals need to be stabilised to avoid aggregate. Two general strategies developed are electrostatic stabilisation, i.e., the use of a core-shell structure, and steric hindrance whereby organic materials are adsorbed onto the surface of the QD (Figure 2). The main methods of stabilising QDs with organic materials have included the use of long alkyl thiols, alkyl phosphine oxides, polymeric phosphine oxides, linear oligothiophenyl phosphonic acids, and DNA. To give better protection and stabilisation of the central QD cores, we are developing new dendritic materials to encapsulate the QDs to facilitate these specific applications.

Available projects include the following research areas;
• Advanced materials for opto-electronics: OLEDs and solar cells
Organic light diodes (OLEDs) are a key technology for the future of flat-panel displays (FPDs) and solid-state lighting. OLEDs have the advantage over other FPD technologies for their superior display quality and superb energy efficiency (over 40% less on power consumption than current TFT-LCD displays); (and this coupled with the potential for) more power efficient lighting could lead to a substantial decrease in energy usage. With the excellent photostability and narrow emission wavelengths for potentially better lifetimes and colour purity, the performance of QD-LEDs, however, has thus far lagged behind those of phosphorescent OLEDs. The low efficiency of QD-LEDs relative to their potential is primarily due to poor charge transport in the films of the QDs for their electrical insulator shells and charge trapping in the QDs. The research is aiming to overcome the current limitation of QDs for the use as light emitting as well as solar cell materials as cheap and renewable energy sources.

Clean energy: Hydrogen generation and storage

The use of hydrogen as a renewable and clean energy is one of the most important and exciting research fields. To meet practical needs of hydrogen-powered vehicles with a driving range of greater than 500 km, it will require 5-10 kg of hydrogen stored on-board. Finding efficient hydrogen production and safe storage materials for such an amount of hydrogen is critical for the technology. While the research aims to create new materials for on-board hydrogen storage, efficient photoinduced hydrogen production will be developed.

Health care: Biomaterials for imaging and treatment

Photodynamic therapy (PDT) has been developed to provide non-invasive (compared with conventional surgery) and less side effects (compared to chemotherapy) for cancer treatment. PDT can be accurately targeted, and repeatedly administered without the total-dose limitations related with radiotherapy and result in little or no scarring after healing. To facilitate the advantages of PDT, we are developing novel bio-compatible photodynamic therapy agents for deep tissue treatment with less photodamage. The research will also develop high-resolution 3D imaging agents.

Single molecular devices:

The excitement and importance of molecular devices is that they are small in size, fast response and more energy-efficient than what is available today. Currently, it is possible to probe charge transport properties (conductivity) in a single molecule by using scanning tunnelling microscopy (SEM) from self-assembled monolayer devices. It is challenge to effectively wire the tiny active single molecule with the desired device electrodes in the nano-devices. The objective of the research is to develop more reliable and robust new technology for nano-molecular devices as next generation electronic devices.
The group uses computer simulation techniques to model the dynamic behaviour of biomolecular systems such as proteins, nucleic acids and lipid aggregates, in atomic detail. The simulation software and atomic force fields we develop are used to understand the biomolecule:biomolecule (e.g., protein:lipid) and biomolecule:ligand interactions in molecular recognition. We look for students with strong backgrounds in structural biology, chemistry, physics or computational science interested in working at the interface between these disciplines.

Possible Projects include:
Automated Topology Builder (ATB; http://compbio.chemistry.uq.edu.au/atb/)
[Dr. Alpesh Malde, a.malde@uq.edu.au, 3365 7562; http://compbio.chemistry.uq.edu.au/mediawiki/index.php/Dr._Alpesh_Malde]

The aim of this project is to further develop and validate an automated force field topology builder (ATB) for heteromolecules for use in studying the ligand-macromolecule interactions with potential applications in drug design and X-ray refinement. The ATB also serves as a repository for building blocks of biomolecules. Well-parameterized force fields are widely available for the simulation of common biomolecules such as proteins, nucleic acids, lipids, sugars, etc. In contrast parameters for small heteromolecular ligands such as substrates, inhibitors, drug molecules or co-factors are in general far from optimal. Manually optimizing parameters for novel molecules is both extremely time consuming as well as error prone and current automated approaches are largely not validated.

The specific aspects of the project are:
(i) Develop and implement a protocol for deriving force constants to describe bonded interactions based on the Hessian (force constant) matrix derived quantum mechanically incorporating corrections for non-bonded terms of classical force field.
(ii) Validation of the ATB against the experimental solvation free energies for a wide range of drug like heteromolecules including the datasets from SAMPL (Statistical Assessment of the Modeling of Proteins and Ligands) challenges.

The project will involve quantum chemical calculations, programming in python and mysql, matrix algebra, small molecule simulations and free energy calculations.

Binding modes of non-standard ligand molecules in X-ray crystal complexes
[Dr. Alpesh Malde]

X-ray crystallography is an indispensable tool in structural biology and drug design. However, while the overall structure of the protein component within a given complex can be resolved in near atomic detail the position, the binding modes (stereochemistry, orientation, conformation, protonation state and tautomeric state of small molecular ligands like cofactors, substrates, inhibitors, drug molecules, etc.) are often much less certain in medium to low resolution structures. Even slight errors in the binding modes of the ligands readily lead to the misinterpretation of biochemical mechanisms and/or the failure of computational drug design approaches. The project will focus on the use of molecular dynamics (MD) simulations and free energy (FE) calculations to detect possible errors and identify the correct binding modes of ligands in the X-ray crystal complexes.
Warfarin, the most frequently prescribed anticoagulant drug and administered as the racemate, exhibits large number of drug interactions, both with other drugs and with environmental and dietary factors. Warfarin is bound to the serum albumin and is extensively metabolized by cytochrome P-450 (CYP) isoenzymes, in particular CYP2C9. Hence, patients on warfarin therapy are to be monitored for the appropriate level of anticoagulation. The crystal structure complex of CYP2C9 with S-warfarin exhibits presence of multiple binding pockets for the drug molecule. The tautomer of warfarin described in the crystal structure complex is ill suited for generation of the major metabolite of warfarin. Warfarin can exists in solution in potentially as many as 40 topologically distinct tautomeric forms (20 for each enantiomer). FE calculations will be used to identify the thermodynamically preferred tautomer of warfarin in solution as well as in the binding pockets of CYP2C9 to understand the role of tautomerism in the biological fate of warfarin.

The project will involve force field parameterization (using ATB) and quantum chemical calculations of ligand molecules (warfarin and heme); and classical molecular dynamics simulation of biomolecules.

References

Force fields for lipids
Dr. David Poger
E: d.poger@uq.edu.au | P: 3365 7562 | W: http://compbio.chemistry.uq.edu.au/~david

Lipid molecules are fundamental components of biological membranes. Not only do they play a role in the compartmentalization of cells and organelles but, in addition, they participate in numerous fundamental processes such as cell division and intracellular trafficking. Pure phospholipid bilayers have been extensively studied as models for biomembranes. Depending of the nature of their headgroup (choline, ethanolamine, serine, glycerol, myo-inositol, hydrogen) and the number of acyl chains (diacylphospholipid or 1- or 2-lysophospholipid), phospholipids can adopt a variety of alternative phases (such as the hexagonal and liquid-crystalline phases). We have developed force-field parameters for phosphatidylcholines which allow to reproduce the fluid and gel lamellar phases. To be able to mimic biological membranes, force-field parameters for other classes or phospholipids are needed.

The aim of this project is the development and validation of parameters for the GROMOS force field for phosphatidylserines, phosphatidyglycerols and cardiolipins.


Spontaneous assembly of phosphatidylcholine molecules into a fluid-phase bilayer (in blue, water molecules, in yellow and red, lipid headgroups, in grey, lipid tails).
My research interests lie in the areas of biological/medicinal chemistry and synthetic methodology. I hold a joint appointment with UQ’s School of Pharmacy. Several projects are available which are suitable for Honours students, and these students will gain experience in synthetic organic chemistry, inhibitor design, structure elucidation, instrumental techniques and bioassays, if appropriate. Joint projects are available with Drs Guddat and Schenk of this School. These projects range from very pure, curiosity-driven science, to research with a clear commercial focus. I encourage students to contact me to discuss these projects and for more detailed project descriptions. New projects are available from time to time, and additional information can be found at my website:


Designing New Reactions

We have been exploring the synthetic utility of 2-mercaptobenzothiazole 1, and we have recently developed a simple and mild method for the conversion of epoxides into alkenes 2, with retention of stereochemistry. Previous methods for achieving this transformation employed harsh reaction conditions that were incompatible with many functional groups. We are currently examining the scope and limitations of this new reaction and we are investigating related reactions to convert α-halo ketones to alkynes 3, to prepare vinyl sulfones for cycloaddition reactions 4, and to develop mild and efficient chemistry for malonate-type ester preparations 5.
The Roles of Substituents and New Catalysts in the Claisen Rearrangement

The rearrangement of allyl vinyl ethers $8$ to give $\gamma,\delta$-unsaturated carbonyl derivatives $9$ (the Claisen rearrangement) has proven to be a general and reliable way to introduce contiguous chiral centres into carbon frameworks. As such, the Claisen rearrangement has been widely used in the synthesis of complex natural products. Studies have shown that the rate of the Claisen rearrangement can be greatly enhanced by electron-withdrawing substituents, such as a nitrile group at the allylic carbon adjacent to the oxygen atom in $8$. This promises to significantly extend the scope of this reaction.

Recent work from our lab has revealed new methodology for performing the Claisen rearrangement, either thermally or with Lewis acid catalysts. This project will examine the Claisen rearrangement of allyl vinyl ethers $8$, derived from allylic alcohol or cyanohydrins.

S,N-Acetals (In collaboration with Prof Christopher Schofield, Oxford University)

The condensation products of amines, thiols and aldehydes are S,N-acetals. This reaction is rapid, reversible and occurs without the need for acid catalysis. Surprisingly, this reaction has not yet been extensively studied.

As part of a recent sabbatical visit to Oxford University with Professor Christopher Schofield, we began to investigate the scope and limitations of this chemistry, with an eventual aim of applying this knowledge to biological systems. Several projects suitable for Honours or PhD students are available in this area.
Design and Synthesis of Inhibitors of Purple Acid Phosphatases

Purple acid phosphatase (PAP) is a binuclear metalloenzyme that occurs in animals, plants, fungi, and some bacteria. The enzyme contains either an Fe$^{III}$-Fe$^{II}$, Fe$^{III}$-Zn$^{II}$ or Fe$^{III}$-Mn$^{II}$ binuclear centre in the active site.

While all of the biological roles of the PAPs have yet to be elucidated, it is clear that, in mammals, they play an important role in bone resorption (osteoporosis). Inhibition of the human enzyme is therefore a promising possible strategy for the treatment of this disease.

The crystal structures of a number of variants of this enzyme have been determined and some progress has been made on discovering the likely mode of action of these inhibitors. An opportunity now exists to use this knowledge to design inhibitors and better understand the mechanism of action of the enzyme.

This project will involve organic synthesis, enzyme assays, computer modelling and drug design.
STRUVITE RECOVERY FROM SYNTHETIC WASTEWATER

Traditionally in the wastewater treatment sector, solids precipitation/crystallisation treatment processes have been approached from the perspective of removal of nutrients. However, there has been growing interest in using crystallisation from wastewater to generate valuable products. A commonly known example is the crystallisation of magnesium ammonium phosphate (or *struvite*) which acts to remove nitrogen and phosphorus from the wastewater, but can potentially be harnessed to produce a slow release fertiliser product. Struvite crystallisation studies have been very applied, with limited focus on the fundamental mechanisms of crystallisation. This limits the applicability of results to that specific wastewater, and reduces options to improve crystallisation performance and product quality. This project will provide kinetic data for struvite crystallisation from synthetic wastewater with the intent that this information be used to model a struvite crystallisation process and allow some predictability.
• Synthesis and application of stable free radicals (nitroxides) as antioxidants and probes of complex systems
• Investigation of halogen-bonding by nitroxide radicals as a new paradigm in the synthesis of functional materials
• Development of multifunctional imaging agents based on nitroxide-containing phthalocyanines
• Development of new photosensitisers, based on porphyrinic macrocycles (phthalocyanines and porphyrazines), for Photodynamic Therapy in the treatment of cancer and other conditions.


Halogen atoms are known to form electron donor-acceptor interactions with electronegative atoms possessing lone pairs of electrons (e.g. N, O, S) in a process known as halogen bonding. This process is analogous to hydrogen bonding and the two processes share a number of common properties. It has recently been discovered that stable nitroxide radicals form particularly strong halogen bonds with halo-perfluorocarbons and we have obtained the 2nd known crystal structure of such a system (see above). This project will involve investigation of some of the fundamental aspects of nitroxide-halogen bonding with respect to the nitroxide donor and halogen acceptor species, as well as the assembly of multi-dimensional halogen-bonded arrays of nitroxides, with potential application as functional molecular materials.

[2+2+2] Alkyne Cyclotrimerisation for the Synthesis of Functionalised Isoindoline Nitroxides

Isoindoline nitroxides exhibit advantages over other classes of nitroxides and are currently showing promise as antioxidants for the treatment of neurodegenerative disease and as probes for the *in vivo* measurement of tissue oxygenation.1,2 The large-scale synthesis of these compounds however, is hindered by a low-yielding Grignard reaction. Additionally, functionalising the aromatic ring is non-trivial, but essential for biological delivery and further synthetic modification. There is literature precedent for the use of an alternative approach for forming the isoindoline skeleton - transition-metal catalysed [2+2+2] alkyne cycloadditions3 - which would avoid the current synthetic limitations. This project will elaborate upon these cycloaddition strategies to develop novel and efficient routes to functionalised isoindoline nitroxides.

Living Polymers

Polymers made by living radical polymerization have well-defined chain length and architecture. The structures that can be synthesised are block, star, branched, gradient and even dendrimer. The advantage of such a technique is the wide range of functional monomers that can be incorporated in these architectures, allowing materials from biomedical applications to coatings to electronic devices to be prepared.

1. Nanostructures for Drug Delivery

The aim of the project is to synthesis the next generation of nanostructures built from linear polymer chains. The project will attempt to make a wide range of architectures that are currently unavailable and in collaboration with Cell Biologists use these as vehicles for drug and vaccine delivery devices. (ARC Discovery granted 2009)


2. ‘Smart’ Nanoreactors for Environmentally Friendly Organic and Polymer Reactions

Nanoreactors provide the ideal setting where selected chemical reactions can take place with high efficiency in controlled environments. The aim of this project is to use these ‘smart’ nanoreactors in the synthesis of molecules and macromolecules with high chemical selectivity and rapidly. This opens a method for the synthesis of new compounds and polymers previously unaccessibly. (ARC Discovery granted 2009)

3. Smart Nanostructures for Drug Delivery
The aim of this project is to synthesis polymers with complex architectures on the nanoscale in an environmentally friendly medium, water. Once these well-defined nanostructures have been made their structure-property relationship will be evaluated using structural characterization techniques such as electron microscopy for size and morphology, and will be functionalised for use as drug and gene delivery devices.


4. Nanopolymer Composites Prepared in Water
The aim of this project is to synthesis polymers with complex architectures (as shown above) on the nanoscale in an environmentally friendly medium, water. The synthesis will involve using a wide range of Living radical polymerizations towards a deeper mechanistic understanding of the reaction pathways. Once these well-defined nanostructures have been made their structure-property relationship will be evaluated using structural characterization techniques such as electron microscopy for size and morphology, and will be functionalised for use as drug and gene delivery devices.


5. Mechanisms in Living Radical Polymerization
Understanding the mechanisms in living radical polymerization allows for better design of the living agents and the optimal use of living polymerizations. The project will involve the determination of the initiation mechanisms involved in Atom Radical Transfer and Reversible Addition-Fragmentation chain Transfer polymerizations. This will enable us to determine the dominant mechanisms and what factors control addition, fragmentation and transfer reactions for these living processes.

POLYMER CHEMISTRY GROUP

PROFESSOR ANDREW WHITTAKER
AFFILIATED PROFESSOR
Centre for Magnetic Resonance and Australian Institute for Bioengineering and Nanotechnology

CMR, Phone: 3365-4100, AIBN, Phone: 3346-3885
E-mail: andrew.whittaker@cmr.uq.edu.au


Prof Whittaker is a Professorial Research Fellow at the Centre for Magnetic Resonance and the Australian Institute for Bioengineering and Nanotechnology, and holds an adjunct appointment in the SMMS. His research interests include the fields of nanotechnology, biopolymers and polymer hydrogels, polymer degradation, polymer devices, and the application of spectroscopic (especially NMR) methods to polymer research.

The Polymer Chemistry Group consists of 38 researchers, with two academic staff (Andrew Whittaker and Dave Hill), 12 Research Fellows (listed above) and 14 PhD and Honours students. The group is very active, holding weekly group meetings, and encourages students to travel to national and international conferences to present their work. We have outstanding links with national and international polymer groups. Our aim is to provide a supportive and stimulating environment for the training of young scientists. The projects listed below are all highly collaborative involving more than one of the scientists above. We aim in all of these projects to impart detailed knowledge of important chemical systems, and train the student in modern analytical techniques.

POLYMER HYDROGELS

Project 1: Novel Tri-Block Copolymers for Controlled Release of Proteins for Osteogenesis

The aim of this project is to produce a biodegradable controlled drug / protein release material for tissue engineering applications. Gene sequences, angiogenic and osteogenic factors are finding regular application in the clinical setting, however their efficacy is highly dependent on the correct dose that is delivered. Most delivery systems, particularly those based on hydrogels, rely on Fickian diffusion, which doesn't mimic the profile required by the body to initiate wound healing. Non-hydrogel delivery systems, such as PLGA microspheres, require the growth factors to be loaded from an organic solvent which inherently denature the protein. The basis of this project is to synthesise a triblock copolymer that is predominantly a hydrogel-like material, with interlinking hydrophobic groups that can encapsulate and release the growth factor. This project will involve polymer synthesis and characterisation using IR, NMR, SEM and mechanical testing.

Responsible Scientist Firas Rasoul
POLYMERS FOR TISSUE ENGINEERING

Project 2: Bio-polymer Beads for Drug Delivery

This project aims at synthesis and characterisation of biopolymers specifically targeting the delivery of drugs with poor bioavailability. This polymeric template will be made from a water soluble hyper-branched nano beads having several reactive sites that can be functionalised with different polymeric chains. The objective of this project is to use combination of polymerisation techniques to initiate polymerisation with controlled architecture and hydrophilicity. A project in this area would involve polymer synthesis and characterisation using techniques such as FT-IR, NMR and GPC. The developed polymer will be tested for drug delivery. 

Responsible Scientist: Firas Rasoul

POLYMER DEVICES

Project 3: Polymer Stabilised Nanoparticle Devices for Bio-sensing Applications

Noble metal nanoparticles such as gold nanoparticles have a range of interesting optical properties, which make them useful in the field of in vitro diagnostics. However, on their own they lack physiochemical stability and functionality. In this project a range polymer-stabilised nanoparticles will be prepared. The polymer will serve to stabilise the gold nanoparticles and also contain functionality for bio-sensing and bio-recognition. The project will involve polymer synthesis, polymer-nanoparticle self assembly and advanced characterisation.

Responsible Scientist: Idriss Blakey

Project 4: Thermo-responsive Polymers for Biomedical Applications

Thermo-responsive polymers have a change in solubility as a result of a temperature change. These types of polymers have applications in drug delivery devices. In this project a range of polymers will be synthesised where the composition is varied to tune the point at which the change is solubility occurs. These polymers will be assembled into polymer micelles and the thermo-responsive properties will be studied with a range of advanced characterisation techniques.

Responsible Scientists: Idriss Blakey and Kris Thurecht

Project 5: Hyperbranched Polymers for Drug Delivery and Medical Imaging

Hyperbranched polymers are a class of dendritic macromolecules that have received increased attention due to their favourable structural properties. In general, hyperbranched polymers are simple to synthesise by a range of polymerisation techniques and thus have the ability to present a wide range of chemical functionalities. In this project, hyperbranched polymers formed via controlled free-radical polymerization will be investigated. By incorporating various functionalities into the polymer, it can be assessed in terms of hydrolytic degradation, duel hydrophilicity and its applicability as a contrast agent for magnetic resonance imaging (MRI). A range of interesting chemistries will be utilized in the polymer synthesis (including RAFT, ATRP and click chemistry) in addition to characterization by various advanced techniques (NMR, MRI, GPC, electron microscopy, thermal analysis and vibrational spectroscopy).

Responsible Scientists: Idriss Blakey and Kris Thurecht

Project 6: Antimicrobial Surfaces

This project will involve in the synthesis and characterization of surface grafted polymers using modern surface initiated polymerization techniques (graft-from approach). The main aim of this project is to develop novel polymer-graft surfaces with prolonged activity against microbes. The approaches which will be adopted in this work consist of surface grafting of both hydrophilic and hydrophobic polymers which will be tested against both strains of bacteria Gram-positive (Staphylococcus aureus, which is the cause of skin, soft tissue and respiratory infection) and Gram-negative bacteria (Pseudomonas aeruginosa, which is the major pathogens associated with nosocomial infections). The materials and approaches developed in the project have the potential to contribute significantly to a reduction in healthcare-acquired infection and thus lead to improved treatment outcomes in hospitals and medical clinics.

Responsible Scientists: Firas Rasoul and Andrew Whittaker
Project 7: Water-born Biodegradable Polyurethane Foams for Biomedical Applications

Biodegradable polyurethane elastomers are expected to be suited for any application requiring the use of a flexible elastic material such as soft-porous tissue engineering scaffolds for skin grafting and vasculature. Biodegradable polyurethane (PU) is generally achieved by incorporating labile moieties susceptible to hydrolysis in the polymer chain (soft segment). The aim of this project is to develop novel water-crosslinkable biodegradable polyurethane for applications as porous tissue scaffold. The project will involve the use of polycondensation polymerization to synthesise a small library of biodegradable PU with range of mechanical properties and degradation rates. Advanced characterization techniques will be used in this project which includes NMR, FTIR, Differential scanning calorimetry (DSC), SEM and mechanical analysis (tensile strength and modulus of elasticity). Responsible Scientist Firas Rasoul
Promiscuous and Flexible!

The glycerophosphodiesterase (GpdQ) from *Enterobacter aerogenes* is one of the most (if not THE most) promiscuous binuclear metallohydrolase that catalyzes the hydrolysis of mono-, di- and triester substrates, including some organophosphate pesticides and products of the degradation of nerve agents. GpdQ has attracted recent attention as a promising enzymatic bioremediator. Our group in collaboration with Prof. David Ollis (The Australian National University) have employed kinetic (steady-state and stopped-flow) measurements and spectroscopic techniques to demonstrate that a gradual structural change in the vicinity of the enzyme’s active site leads to a kinetically optimal catalyst. Using site-specific mutations it was shown that these structural changes are associated with the flexible coordination of one of the ligands in the active site. This ligand, Asn80, is initially needed, together with the substrate (S), to assemble the binuclear metal centre (E_b) from its mononuclear precursor (E_m), but its coordination bond is broken as the enzyme attains optimal catalytic efficiency. This flexibility may enable the enzyme to accommodate a large number of substrates, thus making it an adaptable bioremediator. In this project the student will probe the role(s) of both the metal ions and specific amino acids in the reaction catalysed by GpdQ. The ultimate aim is to construct, *in vitro*, an enzyme with improved efficiency in bioremediation.

References:


ASSOC PROF GARY SCHENK and PROF LAWRIE GAHAN

NOVEL ENZYMES WITH “OLD” FUNCTIONS, OR OLD ENZYMES WITH “NOVEL” FUNCTIONS?

Our group has been studying a group of enzymes called binuclear metallohydrolases, proteins that require two metal ions to carry out hydrolytic reactions (Fig. 1).1-9 Since the advance of synthetic gene synthesis is has become possible to express, purify and characterise novel proteins of interest without having to embark on lengthy and, often, tedious cloning strategies. Based on comparisons of amino acid sequences we have recently selected a number of genes encoding proteins related to those we have already studies to some extent, but which are likely to have different biological functions and may catalyse different chemical reactions. This so called “functional promiscuity” is an emerging hot topic in protein chemistry and biotechnology since it harbours the potential to tweak the function of biological catalysts to a tailored need. In this project, which is part of a larger collaborative effort within our School also involving Assoc Prof Luke Guddat and Dr Ross McGeary, the student will carry out preliminary mechanistic characterisations of enzymes that may be targeted for use either in bioremediation or in the fight against the emergence of antibiotics resistance. Techniques employed range from protein extraction to spectroscopy, and from DNA manipulation to chemical kinetics, and the student will join a multi-disciplinary, well established research group with several postdocs and PhD students.

References from our group for further reading:

ASSOC PROF GARY SCHENK, DR ROSS McGEARY and ASSOC PROF LUKE GUDDAT

OSTEOPOROSIS: A Growing Problem for an Ageing Population

Osteoporosis is a disease which affects the elderly and in particular postmenopausal women. In developed countries mortality and morbidity are increasing in parallel with life expectancies. For women in the developed world, it has been estimated that 15% at age 50 will have osteoporosis. This number will increase to 40% at the age of 80. An estimated 2.2 million Australians have an osteoporosis related condition; this will rise to 3 million by 2021 as the population ages. Every 5-6 minutes, a patient is admitted to an Australian hospital with an osteoporotic fracture, and the total direct annual costs of this disease in Australia exceed $1.9 billion. Current treatments for osteoporosis include vitamin and calcium dietary supplements. Bisphosphonates are the most common drug administered to slow the rate of bone resorption, but these have significant side effects and/or compliance issues. Thus, osteoporosis is a major health problem in Australia and there is an urgent need to develop new and effective therapeutic agents for this enfeebling disease.

Our target for the discovery and development of new anti-osteoporotic drug leads is the enzyme purple acid phosphatase (PAP).1-3 In this project, the student(s) will have the opportunity to characterise recombinant human PAP (both wild type and selected mutants) and/or design novel potent inhibitors. This project is part of a larger collaborative effort within our School and lies at the interface between organic/medicinal chemistry, biochemistry and structural biology.

![Figure 1: Docking of an inhibitor into the active site of human PAP.3 This phosphonate compound is the most effective inhibitor for PAPs to date.](image)

References:


ASSOC PROF GARY SCHENK and DR ROSS McGEARY

FEAR: The Fight against the Emergence of Antibiotics Resistance

The rapid emergence of antibiotic-resistant pathogens has become a major global health concern. An increasing number of pathogenic bacteria make use of a group of enzymes that confer resistance to treatment with all the known β-lactam antibiotics. These enzymes are termed metallo-β-lactamases (MBLs). Significantly, clinically useful MBL inhibitors are not yet available.¹ ² Consequently, MBLs are important targets for the development of new chemotherapeutics, for which a comprehensive understanding of these enzymes' structure and function is essential. Our group has begun to investigate the chemical mechanisms of several MBLs, and the acquired knowledge will be used to synthesise potent and specific lead compounds for the development of clinically useful therapeutic agents. Two (2) Honours projects are on offer in our group in 2011 that cover a broad range of methodologies from protein and medicinal/synthetic chemistry. Importantly, we aim to mimic natural evolution by randomly mutating the MBLs and screen for mutations that enable the enzymes to become resistant to a particular drug – in essence, we attempt to pre-empt Nature’s response to a new chemotherapeutic. The interested student will join a well established research group and may have the opportunity to spend part of his/her research in the laboratory of our collaborator Prof. David Ollis at the Research School of Chemistry at the Australian National University, Canberra.

Fig. 1 (left): Structures of the three classes of β-lactam antibiotics. MBLs are able to inactivate all of these antibiotics by hydrolysing the lactam bond in the 4-membered ring of these drugs.

Fig. 2 (right): Active site structure of the MBL from Chryseobacterium meningosepticum. The catalytically relevant active site contains two metal ions (mostly Zn²⁺, but Mn²⁺, Fe²⁺ or Co²⁺ are also found). The inhibitor D-captopril binds to both metal ions and may provide a good starting point for the development of novel drug leads.

References:
NMR-Based Metabonomics in Clinical Applications and Environmental Science (5 projects)

How do challenges such as disease, environmental stress, diet or mutations impact on an organism? We try to solve these questions with NMR metabonomics and systems biology. NMR metabonomics is a novel and innovative approach to analyse biological or clinical samples, such as cell extracts, urine, and blood, by looking at the global composition of body fluids. We want to identify systematic patterns or metabolic fingerprints that are associated with diseases, specific physiological states, environmental or genetic conditions.

Diseases and related conditions, as well as environmental or genetic changes lead to global metabolic changes that are reflected in the composition of biofluids and can thus be identified. These changes can then be used as diagnostic markers for identifying individuals at risk, for identifying successful intervention strategies, and for following and monitoring treatment in patients. The technique is powerful, as it can identify trends and metabolic changes that are either sub-clinical or that could be missed by narrow screening approaches.

We study metabolic changes by investigating the chemical composition of biofluids with NMR spectroscopy. Changes in the metabolic profile of e.g. urine are then studied by multivariate statistical analysis and let us pinpoint, which parts of the organism’s metabolism are disturbed. Thus, by understanding how disease affects the metabolism of an individual and by understanding the metabolic consequences of a disease we might learn something about the mechanism of a particular disease itself. I have several projects available in this area, focussing on a variety of model diseases.

Current projects involve several projects aimed at developing NMR metabonomics as a tool for clinical diagnosis, the study of the effects of growth hormone receptor mutations in mice, the mechanism of phosphine resistance in *C. elegans*. Some of our animal model systems are very well understood, and in these cases we are trying to take the next step by investigating the connection...
between genotype and phenotype on a systematic level. Thus, projects in developing methods in computational biology/bioinformatics are also available.

**Individual Projects:**
Several main projects in NMR-based metabonomics are available in 2010/11:

1. "This won't hurt a bit" – non-invasive methods for detecting prostate cancer:
   This project centres on the early detection of Prostate Cancer and will be conducted in collaboration with Prof Frank Gardiner (UQ Centre for Clinical Research/Royal Brisbane and Women’s Hospital).

2. "I'm not afluenced by incohol as many thinkle peop!" – investigating a novel mechanism of alcohol neurotoxicity:
   The second project focuses on a new mechanism of alcohol toxicity that involves metabolic and permeability changes in the blood-brain barrier and alters the metaboliter composition of cerebrospinal fluid. The project is in collaboration with Prof Peter Nixon (SCMB) and Dr Simon Worrall (SCMB).

3. From genotype to phenotype – developing the big picture:
   In collaboration with Prof Mike Waters (IMB) we are trying to decipher the effects of growth hormone receptor mutations in mice that develop late-onset obesity. The project will involve correlation of metabolic with genetic data and aims at developing computational models.

4. Phosphine resistance in C.elegans:
   Similarly to project 3) we are looking at the genetic and metabolic alteration involving the resistance of *C. elegans* (as a model system for insects) towards phosphine (the most widespread fumigant in agricultural storage). This is a collaboration with Prof Paul Ebert (SCMB, SB).

5. "I'm a scientist and I am OK, I hack all night and I code all day" – method development in systems biology:
   The practical use of NMR metabonomics involves the analysis of a multitude of NMR spectra and correlation of these data with other data from physiology, biochemistry, or clinical assessments. This multimodal analysis is at the cutting edge of systems biology and requires the development of novel analytical tools and techniques. Thus, students with an interest or background in computational biology/bioinformatics, multivariate statistics and/or programming are highly welcome in this environment, next to students with experience in chemistry and/or biochemistry.

   All projects will be conducted in SCMB using the extensive NMR infrastructure of the Centre for Magnetic Resonance and the Institute for Molecular Bioscience, including the most powerful NMR-spectrometer in the Southern Hemisphere.
PROFESSOR SEAN SMITH

Phone: 3346-3949
Email: s.smith@uq.edu.au

I direct the Centre for Computational Molecular Science at UQ. Within the Centre we pursue a range of interdisciplinary projects including: theories and computational methods for the quantum description of molecular reactions; computational studies of fluorescent proteins; computational modelling of hydrogen storage in new materials; computational studies of DNA capture and delivery into cells by nanoparticles; characterisation of the mechanism for multi-step proton transfer in proteins.

Projects:

Fluorescent Proteins
Computational studies of the mechanism and functionality of fluorescent proteins with a view to designing new proteins for use in cellular and medical imaging applications. The fluorescent properties of these proteins depend on the intrinsic nature or the embedded chromophore, as well as its subtle interactions with the nearby amino acid residues in the enveloping protein matrix. Quantum chemical studies, coupled with quantum and molecular dynamical calculations reveal the key features that control the properties which we wish to design into new engineered fluorescent proteins.

Hydrogen Storage in New Materials
Computational studies of the interactions of molecular and atomic hydrogen with a range of novel nanomaterials being designed for the objective of hydrogen storage. These materials are based on carbon nanotubes and magnesium, with importation of small amounts of impurities such as heavy metals that assist in catalysing the adsorption and release of hydrogen. In silico studies are an essential counterpart to experimental work in order to move this research area of enormous economic significance forward.

Computational Studies of Drug Delivery
Studies of the mechanism of action of a number of new nanoparticles which have been found to be extremely effective as agents for the delivery of targeted DNA across the cell membrane. These new technologies have far reaching consequences for medicinal applications and the mechanism by which they operate is presently unknown or speculative.
A Novel System for Peptide Delivery

We have developed a novel drug-delivery system for the oral administration of drugs and peptides. The method involves combining the peptide or drug with a lipoamino acid (LAA) or a lipopeptide (LP), which acts as a carrier. LAAs combine the properties of amino acids (NH2 and COOH groups) with those of lipids (hydrophobic side chains). Combining a LAA with a peptide or drug, therefore provides a means of getting the compound into the body in a stable and biologically active form. We have shown, for example, that the systemic bioavailability of the following compounds is improved when they are administered orally as LAA-drug conjugates: anti-inflammatory alkaloids, analgesics, GABA, penicillins and cephalosporins, and several anti-cancer agents. These findings have confirmed the principle that conjugation with one or more LAAs, has had the capacity to increase the uptake of molecules across the epithelium of the gut and skin, and to increase their resistance to proteolysis.

This project deals with the 11-residue peptide hormone LHRH. The LAAs and their homo-oligomers, the LPs, will be covalently conjugated to or incorporated into LHRH either with an amide bond or prodrug type linkages. The project has been divided: (1) chemical synthesis of lipoamino acid libraries and a series of delivery system-peptide conjugates with different linkages, (2) examination of biological stability, (3) uptake studies, (4) biological activity assessment.

A Novel System for Gene Delivery

Numerous antisense DNA sequences have been identified as potential new drugs but few have progressed into the clinic, due to (i) lack of absorption/uptake and (ii) rapid enzymatic breakdown. Our project will address these major issues through a highly novel strategy involving ion pair formation of lipophilic dendrimer constructs with an oligonucleotide sequence ODN. We will develop new dendrimer/ODN1 complexes and test them in a well-established animal model for choroidal neovascularisation (CNV).

Particular aims of the project:
1. To produce new dendrimer-oligonucleotide (ODN1) complexes.
2. To test the biological stability and permeability of these dendrimer complexes.
3. Using isothermal micro-calorimetry determine the optimal ratio of the delivery system and the antisense DNA.
4. To test the uptake and biological activity of dendrimer complexes in retinal cells and select the most effective complex for in vivo studies.

Oral Vaccine Delivery

This project aims to develop a novel carrier system, the Lipidic Amino Acid (LAA) system, for the oral delivery of vaccines by exploiting the particulate-forming properties of LAA and LCP amphiphiles, to form micro-particulate oral antigens. The feasibility of these approaches will be investigated using novel peptide antigens currently under
development for a variety of diseases, including those for which no suitable vaccine yet exists.

Exploiting the vesicle-forming properties of LAA and LCP amphiphiles, to form particulate antigens, exploiting the phenomenon of particulate uptake from the GI tract by the GALT or other intestinal sites. The amphipathic structure of these moieties gives rise to characteristic aggregation behaviour, e.g. NMR spectroscopy has demonstrated that LAAs coupled to highly hydrophilic compounds (lactic, glycolic and gluconic acids) formed micelles in aqueous environments, and inverted micelles in the presence of organic solvents. Amphiphiles with appropriate structures spontaneously give supramolecular assemblies such as vesicles when dispersed in water above their transition temperature, and preliminary experiments with a limited number of LAAs have demonstrated their ability to form vesicles alone, or in the presence of cholesterol (unpublished observations) and we propose to proceed with further intensive investigations. Our investigations would extend existing liposomal technology, by developing novel vesicular drug delivery systems, in which vaccine, adjuvant and particulate carrier are contained in the same molecular entity, with considerable control possible, over vesicle size, stability, drug loading, permeability, lipophilicity, antigenicity, in vivo behaviour and other factors.
Our group focuses on using innovative chemistry to produce nanoscaled materials and devices with applications in biology, biotechnology and medicine. Our newly formed research Centre for Biomarker Research and Development is located on the 5th floor of the Australian Institute for Bioengineering and Nanotechnology (AIBN) and has access to state-of-the-art chemistry synthesis and characterisation facilities. Honours students working in these areas will have the opportunity to create nanoscaled biosensor devices for applications in cancer, infectious disease, novel therapeutics, biosecurity and point-of-care devices. Students will also be given the opportunity to work with leading geneticists, epigeneticists and clinical researchers in order to test constructed devices in a real world setting.

Current projects available include:

1) Mining for Biomarkers with Nanotechnology: Early Disease Detection

Diagnostics that detect diseases such as cancer at an early stage, when the disease is most responsive to contemporary therapies, provide the greatest social and economic benefits to society. Unfortunately, current diagnostic protocols typically depend on a complicated variety of tests based on a wide range of different, and often expensive, technological platforms. Each different platform requires significant investment in single-use equipment and training. Despite this investment, results can be ambiguous and require multiple, different tests to produce a confirmed result for a single pathogen. Nanotechnology offers the promise of miniaturized, inexpensive, flexible and robust “plug-and-play” molecular reading systems which can be effectively deployed in the field. In this project, students will develop novel biosensor systems which may be used to greatly aid the discovery and utilisation genetic, epigenetic or proteomic biomarkers for applications in disease diagnosis.

2) Elastic Nanopores for Single Molecule Readout

Genomic differences, including single nucleotide polymorphisms (SNPs) and DNA methylation can be used as potential biomarkers for detecting the predisposition of a patient to a range of diseases. Over the last decade nanopores have generated considerable interest for the high throughput sequencing of DNA. In collaboration with our commercial partner (Izon Pty Ltd), this project will investigate single molecule readout systems utilising a novel flexible nanopore technology. By stretching the nanopore and changing the pore size this instrument can be used for single molecule detection. Students will gain hands on experience in the single molecule
manipulation, along with gaining an understanding of a number of biological and chemistry characterisation techniques.

Schematic showing the elastic nanopore for the detection of DNA-nanoparticle dumbbells for diagnostic applications.

3) DNA Nanomachines for Early Breast Cancer Detection

Every 3 minutes a woman is diagnosed with breast cancer. Despite the increasing incidence of breast cancer in the Western world, death rates have been decreasing since 1990. This is the result of treatment advances, increased awareness and early detection. It is widely accepted that early detection results in much higher survival rates, but it is proving difficult to detect the cancer in its early stages. Subsets of RNA that are not translated into proteins have recently been identified in cancerous growths. These non-coding (nc) RNAs serve as potential biomarkers of disease. Our group is designing, developing and evaluating novel DNA nanomachines to perform tasks that are currently beyond the reach of existing molecular readout technologies. We aim to use these nanomachines as a new technology platform to rapidly detect ncRNA biomarkers in breast cancer patients. This interdisciplinary project combines the latest developments in molecular genetics with cutting edge nanobiotechnology and will provide an opportunity for students to acquire diverse skills in chemistry, molecular biology and biological engineering.

4) Point-of-Care Diagnostics

Point-of-care (POC) diagnostics have the potential to revolutionise global health care by enabling diseases to be rapidly diagnosed ‘on the spot’ using assays that require minimal specialised infrastructure. The simplicity of POC assays enables them to be performed by health care workers or even the patient, which enables rapid diagnosis of a disease. This improves the time taken to treat a disease, leading to better patient care and a reduced rate of mortality and morbidity. POC devices need to be practical, cost effective and portable with high sensitivity and specificity if they are to be used in resource limited settings.

Within our Centre we have an ongoing research program focused on designing and building simple (nanotechnology-based) molecular assays to generate new POC diagnostic technologies. This Honours project will be involved in designing, developing and evaluating novel methods to rapidly amplify and detect pathogenic DNA and RNA using everyday devices such as mobile telephones. This interdisciplinary project combines the latest developments in biological chemistry with cutting edge nanobiotechnology and will provide an opportunity to acquire diverse skills in chemistry, molecular biology, biological engineering, and biotechnology.
Nanoscaled Biosensors for Early Detection of Breast Cancer

We are currently running a major collaborative research project funded by the National Breast Cancer Foundation (NBCF) of Australia. One of the aims of this project is to develop a nanoscaled biosensor technology which can be translated into the clinic for accurate prediction, early detection and diagnosis of breast cancer. This national collaboration involves a unique team of Australian researchers and includes experts in nanotechnology, surgical oncology, epigenetics, cancer genetics, pathology and bioinformatics. There exist opportunities for Honours students with appropriate chemistry or biochemistry experience to join this team in order to work on this exciting project.

Advanced breast cancer is the most complex stage of breast cancer. The identification and treatment of women with early stage breast cancer, who are at risk of developing advanced breast cancer, remains a significant dilemma in breast cancer management. This project aims to address this issue. A novel Nanoscaled biosensor technology (developed within our group) will be coupled with new epigenetic breast cancer markers identified by the Garvan Research Institute in Sydney.

Epigenetics is the term used to describe heritable changes in gene function that occur without a change in the DNA sequence. Mining the aberrant DNA methylation patterns in cancer is critical to understanding the mechanism underlying epigenetic change as CpG methylation is often heterogeneous in clinical samples, with certain CpG sites within the CpG islands acting as ‘seeds’ or ‘hot-spots’ of methylation. These ‘hot-spots’ of methylation provide a positive DNA signal or ‘signature’ that is cancer specific. Recent work has concluded that DNA methylation signatures can be used as an effective and sensitive marker of cancer outcome and therapeutic responsiveness.

This project will involve development of biosensor assays that can ultimately determine methylation signatures from clinical samples.
Synthesis of Photochromic Molecules for Optically-Addressed Electronic-Read Non-Destructive Memory

Organic photochromic molecules are molecules that reversibly switch colour with light, i.e. photoswitch, as shown in Figure 1. Mechanistically, upon exposure of the photochromic molecule to UV-light, there is a geometrical change in the molecule, which alters the \( \pi \)-delocalization, as depicted in azobenzenes in Figure 1.

![Figure 1: A typical photochromic molecule (azobenzene) that changes colour in the presence of light due to a change in conformation.](image)

These photochromic molecules have shown promise for inexpensive optical-based storage media, where the \( \text{trans} \)-isomer could be the “0” logic element and the \( \text{cis} \)-isomer could be the “1” logic element. However, these memory devices are limited because they rely on an ‘optical write’ and ‘optical read’ processes, whereby the ‘optical read’ process actually erases the information (i.e. destructive readout). As illustrated in Figure 1, UV light is used to write (to form the \( \text{cis} \) isomer) while visible light is used to read (to observe the colour). This optical read process actually transforms the molecule back to the \( \text{trans} \)-conformation, thus destroying the state of the molecule. Interestingly, the change in optical properties of organic photochromic molecules also corresponds to a change in the electronic properties (charge transport) of the material, where they switch from insulating to semi-conducting states.

In this project, you will systematically synthesize photochromic molecules to maximize this difference between the insulating to semiconductive states for their use in memory devices. Specifically, you will prepare photochromic molecules (giving you experience in synthetic Organic Chemistry), study their structural, thermal, electronic and photophysical properties (giving you experience in Physical Chemistry) and possibly incorporate into prototype plastic electronic devices.

For more information, please contact Dr. George Vamvounis (g.vamvounis@uq.edu.au) or Kwan Lee (Leek@physics.uq.edu.au) at the Centre for Organic Photonics & Electronics.
Our primary research focus and expertise is orientated around constructing and attempting to construct complex biologically active natural products, drug-like molecules and molecules applicable to nanodevices. These projects not only offer a high level of chemical training but have instilled high level chemical competency in our group. Furthermore, we have established fruitful collaborative synergies with a host of biologists and chemists in Industry and University institutions, see projects below and on subsequent pages.

**Tetranortriterpenes**: We are currently investigating total syntheses of the rearranged tetranortriterpenes, such as, mexicanolide 1. Our group was the first to synthesis azedaralide 2, which for our purposes acts as an advanced intermediate for the total synthesis of both mexicanolide 1 and odoratin 3. In addition, we have isolated authentic tetranortriterpene samples from the *Maliaceae* in Northern Queensland and undertaken chemical modification studies. We are also in collaboration with Dr Trevor Yee and Prof Helen Jacobs from the University of West Indies on the isolation of compounds from Cedrela.

![Chemical structures of mexicanolide 1, azedaralide 2, and odoratin 3](image)

**Diterpene Alkaloids (in collaboration with Dr Paul Savage from the CSIRO)**: The majority of the group’s synthetic expertise derives from on-going investigations into the total syntheses of C20- and C19-diterpene alkaloids and rearranged variants, for example, nominine 4, methyllycaconitine (MLA) 5 and rearranged 6.

![Chemical structures of nominine 4, MLA 5, and rearranged 6](image)

We have successfully synthesised the advanced intermediate 7 and are close to completion of 8, not to mention synthesising countless derivatives for screening.

![Chemical structures of intermediates 7 and 8](image)

**Nanodevices from Organosilver reagents (in collaboration with Dr Jason Harper and Prof Justin Gooding at UNSW)**: In 2007 the Williams group published new methodology for making carbon-carbon bonds at quaternary carbons using organosilver reagents, for example,
compounds 9-11. This work demonstrated that molecules amenable to certain nanotechnological development are now accessible.

Projects in this area will involve investigating new dimensions in organosilver reactivity and synthesising molecules suitable for surface modification (nanodevices).

**Cubane Chemistry: A Benzene Ring Drug Isostere? (in collaboration with Dr Paul Savage from the CSIRO):** Cubane 12, when viewed from the corners can be considered roughly the same size as a benzene ring (i.e. 13). This is equally true when you take into consideration the pi clouds of benzene, that is, cubane is about the same "thickness". Therefore the 1,2-, 1,3- and 1,4-substituted cubanes are similar to o-, m-, and p-substituted benzenes respectively. Furthermore, the cubane structure is actually very stable – cubane ring-opening is thermally disallowed by orbital symmetry.

With this in mind the project would involve replacing the phenyl ring in a current drug molecule and comparing biological assay data.

**Vibsanin Diterpenes:** Recently we have completed the total synthesis of Vibsanin E (14) and O-methylneoivibsanin H 15 using a proposed biosynthetic pathway. With this success we foresee access to other natural products in this family.

**Design and Synthesis of Anti-Breast Cancer Compounds:** (in collaboration with Dr Melissa Brown and Dr Luke Guddat from Biochemistry). Three enzymes have been identified by microarray data to be targets for the development of breast cancer drugs. Structure-based design techniques will be used to discover inhibitors of these enzymes. Projects in organic synthesis and rational structure based drug design are available.

**Discovery and Development of Novel Analgesics:** (in collaboration with Prof Maree Smith from Pharmacy). The prevalence of painful diabetic neuropathy (PDN) is 7% within a year of diagnosis of diabetes and 50% by 25 yrs of diabetes. The medicines currently used to treat PDN are not effective in ≥ 50% of patients. Hence, we propose to develop new, effective medicines for the alleviation of PDN.

Honours and PhD projects are available in all aspects of our work.