A*Star-Oxford Programme

Project Booklet

March 2010
This booklet contains just a selection of the many projects on offer at University of Oxford in 20010-11 to holders of A*Star Graduate Scholarships and National Science Scholarships (PhD). All the supervisors listed here are interested in hearing from you and exploring whether your scientific interests match their own.

The 72 projects listed here are just a starting point for you. Look at the websites for further information about the department, research group, or project. You will find further projects on offer or other research groups that you might like to work with. If you are keen to work with a group not listed in this guide, then write a short email (initially) to the Principal Investigator to see if he or she is able to accept a research student at this time. Always copy your correspondence to astar@medsci.ox.ac.uk so that we can help both you and the supervisor to agree a suitable project.

You may also wish to start exploring research studies at University of Oxford by looking at the Graduate Prospectus – go to http://www.ox.ac.uk/ and follow information for 'Admissions - Postgraduate Courses'. You will find links to all the relevant departments in the Medical Sciences Division and the Mathematical, Physical and Life Sciences Division. In every department there is a Director of Graduate Studies who will be pleased to help answer your queries about working there.

The Oxford administrator for the A*Star-Oxford Programme can be contacted by email at: astar@medsci.ox.ac.uk.

Last updated 5 March 2010
In this booklet, projects are grouped by Department, Institute or Unit

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For further projects in the Nuffield Department of Clinical Medicine see:

http://www.ndm.ox.ac.uk/page/graduate-studies
The following projects are available for A*Star students subject to a suitable A*Star co-supervisor being identified, and subject to approval of the Academic and Advisory Board of the A*Star-Oxford Programme

**Biochemistry**

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<th>Supervisor: Professor Judith Armitage, Department of Biochemistry</th>
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**Project title:** Interdisciplinary analysis of protein dynamics in bacterial sensory systems.

**Project description:** Interdisciplinary analysis of protein dynamics in bacterial sensory systems. We are using R. sphaeroides to investigate (i) the mechanisms involved in controlling expression of the different chemotaxis genes, (ii) the localisation of the different chemotaxis protein homologues to different sites in the bacterial cell, (iii) the segregation of chemotaxis proteins on cell division, (iv) the integration of the different environmental signals, (v) the mathematical modelling of the signalling pathway from the receptors to the flagellar motor.

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<th>Supervisor: Professor Neil Brockdorff, Department of Biochemistry</th>
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**Project title:** Developmental Epigenetics.

**Project description:** Developmental Epigenetics. Epigenetic mechanisms, notably post-translational modification of histones, non-coding RNAs, and DNA methylation, play a key role in selective gene expression. We are interested in understanding X chromosome inactivation, a classical model for epigenetic regulation of the genome. Key questions that we are addressing are:

1. How do cells regulate Xist expression to ensure appropriate X inactivation patterns are established in early development?
2. How does Xist RNA induce chromosome wide silencing?
3. What are the mechanisms for maintaining X inactivation through successive cell divisions? and
4. How is stable silencing of the inactive X reversed in pluripotent cells?
**Supervisor:** Professor Louis Mahadevan, Department of Biochemistry; A*Star collaborator: Dr Huck Ng, Genome Institute of Singapore  

*For further information:*  
http://www.bioch.ox.ac.uk/aspsite/research/brochure/Mahadevan/  

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**Project title:** Signal transduction, chromatin modification, and gene regulation in mammalian cells.  

**Project description:** Present research in this laboratory centres (i) on understanding the complexity of signalling systems controlling IE genes especially the quantitative influences observed, (ii) on linking modified nucleosomes directly with IE gene chromatin and associated transcription factors and coactivators by immunoselection with antibodies that recognise modified histones and (iii) on developing chromatinised transfection-based model systems in which the complexity of these processes is preserved and can be conveniently studied.

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**Supervisor:** Dr Alison Woollard, Department of Biochemistry; A*Star collaborator: Professor Yoshi Ito  

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**Project title:** Regulating stem cell proliferation and differentiation in C. elegans  

**Project description:** We are using the superb model organism *Caenorhabditis elegans* to study stem cell biology. Using genetic approaches we have isolated mutants that have defects in the division patterns of the neuroectodermal seam stem cells and thus identified genes that are important for stem cell proliferation and differentiation. Amongst the genes we are working on are homologues of several known regulators of human stem cells, including the Runx/CBFb transcriptional partnership implicated in several cancers including leukaemias. Thus we are using the worm as a model system to identify conserved gene networks that may contribute to human disease.

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**Supervisor:** Dr Phil Biggin, Department of Biochemistry  

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**Project title:** Molecular Dynamics simulations of Ionotropic glutamate receptors.  

**Project description:** We are developing and applying computational methods to examine conformational changes and properties of ligand-binding that occur within receptor proteins. We are particularly interested in two distinct families of receptors: 1. The
ionotropic glutamate receptors and 2. The nicotinic acetylcholine receptor. Although there has been a recent increase in the amount of structural information available, many questions still remain concerning the dynamics associated with these processes (see Figure 1). For example, how does the binding of agonist cause the transmembrane domain to open? What determines whether an agonist will act as a full or partial agonist? How can channel opening be modulated? How do certain compounds interfere with the process of desensitization?

Project title: Molecular interactions in human fibronectin.

Project description: Fibronectin (FN) is a vital protein of the extracellular matrix (ECM) which is the structure used to support and anchor tissue cells. FN is comprised of many, relatively small, domains that have been well studied in isolation1 but the details of many of the interactions, as well as the structural properties of large FN fragments, are not well understood2. This laboratory has studied FN for a number of years and now has well established protocols for producing a wide range of FN fragments for biophysical studies. The laboratory also has high level expertise in NMR, X-ray crystallography and a wide range of biophysical methods.

Cancer Research, Ludwig Institute of

Project title: Regulating p53 function by the ASPP family of proteins in Zebrafish

Project description: The apoptosis stimulating proteins of p53 (ASPP) family consists of three members: ASPP1, ASPP2 and iASPP. They bind to proteins such as p53, Bcl-2 and RelA/p65, key players in the control of apoptosis, and proteins involved in cell growth such as APCL and PPI. ASPP is an evolutionarily conserved protein family. Invertebrates such as *C. elegans* have only one member of the ASPP family, iASPP, which inhibits p53 induced apoptosis in germ cells in response to DNA damage. Importantly, the ability of iASPP to inhibit p53 induced apoptosis is conserved from *C. elegans* to humans (Bergamaschi *et al.*, 2003). iASPP is, therefore, one of the most conserved inhibitors of p53 identified to date. Interestingly, in vertebrates, there are three members of the ASPP family (ASPP1, ASPP2 and iASPP). This evolutionary pattern also exists for p53, as
there are three p53 family members: p53, p63 and p73 (Trigiante and Lu, 2006).

The tumour suppressor protein p53 is lost or mutated in over 50% of human cancers, with defects in its regulatory pathway in the other half. A transcription factor, p53 plays an important role in regulating the proliferation of cells, either through apoptosis or cell-cycle arrest. Our previous studies have shown that the ASPP family proteins are common regulators of the p53 family (Murray-Zmijewski et al., 2008). Furthermore, unlike iASPP, ASPP1 and ASPP2 stimulate the apoptotic function of p53 and its family members, p63 and p73. However, it remains unknown how the specific regulation between the ASPP and p53 family members is achieved. Understanding how the ASPP family selectively regulates the p53 family of proteins is essential to our understanding of human cancers, and an important step in the quest to identify agents that can selectively activate the tumour suppressor function of p53. Transgenic mouse studies have shown that both p63 and p73 play important roles in controlling mouse development, whereas p53 deficient mice are viable without gross developmental defects. However, the evolutionary conservation of the ASPP and p53 families enables us to also conduct knockout studies in Zebrafish, a well-established vertebrate model system in which p53 has been extensively studied (Lee et al., 2008). This system enables knockouts to be generated much quicker than is possible in mice. This project, in collaboration with David Lane’s research laboratory, will therefore use Zebrafish to investigate the specific regulation of the p53 protein family by the ASPP protein family, in addition to the application of molecular and cellular biology techniques.

Supervisor: Professor Xin Lu, Ludwig Institute for Cancer Research; A*Star collaborator: Dr. Jean Paul Thierry at IMCB

For further information: http://www.ludwig.ox.ac.uk/

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Project title: Investigating the role of the ASPP family of proteins in regulating adherence junction

Project description: Adherens junctions have been shown to be important in the initiation and stabilisation of cell-cell adhesion, intracellular signalling and the regulation of transcription. Major components involved in the formation of adherens junctions are the cadherin superfamily and the catenin family, which includes γ-catenin. In addition to being a constituent part of adherens junctions, γ-catenin acts as a transcriptional co-activator of the Wnt signalling pathway, which is associated with the maintenance or activation of stem cells. Importantly, many of the genes activated in response to the Wnt/γ-catenin signalling pathway are implicated in the progression of cancer, and the involvement of γ-catenin in cellular adhesion also has important implications in how tumour cells metastasise within the body (Barker, 2008). Furthermore, adherens junctions and the Wnt/γ-catenin signalling pathway are known to play important roles in the control of the development of the CNS (Thiery, 2003). Unpublished data from the detailed analysis of ASPP2 transgenic mice has revealed that, in addition to its ability to suppress tumour growth and enhance the tumour suppression function of p53, ASPP2 controls the integrity of adherens junctions of neural progenitor cells. This project, in collaboration with Jean Paul Thiery’s research group, will focus on the function of the
ASPP proteins at both adherens junctions and in the Wnt signalling pathway, using \textit{in vivo} mouse models and a variety of molecular and cellular biology techniques including confocal and time-lapse microscopy. Analysis of whether or not the ASPP family of proteins is important for Wnt signalling will also be conducted. Importantly, this project may shed light on the molecular basis of cell migration and tumour metastasis, as these processes are fundamental to tumour growth and progression.

### Chemistry

**Supervisor:** Professor Véronique Gouverneur, Chemistry Research Laboratory  
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**Project title:** Innovative 18F-Radiochemistry to Advance Biomedical Imaging  
**Project description:** Non-invasive biomedical imaging technologies are believed to be important tools to reduce dramatically the high cost associated with drug discovery and development. Functional molecular imaging such as Positron Emission Tomography (PET) is widely recognised as a valuable modality for early systems biology measurements and to answer follow-on translational questions. In addition to accelerate novel therapeutics discovery, PET (non-metallic positron emitters are 11C, 18F, 15O) is a very useful enabling technology to understand disease state and therefore contribute to rapid progress in the diagnosis and management of diseases. These considerations have fuelled a lot of interest in 18F radiochemistry and in the development of methodologies for late fluorination (18F, \( t_{1/2} = 109.7 \) min). This research project will focus on the development of novel 18F-radiochemistry for PET with the longer-term aim to prepare 18F-radiotracers designed to support drug discovery programmes within the pharmaceutical industry. We propose to approach this problem by exploring transition metal chemistry for the production of important 18F-radiotracers, which are not within reach with the radiochemistry available to date.

**Supervisor:** Dr Jeremy Robertson  
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**Project title:** Mechanism based complexity generating reactions for efficient organic synthesis  
**Project description:** This project will develop further our ongoing interest in developing cascade reaction sequences that result in polycyclic products with defined stereochemistry from simple acyclic precursors in a single reaction vessel. Typically, these processes are characterised by the formation of 'high chemical potential' intermediates by the combination of two 'loaded' functional groups; these intermediates are then entered into a diverse range of secondary processes depending on the presence or addition of activating electrophile/nucleophile combinations or cycloaddition
components. Examples will include processes initiating from allene + azide or allene + metal nitrenoids that result in nitrogen heterocycles. The methodology will be applied in the total synthesis of structurally complex bioactive alkaloids.

**Supervisor:** Dr Mark G. Moloney  
**For further information:** [http://www.chem.ox.ac.uk/researchguide/mgmoloney.html](http://www.chem.ox.ac.uk/researchguide/mgmoloney.html)  
**To contact:** mark.moloney@chem.ox.ac.uk

**Project title:** Synthetic Organic Chemistry for Novel Antibacterials and Bioactive Polymers  
**Project description:** Research interests encompass the synthesis of functionalised, saturated enantiopure nitrogen heterocycles, the development of new synthetic methodology using main group metal-mediated reactions, and the development of direct chemical methods for the surface functionalisation of materials, and their commercial exploitation. The current focus unifies these diverse themes into the development of wholly novel bioactive polymers designed for the targeted delivery of antibacterial agents.

**Supervisor:** Chris Schofield  
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**Project title:** The chemistry of epigenetics and oxygen sensing  
**Project description:** Projects are available in chemical, structural, and biological aspects of work on oxygen sensing and epigenetic regulation by enzymes. Our work involves the design and synthesis of inhibitors for use as mechanistic probes, structural and mechanistic work on enzymes of biomedical importance, and basic science work on the regulation of transcription by oxygen. Recent publications: Structural Basis for Binding of Hypoxia-Inducible Factor to the Oxygen-Sensing Prolyl Hydroxylases, Structure, 2009, 17, 981-989; Jmjd6 Catalyses Lysyl-Hydroxylation of U2AF65, a Protein Associated with RNA Splicing, Science 2009, 325, 90-93; Structural and mechanistic basis of penicillin-binding protein inhibition by lacticins, Nature Chemical Biology 2007, 3, 565-569; Crystal structures of histone demethylase JMJD2A reveal basis for substrate specificity., Nature 2007, 448: 87-91.

**Supervisor:** Professor Ben Davis  
**For further information:** [http://users.ox.ac.uk/~dplb0149/research/index.html](http://users.ox.ac.uk/~dplb0149/research/index.html)  
**To contact:** ben.davis@chem.ox.ac.uk

Research projects falling under the broad headings of carbohydrate and protein chemical biology
**Supervisor:** Dr Michael Willis  
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*To contact:* michael.willis@chem.ox.ac.uk

**Project title:** New Applications of Palladium Catalysis in Natural Product and Medicinal Chemistry  
**Project description:** The project will be based on developing new palladium catalyzed processes such as C-H functionalisation and sulfonylation-type reactions, and then exploring their utility in synthesis. In particular, we will target specific natural product and medicinal chemistry target molecules.

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**Supervisor:** Professor Darren J. Dixon  
*For further information:* [http://www.chem.ox.ac.uk/researchguide/ddixon.html](http://www.chem.ox.ac.uk/researchguide/ddixon.html)  
*To contact:* darren.dixon@chem.ox.ac.uk

**Project title:** Discovery and development of new synthetically powerful catalytic methodologies for the construction of complex natural products  
**Project description:** The complex three-dimensional structures of many natural products give rise to their exquisite and desirable biological properties (anti-cancer, anti-malarial etc. activities, potency, selectivity, bioavailability) but prevent access via the traditional, one-step, one-pot chemical synthesis approaches. However, the development and strategic implementation of new synthesis-enabling reaction methodologies and reaction cascades into chemical routes from appropriate and readily available starting materials can now allow the construction of the complex target molecules in 10-15 steps, compared with 30-40 steps using traditional approaches. Accordingly these molecules (and libraries of analogues) may now be made at speed and on gram scale. Relevant to the synthesis of a broad range of complex alkaloid natural products the following methodology discovery and development projects are available:  
1) New catalytic asymmetric organocatalytic intramolecular Michael addition reactions to access natural product cores with high enantio- and diastereoselectivity.  
2) New chiral Bronsted acid catalysed N-acyliminium ion cyclization cascades to construct architecturally complex natural products in enantiopure form in one step.  
3) Unprecedented dual transition metal ion and organocatalyst methodologies for the asymmetric construction of carbon-carbon bonds from low reactivity substrates.
Computing Laboratory

Supervisor: Dr Andrew Martin, Computing Laboratory; Singapore Supervisor: Prof. DONG Jin Song (NUS Graduate School)
For further information: www.trustedcomputinggroup.org
To contact: andrew.martin@comlab.ox.ac.uk

Project title: Verifiable Trusted Computing

Project description: The technologies of Trusted Computing have immense potential to improve the security of distributed computing systems, infrastructure, and mobile devices. However, software continues to be deployed which exhibits weaknesses and vulnerabilities. Many of the components of trusted infrastructure have not themselves been verified for correctness or freedom from implementation flaws. This project will explore how to combine the best technologies for a priori software verification - proof and model-checking - with the trusted computing capabilities for runtime assurance: so that over-all, we may know that the software is correct, and that the correct software is loaded on a remote device. In this it will draw on expertise in Oxford on trusted computing, and in NUS in software verification.

Supervisor: Dr Jeremy Gibbons, Computing Laboratory
For further information: http://www.comlab.ox.ac.uk/projects/gip/index.html
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Project title: Generic and indexed programming

Project description: "Generic programming" is about making programs more widely applicable via exotic kinds of parametrization: not just along the dimensions of values or of types, but of things such as the shape of data, algebraic structures, strategies, computational paradigms, and so on. "Indexed programming" is a lightweight form of dependently typed programming, constraining flexibility by allowing one to state and check relationships between parameters: that the shapes of two arguments agree, that an encoded value matches some type, that values transmitted along a channel conform to some protocol, and so on. The two forces of genericity and indexing balance each other nicely, simultaneously promoting and controlling generality. We have been exploring this area, looking particularly at its influence on the design of programming languages.
### Reusability and Dependent Types

**Project title:** Reusability and Dependent Types

**Project description:** "Well-typed programs cannot go wrong": types can be used to catch runtime errors. Dependently typed programming exploits the power of very expressive type systems to deliver stronger guarantees of correctness — but also additional support for software development, using types to guide the development process. However, expressive type systems have their price: more specific types inhibit code reuse. This phenomenon already shows up in the traditional Hindley-Milner style type system of ML and Haskell; it becomes even more prevalent in a dependently typed setting. Luckily, all is not lost: dependent types are expressive enough that they can talk about themselves reflectively, making meta-programming one of its potential killer applications: combining expressive types and reusable software components. We are exploring two approaches to supporting reliable reuse of software components — reusability by structure and reusability by design — both expressed within a dependently typed framework.

**Supervisor:** Dr Jeremy Gibbons, Computing Laboratory

**For further information:** [http://www.comlab.ox.ac.uk/projects/gip/index.html](http://www.comlab.ox.ac.uk/projects/gip/index.html)

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### Model checking for ubiquitous computing software

**Project title:** Model checking for ubiquitous computing software

**Project description:** Ubiquitous computing is now widespread, involving a range of computing devices, such as laptops, mobile phones and sensor equipment. Two important characteristics pertain to ubiquitous computing software: increased rate of failure, due to inherent unreliability of wireless transmission and low power, and limited resources such as memory and computing power, in view of their embedded nature. This project aims to develop software verification methods for ubiquitous computing, with emphasis on static quantitative predictions of resource usage, such as sizes of data structures, memory bounds and expected time, in presence of probabilistic failures and pointer-based data structures. The project will build on recent advances at Oxford and NUS, respectively concerning verification of probabilistic programs ([http://www.prismmodelchecker.org/bibitem.php?key=KKNP09](http://www.prismmodelchecker.org/bibitem.php?key=KKNP09)) and automated inference of resource bounds ([http://www.comp.nus.edu.sg/~chinwn/papers/ismm08.pdf](http://www.comp.nus.edu.sg/~chinwn/papers/ismm08.pdf)).

**Supervisor:** Professor Marta Kwiatkowska, Computing Laboratory; A*Star collaborator: Chin Wei Ngan

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Supervisor: Professor Nicolas Smith and Professor Jon Chapman, Computing Laboratory
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Project title: Developing patient specific continuum model of blood supply to the heart

Project description: Advances in high performance medical imaging and modelling have led to the development of detailed models of vascular structure. Recent developments in Nuclear Medicine (PET imaging) from our industrial and clinical collaborators (Philips Research and St Thomas' Hospital respectively) now also provide the ability to accurately measure blood volume in cardiac tissue. This presents a new opportunity to develop a novel computational modelling framework combining the principles of solid and fluid mechanics to predict whole organ perfusion through the development a multi-scale porous-flow model. By personalizing this model to individual patients the goal of this work will be to directly interpret clinically acquired perfusion images and guide coronary revascularisation strategies.

Engineering Science

Supervisor: Dr Ian Reid, Department of Engineering Science
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Project title: Smart visual sensing

Project description: Using techniques and algorithms developed over the course of the last two decades, computers can now routinely be connected to video cameras and compute various useful data about the environment such as the geometry of a scene, to track targets, or to recognise specific objects. Nevertheless there remains a significant gap between the effortless way that humans both acquire and use sensed data, and in particular the apparently fluid way that high and low-level information is combined. Notably missing from existing computer vision algorithms is the set of connections between high-level interpretations of scenes, reasoning about visual scenes, and the role of sensing. The aim of this project is to consider mechanisms for reasoning about high-level visual information in order to influence subsequent sensing decisions, such as where a robot should move, or where a pan-tilt-zoom camera should look. More specifically, within the Active Vision Group we have been pursuing an information theoretic approach to sensor placement and sensor control, in parallel with novel algorithms for action recognition. In this project we aim to bring these together to investigate how high-level reasoning can influence sensing decisions, and how strategic sensing can positively benefit high-level visual interpretation.
Project title: Structure, strength and stiffness of porous (bio)materials

Project description: Porous materials offer very interesting combinations of stiffness and strength with low density, and are widespread in biological systems (e.g. bones) and in structural engineering applications. The relationship between the structure and mechanical properties of these systems have been the subject of extensive studies. Whereas in most cases the structures are investigated by considering two-dimensional cross-sections, in the present study three-dimensional structural and mechanical analyses will be carried out with the help of synchrotron X-ray tomographic imaging and diffraction. Special in situ loading arrangement will be developed for use on the JEEP engineering beamline station at Diamond Light Source near Oxford. Finite element models will be developed to represent the structures, and deformation of porous structures will be simulated. The results will improve the understanding of the properties of natural systems, and improve the ability to design porous load-bearing structures.

Project title: Preclinical image analysis of hypoxia

Project description: In molecular imaging, imaging devices such as microPET-CT and microMRI are being used increasingly to investigate the efficacy of novel imaging agents, including radiotracers (PET) and contrast agents (MRI, Ultrasound) both to deepen our knowledge of cancer and to determine novel targets for chemotherapy and radiotherapy. In an ongoing collaboration between the Departments of Engineering Science, Chemistry, and ROB (supported by Siemens and the UK Department of Industry), we are assessing the potential of novel hypoxia-selective compounds at the in vitro level. This work includes studying and modelling hypoxia selectivity, redox potential, mechanism of action, lipophilicity, and mode of cellular transport. The preclinical imaging suite at ROB, similar to that in existence at A*STAR, offers a range of microPET-CT, US and microMRI imaging devices (as well as a range of optical microscopy) to determine biodistribution and spatiotemporal tumoral kinetics as well as physiological measures such as flow. This project complements the work currently underway in Oxford by concentrating on image analysis. More specifically, robust image analysis techniques are needed to reliably determine tumour blood flow, vascular permeability and the true spatiotemporal distribution of hypoxia tracers from noisy data. Biology-inspired models are needed to translate findings from in vitro data to the results of multimodal preclinical studies. It is anticipated that the results of this work would feedback into the development process of new hypoxia tracers.
**Project title:** Large volume offshore structures and waves in the deck

**Project description:** Waves into the deck of structures are still a major cause of structural damage and operational downtime for oil and gas production offshore. This occurs for both concrete gravity based fixed platforms and also floating structures such as TLPs and semis. Thus, this remains a major concern to both platform designers and operators.

Given the new initiative at NUS through the A* programme to look at waves in the deck of steel jacket-type platforms, we seek to extend their work and to link it in with our research in Oxford. For multi-column structures violent wave-structure interaction can lead to extreme water projection upwards. This can occur in front and between the front legs, close to the legs or beneath the middle of the platform, the precise location and severity being very dependent on the details of the incoming wavefield.

At Oxford we have developed one of the leading wave diffraction codes, emphasising in recent years free-surface motion around structures. As of Jan.09 we are just starting a new BP sponsored CASE award to examine Gulf of Mexico semis in extreme waves. We seek to collaborate with Prof Choo’s group in Civil Engineering at NUS, with whom we have had some preliminary discussions. A student from Singapore could build and model test particular structural layouts in a wave basin at NUS, and analyse and compare the physical water motion against the diffraction results.

This collaboration would be very useful training in both leading experimental techniques and data analysis, as well as diffraction analysis which would be carried out in Oxford. The use of localised wave groups in the tank would provide high quality experimental data to explore the degree to which 2nd order diffraction modelling can be used for optimization of layouts to reduce the risk of structural damage.

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**Supervisor:** Professor David Murray, Department of Engineering Science

**For further information:** [http://www.eng.ox.ac.uk/postgrad/research.html](http://www.eng.ox.ac.uk/postgrad/research.html)

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**Project title:** Interactive video-rate model-building for augmented reality

**Project description:** Augmented reality differs from virtual reality in that augmentations are applied to live video images of real scenes. This is an extremely challenging problem, requiring recovery of the 3D structure of the environment, the camera’s location within that environment, and understanding or recognition of the environment sufficient to add graphical augmentations of real value to the user. In current applications of AR this is achieved by having a strong model of what is being viewed -- for example the camera user might be a maintenance technician viewing a jet engine whose CAD model is available. Recent advances in both the recovery of structure from
motion and the appearance-based recognition of objects at video-rate hold great promise, but there is substantial work still to do in the gap between geometry and appearance, which are both based on sparse point representations. This project will address issues in the on-line building of object models, their insertion into the scene, and their use as an aid to camera tracking. To aim for complete autonomy is out of the question, and a key issue will be how actively to involve the user in these processes.

**Supervisor:** Professor Steven Roberts, Department of Engineering Science  
**For further information:** [http://www.eng.ox.ac.uk/postgrad/research.html](http://www.eng.ox.ac.uk/postgrad/research.html)  
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**Project title:** Sequential decision making in uncertain, dynamic environments  
**Project description:** Optimal decision theory, based on maximizing Bayesian probabilities, allows for decisions to be made based on observed data. In many real applications, however, the assumptions often made in such models are not viable. Real systems have missing, corrupted and delayed observations and the utility of decisions and actions may change with time. Furthermore, data is observed sequentially and actions, once decided upon, cannot be undone. This project aims to develop highly adaptive sequential models for multiple action and decision making and to extend the theory and the models to enable coping with:  
- delayed or missing data,  
- unknown systematic and stochastic errors,  
- sequences of decisions are required,  
- observations of the real-world are costly.  
Candidate applications lie in the areas of multi-agent and multi-sensor co-ordination, optimal resource allocation; preliminary work in this area has focused on problem domains from medical signal processing, weather sensor networks and computational finance.

**Supervisor:** Professor Alison Noble, Department of Engineering Science  
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**Project title:** Biomechanical properties measurement for cancer diagnosis and therapy  
**Project description:** Measurement of tissue elasticity (typically strain) is used in diagnosis of cancers (cancers are typically stiffer than health tissue) as well as has the potential to be used in therapy monitoring. In an on-going collaboration between the Department of Engineering Science and the Oxford Breast Care Unit, we have been looking at ultrasound-based tissue elasticity assessment. We have recently completed a 70 patient study on using strain and slip imaging for breast cancer mass characterization and are currently looking at mass sizing based on elasticity images, hypothesizing that sizing based on elasticity gives a better indicator of true size (with true size determined from
The visual correlation of ultrasound elasticity with histology is revealing some fascinating results – possibly suggesting that the strain patterns could be used instead of a(n invasive) biopsy for mass characterization. This project would investigate the relationship between tissue elasticity measurement, changes in a cancer during treatment, and histology in more depth using finite-element modelling and image analysis techniques. Both 2D and 3D elasticity imaging will be considered. Results from this work would clearly have potential impact in healthcare for both cancer diagnosis and therapy monitoring.

**Project title:** A visual Google for Sculptures

**Project description:** There has been tremendous progress in the Computer Vision field over the last decade in recognizing specific objects in images. Advances in visual features and efficient matching methods have enabled an object to be recognized despite changes in view point, imaged size and illumination. For example, given a query image of a building facade, buildings can be retrieved immediately from a database of hundreds of thousands of images by visual matching, in the manner of a Google web page match to a text query. See the demo at http://www.robots.ox.ac.uk/~vgg/research/oxbuildings/. However, these visual methods are currently restricted to near planar objects. This project is aimed at developing the next generation of visual representations that can match 3D objects, such as sculptures. The added visual difficulty of a sculpture is that the surfaces that are seen can be entirely different from distinct view points. As well as investigating visual matching of 3D objects, the project will also research automatically identifying the sculptures. Here an image of a sculpture will be used to search the photos on the web for a match, and hence identify the sculpture from the surrounding text on the web pages.

**Supervisor:** Prof. G.T. Houlbsy, FREng and Dr B.W. Byrne, Department of Engineering Science; Co-supervisor at NUS: Prof. Leung Chun Fai

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**Project title:** Installation of Jack-up Units in Multilayered Soils

**Project description:** Jack-up units are large mobile offshore platforms used for drilling exploratory and production wells for the oil and gas industry. There are some 400 units operating worldwide, and their safe installation and removal is essential to the industry. They are now used increasingly in new regions (e.g. South East Asia, West Africa) outside the areas of principal previous experience (North Sea, Gulf of Mexico). A recent
The joint industry study “InSafeJIP” (see details below) has identified particular areas where significant uncertainties lie in the prediction of the installation of jack-ups. In many new regions, the soils encountered include complex layered systems of sands and silts. The purpose of the proposed research is to develop comprehensive methods for predicting jack-up performance on these layered soils, building on previous research at Oxford on single-layer systems and at NUS on 2-layer systems. As part of the InSafeJIP project an unprecedented database of over 100 case records has been assembled, many of them involving layered soils, and this will provide essential data against which the results of the new research can be tested.

The successful candidate would work principally at Oxford University, using the specialised testing equipment that has been developed there for testing model offshore foundations. He/she would also spend a minimum of 18 months in Prof. Leung’s laboratory at NUS, to carry out a parallel series of tests using the geotechnical centrifuge.

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**Experimental Psychology**

**Supervisor:** Professor Nick Rawlins, Dr David Bannerman and Dr David Sanderson, Experimental Psychology

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**Project title:** Investigating the link between hippocampal long-term potentiation and memory

**Project description:** It is widely believed that LTP-like events in the hippocampus underlie certain forms of learning and memory (see Martin et al., 2000). Evidence in support of this theory has been derived from studies in which manipulations that block LTP have also been found to disrupt hippocampal dependent forms of learning, such as spatial learning. For example, the NMDA receptor antagonist, AP5 blocks the induction of LTP and disrupts spatial learning in the Morris watermaze (Morris et al., 1986). More recently, however, a number of studies have suggested that spatial reference memory acquisition can proceed normally despite the absence of LTP in the hippocampus if the animals have received spatial pretraining prior to testing with the drug (Bannerman et al., 1995; Saucier and Cain, 1995). In contrast, spatial working memory is still impaired by AP5 in pretrained rats (Tonkiss & Rawlins, 1991; Morris & Steele, 1999). Furthermore, studies involving transgenic mice which lack the GluR-A AMPA receptor subunit have been found to be deficient in terms of hippocampal LTP but show apparently normal spatial reference learning and memory in the watermaze (Zamanillo et al., 1999). These GluR-A knockout mice do, however, display a striking spatial working memory impairment (Reisel et al., 2002; Schmitt et al., 2003). These results suggest that different mechanisms within the hippocampus may support different kinds of memory processing, and that NMDAR/GluR-A dependent LTP may support a “non-associative” spatial memory trace but is not required for associative learning such as spatial reference memory acquisition. Experiments will further investigate the relationship between different kinds of hippocampal synaptic plasticity and different
forms of hippocampal-dependent learning and memory. They will involve the
behavioural phenotyping of genetically modified mice in which subunits of either the
AMPA receptor or the NMDA receptor have been altered.

Supervisor: Professor Dorothy Bishop, Department of Experimental Psychology
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Project title: Assessing cerebral lateralisation using functional transcranial Doppler ultrasound (fTCD)

Project description: fTCD is a relatively new method for assessing cerebral lateralisation
by comparing blood flow in the two middle cerebral arteries as the subject performs a
task. This method has been developed by Knecht and colleagues, who have found that
left hemisphere activation is typically seen in a word generation task. The method has
good time resolution and is easier to use than functional MRI, but it is still relatively
new. Our research group has replicated the basic finding of left hemisphere activation in
the word generation task in normal adults. There are several potential projects that
could be developed using this method; of particular interest to the supervisor would be
studies to address the question of what determines whether a language task will show
cerebral lateralisation. So far we have replicated Knecht’s findings with word generation
and also developed a story description that is suitable for children. We would be
especially interested to develop receptive language tasks that could be used with
nonliterate participants.

Unless participants are recruited via the NHS, approval for these studies would be
sought via the University Ethics Committee (IDREC). The student would be given
training in measuring blood flow with fTCD: it takes some skill to learn to locate the
middle cerebral arteries, but it should be possible to become competent in a week or
less.

Functional Magnetic Resonance Imaging Group

Supervisor: Steve Smith & Christian Beckmann, Functional Magnetic Resonance Imaging
Group
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Project title: Mathematical analysis of "resting-state" functional networks in the brain

Project description: In recent years the study of functional networks in the "resting"
brain, as imaged by Functional MRI, has become an exciting area of brain imaging
research. Resting state networks (RSNs) have been the subject of many studies into
their true nature ("Are RSNs really neural functional networks?") and their applications
("Are RSNs sensitive early markers for diseases such as Alzheimer’s and
There are, however, many fundamental questions that still need thorough research, a good number of which relate to the mathematical techniques (primarily independent component analysis) used to analyse resting FMRI data. In this project we will address issues such as: developing optimal analysis techniques for comparing and contrasting the spatial and temporal characteristics of RSNs across different subjects and different pathology groups; investigating temporal relationships between different resting networks; characterising the hierarchy of different resting networks and investigating the consistency of this across different subjects, in part to produce an "RSN atlas"; optimal discrimination of the resting FMRI signal into that truly caused by resting functional networks and that part caused by "uninteresting" non-neural physiological changes; investigating how the networks’ spatial patterns are also present as structured covariance in other MRI modalities such as structural MRI and functional activation databases.

For all Analysis Group projects, students will need good mathematical/engineering and computing skills, and through the projects will acquire a strong set of skills in all or most of the following areas: medical image and signal processing, Bayesian modelling, machine learning, multivariate model-free techniques (e.g. independent component analysis), biophysical modelling.

**Supervisor:** Karla Miller, Functional Magnetic Resonance Imaging Group

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**To contact:** karla@fmrib.ox.ac.uk

**Project title:** Novel image contrast

**Project description:** Magnetic resonance imaging has unprecedented flexibility in its ability to produce images with a wide range of information about different tissues in the body. By combining knowledge of MRI physics with engineering techniques and basic physiology, we have developed a number of methods for manipulating the MRI signal to obtain images with novel contrast in the brain. These include new methods for measuring brain activity, neuronal connections, and tissue microstructure. This work involves research at many different levels, including modeling of the underlying physics, the development of new scanning techniques and development of new analysis methodology. This research requires a strong background in engineering, physics, or mathematics, and good programming skills.

**Supervisor:** Dr Stuart Clare, Functional Magnetic Resonance Imaging Group

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**To contact:** stuart@fmrib.ox.ac.uk

**Project title:** Ultra-high field MRI physics

**Project description:** The FMRIB centre is preparing to site the second 7 Tesla human MRI scanner in the UK. This instrument represents the state-of-the-art in MRI physics,
and will take Oxford to the forefront of research in areas including hardware development, radiofrequency pulse design, and real-time feedback. This research requires a strong background in engineering or physics.

**Supervisor:** Professor Irene Tracey, Functional Magnetic Resonance Imaging Group  
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**To contact:** irene@fmrib.ox.ac.uk

**Project title:** Central Pain Processing in Health and Disease: Non-invasive Measurements in Humans

**Project description:** Until recently it has been difficult to obtain reliable objective information from normal subjects and patients regarding their subjective pain experience. Relating specific neurophysiological markers to perceptual changes induced by sensitisation, behavioural or pharmacological mechanisms and identifying their site of action within the CNS has been a major goal for scientists, clinicians and the pharmaceutical industry. With the advent of functional neuroimaging methods, such as functional magnetic resonance imaging (FMRI, positron emission tomograph (PET) and electroencephalography (EEG) this is now feasible. The Pain Imaging Neuroscience Group is a multidisciplinary research team of scientists and clinicians focused on using FMRI and EEG to study pain processing within the human brain and spinal cord of chronic pain patients (neuropathic, inflammatory and functional), models of key symptoms from these disorders, and normal subjects. We are also interested in understanding the neural basis for pain relief, induced either behaviourally or pharmacologically. Several projects exist within this extensive remit that requires people from a broad range of basic science or clinical backgrounds.

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**Genetics, Wellcome Trust Centre for Human Genetics**

**Supervisor:** Professor Jonathan Flint, Wellcome Trust Centre for Human Genetics  
**For further information:** [http://www.well.ox.ac.uk/flint/publications/MolPsych2007.pdf](http://www.well.ox.ac.uk/flint/publications/MolPsych2007.pdf)  
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**Project title:** Genetic mapping of susceptibility loci for depression

**Project description:** In common with other psychiatric conditions, susceptibility to depression is heritable, but the genetic basis of the condition is complex. The identification of susceptibility loci requires the analysis of very large samples and the application of whole genome high throughput technologies. We are currently establishing a project to collect thousands of cases of depression in Shanghai, together with controls, and will be genotyping all samples with whole genome arrays. The student will be introduced to the methods of whole genome association, the collection of large data sets of patients with depression, and the analysis of genotypes.
**Project title:** Molecular Machines: Structural Studies of Chromatin Remodeling Complexes

**Project description:** Our group is interested in the molecular mechanisms that govern the unravelling of chromatin from histones by chromatin remodelling complexes (CRCs), a process that is key to transcription activities in eukaryotes. Accumulating genetic evidence suggests that ATP-dependent chromatin remodelling plays a crucial role in human tumorigenesis. Misregulation of chromatin structure can cause incorrect gene activation or improper gene silencing. Specifically, several subunits of CRCs possess intrinsic tumour-suppressor activity or are required for the activity of other tumour-suppressor genes. To obtain insights into these cellular processes, we use X-ray crystallography in combination with Cryo-electron microscopy (Cryo-EM). This project aims to contribute to a structural and functional description of mammalian chromatin remodeling ATPases. ATP-dependent chromatin remodeling complexes are evolutionary conserved large (300k-2MDa) multisubunit assemblies, which contain an ATPase protein belonging to the SNF2 subfamily of DEAD/H helicases. There are many members of this family which are grouped into subclasses depending on the domain composition of their ATPase domain. In mammals, the best characterised classes are SWI/SNF, CHD and ISWI. Each has a unique domain (bromo, chromo or sant) which is thought to interact with specific chromatin substrates. One of the current challenges in the study of chromatin regulation is to define the functional and structural differences between the ATPases that are responsible for performing comparable but distinct enzymatic reactions. Prospective students will investigate the structure of chromatin remodelling ATPases on their own and in complex with DNA (either naked DNA or nucleosomes) by a combination of X-ray crystallography and Cryo-electron microscopy. The student will further validate the structural results with biochemical, biophysical and single-molecules studies.

**Supervisor:** Prof. E. Yvonne Jones, Dr. A. Radu Aricescu and Dr. Christian Siebold, Wellcome Trust Centre for Human Genetics

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great challenge for the international structural biology community. Landmark structures have been determined for prokaryotic membrane proteins but eukaryotic membrane proteins pose numerous additional problems. The necessary methodologies have only very recently been developed, and these have now started to bear fruit, so this is a very exciting time for the field of receptor research. We are one of relatively few structural biology laboratories worldwide with the necessary expertise in eukaryotic expression systems and our groups have opportunities for doctoral students to undertake research into the detailed molecular mechanisms of cell surface receptor signaling systems. A flavour of our work on the extracellular side of the cell surface receptors can be gained from recent publications (e.g. Aricescu et al. *Science* **317** (2007); Brown et al. *EMBO J* **27** (2008); Koch et al. *Nature Immunology* **6** (2005)). Current work in the laboratory is now heading into the membrane and increasing involves a spectrum of techniques which seamlessly span from the atomic to the cellular scale.

The core technique of our laboratory is x-ray crystallography, but doctoral students will necessarily gain experience in a broad range of methodologies. These include molecular biology, prokaryotic and eukaryotic expression systems (including tissue culture of insect and mammalian cells), protein purification, biophysical techniques (including surface plasmon resonance and analytical ultracentrifugation), crystallization, synchrotron data collection, *in silico* structural analysis, confocal and electron microscopy. Our extensive network of collaborations with other Oxford, UK and international laboratories allow the students to integrate their results within a broader functional and bio-medical context.

**Supervisor:** Professor David Stuart, Dr E.E.Fry, Wellcome Trust Centre for Human Genetics

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**Project title:** Structure Determination of Human Enterovirus 71 and use in Vaccine Development- a collaboration between Oxford University and Singvax PTE Ltd, Singapore.

**Project description:** Human enterovirus 71 (HEV71), a picornavirus, is most often associated with outbreaks of hand, food and mouth disease in children but can also cause acute neurologic disease. High mortality linked to outbreaks in Malaysia and Taiwan in 1998 and 2000 has heightened public concern. This project, a collaboration between Oxford University and Singvax PTE Ltd., Singapore, will use X-ray crystallography to determine the atomic structure of inactivated virus supplied Singvax PTE Ltd. Knowledge of the structure will support epidemiological and biochemical analyses of the virus in gaining an understanding of its pathogenicity, hopefully feeding back to the design of improved vaccines. The group has considerable experience in virus structure determination, excellent in-house facilities and access to the nearby UK synchrotron, Diamond. We have now obtained crystals of the virus and have shown that they diffract X-rays. The next stage is to use the technology developed at Diamond and Oxford to solve the atomic structure, relate this to the biological properties and use structure-based strategies for vaccine optimisation.
| **Supervisor:** Dr Maria Harkiolaki, Wellcome Trust Centre for Human Genetics  
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To contact: maria@strubi.ox.ac.uk |
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<td><strong>Project title:</strong> Immunity Factors in the Honey Bee: Structural Investigations into the Causes of Colony Collapse Disorder</td>
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<td><strong>Project description:</strong> Colony collapse disorder describes the collective symptoms surrounding substantial and concurrent loss of hives globally whereupon mature worker bees succumb to disease and other stress factors at an alarming rate with dire consequences to dependent agricultural activities. Irrespectively of the individual causes of CCD, it appears likely that affected colonies ultimately fail to elicit a timely and sufficient immune response to pathogenic challenges. Very little is known to date of the exact molecular interactions that elicit an immune response, although the honey bee genome allows the unambiguous identification of the main players involved. This project aims to structurally characterize a select group of Pattern Recognition Receptors and accessory molecules that are implicated in the recognition of exogenous particles in the context of the honey bee innate immunity. Our results should provide the basis for the development of new intervention methods in apiculture as well as provide fundamental insights into the field of Immunity and Inflammation. We will use well-established molecular expression systems, both pro- and eu-karyoric, to achieve high expression levels and desirable modifications, in combination with high through-put semi-automated technologies that will allow the rapid screening of bio-molecules. This will establish a sizable pool of bio-molecules which will thereafter be funneled through a battery of biophysical techniques with emphasis on the crystallographic structure solution of each molecule. Such will be studied individually and in complex with biological partners within the context of pathogen recognition and immune response initiation.</td>
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| **Supervisor:** Dr Kay Grünewald, Wellcome Trust Centre for Human Genetics  
For further information: [http://www.ndm.ox.ac.uk/researcher/kay-grunewald](http://www.ndm.ox.ac.uk/researcher/kay-grunewald)  
To contact: kay@strubi.ox.ac.uk |
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<td><strong>Project title:</strong> Structural analysis of virus-host interactions: Probing basic cellular functions and processes</td>
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<td><strong>Project description:</strong> Our group applies electron cryo tomography (cryo-ET) in combination with other techniques to approach selected aspects of the highly ordered network of cellular macromolecular complexes in the course of their function in situ. We have pioneered the application of cryo-ET to isolated pleomorphic viruses revealing their three-dimensional supramolecular organization. Examples are virions of Herpes simplex virus, HIV-1 and Uukuniemiviruse. More recently we have moved towards the cell biology of virus infection. Understanding the entirety of a virus’ ‘life cycle’ requires an understanding of its transient structures at the molecular level. The aim is a</td>
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comprehensive picture of the functional dynamic interaction between viral protein complexes and cellular structures in the course of the infection. Viruses also serve as dedicated tools to mine the molecular detail of cellular tomograms and to ‘label’ specific processes. The combination of single particle cryo electron microscopy and cellular cryoET provides an excellent platform for interactions with other approaches, like e.g. biochemical studies, immunolabelling, advanced imaging methods, proteomics and higher resolution X-ray crystallographic studies and allows for integration of these results with native sub-cellular structural information. As model systems we as use primarily herpesviruses, retroviruses and selected other viruses well suited for the particular cellular aspect of interest (e.g. membrane fusion during virus entry, endocytotic uptake, intracellular traffic, nuclear pore interactions, membrane envelopment, exocytosis) in the individual student project.

Materials

**Supervisor:** Dr Simon Benjamin, Department of Materials

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**To contact:** simon.benjamin@materials.ox.ac.uk

**Project title:** Measurement based quantum computing and quantum computing using solid state nanostructures.

**Project description:** One can regard quantum entanglement as the fundamental resource needed in order to execute quantum algorithms. Certain kinds of entangled states exist which are universal resources, in the sense that any quantum algorithm can be performed simply by performing a prescribed series of quantum measurements. Moreover, even the entangled state itself can by created by making measurements. These insights have led to many new possible implementations of quantum computers, for example: one that uses only photons, one exploiting crossed atomic beams and others based on optical measurements on colour centres in diamond. Specific topics are: first principles physics of measurement, implementation of error correction or avoidance and entanglement creation by measurement.

We are also looking at how certain solid state nanocrystals (such as quantum dots, carbon molecular arrays or colloidal crystals) can be used to implement quantum gate operations. We have developed methods for coherent quantum control of systems with a range of Hamiltonians. We are also interested in modelling decoherence, which is caused by the interaction of a system with its environment, work which employs in particular the Markovian master equation description of open quantum systems.
**Supervisor: Prof Andrew Briggs, Department of Materials**  
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**Project title:** Nanomaterials for quantum information processing  
**Project description:** Quantum information processing offers one of the most exciting challenges in the study and development of nanomaterials. It is at the cutting edge of quantum nanoelectronics, and we are part of the world wide race to develop a scalable quantum computer. We need materials with quantum states that can be individually controlled and measured, and yet which are sufficiently robust against decoherence that they can sustain a sequence of quantum manipulations and interactions. We lead the world in using the new family of fullerene materials (popularly known as Bucky balls), which can be used to contain atomic and molecular species inside a cage that separates them from the quantum environment. The quantum information may be stored in electron or nuclear spin, and can be exchanged between the two. The spin states can be manipulated and characterized by electron paramagnetic resonance and also optically. We can insert fullerenes into carbon nanotubes to create one-dimensional 'peapod' arrays, which we can image by HRTEM, and we are also developing other schemes for molecular self-assembly of fullerenes and other functional molecules. There will be several projects with these nanomaterials, ranging from synthesis and characterization to experimental implementation of candidate schemes for quantum computing. The research is highly interdisciplinary, and there is scope for a range of skills and interests from materials science and chemistry to quantum physics. In association with the experimental programme which will take place within a large and active research group ([www.qipirc.org](http://www.qipirc.org)), there will be theory and modelling projects with Dr S.C. Benjamin, Dr J Fitzsimons, Dr B W Lovett, Dr J. Wabnig and Professor J H Jefferson. There may be possibilities for industrial support and for international travel and collaboration.

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**Supervisor: Dr Martin Castell, Department of Materials**  
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**To contact:** martin.castell@materials.ox.ac.uk

**Project title:** Electrical conductivity of 2D nanoisland arrays  
**Project description:** Percolation theory can describe the flow of electric currents through random media such as randomly dispersed metal nanoislands on an insulating support. The sizes and distribution of the nanoislands can be determined accurately via scanning probe microscopy. This allows the electrical behaviour to be correlated with the island size distribution. Once this relationship is established it is possible to follow high speed sintering and island shape change events simply by investigating the change in electrical resistance. Percolation theory is able to set the experiments within a meaningful theoretical context. A new dedicated ultra high vacuum chamber is available for this project.
**Project title:** Tissue engineering of scaffolds

**Project description:** Tissue engineering is a rapidly expanding commercial and research area. To date, skin and articular cartilage have been tissue engineered and are available for clinical use. Other larger structures have been more difficult to produce. The major reason for this is the diffusion constraints imposed on the scaffold. We have developed a novel and unique method for producing three dimensional scaffolds from collagen, either by itself or as a composite with hydroxyapatite or other biopolymers. The technique involves rapid prototyping by solid freeform fabrication combined with CT/MRI data scanned directly from patients. Because we use SFF we can create a microvasculature within the scaffold ensuring that nutrients are kept supplied to cells deep within the structure. This is termed a ‘platform technology’ and the following examples show the breadth of tissues which can now be fabricated: bone, meniscal cartilage, heart valves, smooth muscle and arteries. We have a range of collaborations with leaders in their field both within the UK and abroad. The next major area is to look at hybrid structures whereby tissues of more than one type can be generated.

**Supervisor:** Dr Andrew Watt, Department of Materials

**For further information:** [http://www.materials.ox.ac.uk/admissions/postgraduate/](http://www.materials.ox.ac.uk/admissions/postgraduate/)

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**Project title:** New device geometries for low cost organic photovoltaics

**Project description:** The biggest obstacle to scaling up organic solar cells is the sheet resistance of transparent contacts. This project will investigate novel solar cell device geometries which do not require a transparent conductive layer. Using thermoplastic stamping and shadow evaporation techniques, this project will design techniques for preparing A5 substrates for subsequent dip coating aiming for a strategy to produce devices with low cost per watt. We have set this task the challenging target for a completely new device type of power conversions efficiencies of 2%.
### Project title: Epigenetic Programmes in Haematopoietic Differentiation

**Project description:** The Polycomb group of proteins provide a mechanism for epigenetic memory during differentiation and development. First discovered in Drosophila, where they are required for silencing of homeotic gene expression, polycomb proteins have since been found to play a key role in mammalian development and the maintenance of stem cell identity. Their disregulation is associated with aberrant gene expression in a range of malignancies. The general aim of the project is to study the function of Polycomb group proteins at a well defined mammalian locus, the alpha globin gene cluster, in order to establish general principles of Polycomb function in mammals. In embryonic stem cells several hundred genes are bound by Polycomb. During development, removal of Polycomb is essential for activation of lineage-specific genes. The mechanisms governing this removal in mammals remain obscure. The specific goal of the project is to study this process at the alpha globin gene locus. This locus has been the subject of intense investigation by the host laboratory and is consequently amongst the best characterised mammalian gene clusters. The host laboratory has shown that Polycomb proteins bind to regions of the alpha globin cluster silencing expression in embryonic stem and non-erythroid cells but in differentiated erythroid cells binding is absent. The first aim of the project is to establish the timing of Polycomb removal during erythroid differentiation. We will isolate by FACS populations enriched in haematopoietic stem cells and various progenitor populations from primary bone marrow samples. The presence of Polycomb at the alpha globin locus will be determined by chromatin immunoprecipitation (ChIP) and real time PCR. Current ChIP protocols require a minimum of $10^6$ cells, however only $10^3$ to $10^5$ cells of each progenitor population can be obtained from a single bone marrow sample. Therefore we will employ a novel ChIP method in which Drosophila cells are added as a ‘Carrier’. This technique can reliably analyse as few as 100-1000 cells. The second aim of the project is to determine the sequences required for Polycomb recruitment and for removal during differentiation. We will employ mononucleosomal ChIP and a tiled array to determine Polycomb binding at single nucleosome resolution across the alpha globin locus. We will also characterise Polycomb binding in erythroid cell lines (interspecies hybrids) containing deletions of previously identified cis-regulatory regions and of the alpha globin promoters. We hope to discover general principles governing removal of Polycomb during mammalian development.

Training in basic molecular and cellular biology: particular emphasis will be placed on the analysis of epigenetic analysis including DNA methylation and chromatin modification. In addition this work will involve the analysis of microarray platforms and high throughput sequence analysis. In addition the programme will involve training in the purification and evaluation of haematopoietic progenitors.

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**Supervisor:** Professor Douglas Higgs and Dr Richard Gibbons, Clinical Laboratory Sciences and the Institute of Molecular Medicine

**For further information:**
[http://www.imm.ox.ac.uk/pages/research/molecular_haematology.htm](http://www.imm.ox.ac.uk/pages/research/molecular_haematology.htm)

**To contact:** doug.higgs@imm.ox.ac.uk, richard.gibbons@ndcls.ox.ac.uk
**Supervisor:** Dr. Marella de Bruijn, Institute of Molecular Medicine; A*Star collaborator: Walter Hunziker

**For further information:**
[http://www.imm.ox.ac.uk/pages/research/molecular_haematology.htm](http://www.imm.ox.ac.uk/pages/research/molecular_haematology.htm)

**To contact:** marella.debruijn@imm.ox.ac.uk

**Project title:** Runx1 regulatory networks in blood stem cell formation

**Project description:** The transcription factor Runx1 is a critical regulator of blood stem cell generation during embryonic development. Studies in our laboratory focus on how Runx1 exerts this role. In particular, we are interested in identifying and characterising the upstream signalling and transcription pathways that converge on Runx1, and the downstream transcriptional target genes that are regulated by Runx1. Using a combination of comparative genomics and molecular biology methods, we have identified the Runx1 +23 hematopoietic enhancer that is sufficient to drive reporter gene expression in the emerging blood stem cells of the mouse embryo (Nottingham et al., 2007). In addition, other enhancers have been identified that target reporter gene expression to distinct stages of developmental hematopoiesis. These enhancers are valuable tools for our studies, as they facilitate the identification of upstream pathways converging on Runx1 during HSC emergence. In addition, they are instrumental for the purification of distinct subsets of Runx1+ cells for expression profiling. These studies will give us insight into how blood stem cells are programmed in development. This in turn will benefit the development of new, and improvement of existing, therapies of blood related disorders such as leukemia.

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**Supervisor:** Dr Graham Ogg, Human Immunology Unit, Nuffield Department of Clinical Medicine

**For further information:**
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**Project title:** What can the immunological control of a common human virus tell us about better vaccine design?

**Project description:** By understanding how the immune response controls viruses, we will be better placed to generate more effective new vaccines. Varicella zoster virus (VZV) infection is an excellent human system to study as it is a common disease and there is ready access to the skin, where the virus replicates. T cells are likely to be important in the control of VZV infection. We have recently identified several CD4+ T cell epitopes within IE4, IE63, gE and gI proteins of VZV and examined the frequencies and phenotypes of specific T cells in blood of healthy immune donors, vaccinees and those with acute primary infection. These studies have shown that VZV-specific T cells circulate in the peripheral blood of affected individuals and remain at high levels many decades following primary infection.
The aim of the project is to characterise the frequency and phenotype of VZV-specific T cells within the lesional skin of affected individuals during primary infection and re-activation, and correlate these with clinical and virological markers.

We have ethical permission to undertake the study to analyse blood and tissue samples from affected individuals from Sri Lanka where acute VZV infection is more common in adults who attend regional centres. We already have peripheral blood samples from more than 30 acutely affected individuals from which we have generated our knowledge of new VZV epitopes. From 30 new adult participants we will aspirate vesicle fluid for analyses and from individuals with appropriate HLA types.

Ex vivo HLA tetrameric complex staining (based on our new epitopes) will be undertaken with markers of activation (eg CD38), memory (CD45RO, CCR7, CD28, CD27), homing (eg CLA), and function (eg perforin, granzyme, IFN□) to characterise the frequency and phenotype of the specific cells in comparison to concurrent blood samples. In addition, we will investigate T cell function using ELISpot analyses in response to peptides, viral lysate and vaccine. These data will be compared to the clinical severity scores, immunoglobulin type and titre and viral loads. All of these approaches are established already.

The work will have implications for the understanding of T cell immunity to VZV, and will generate insights to the development of new approaches to vaccination. There are considerable opportunities to learn about the details of principles and practice of human T cell immunology specific for a common virus, as well as gaining a broader perspective on other aspects of immunology. These are skills that would represent an excellent base for subsequent career development within immunology.

Supervisor: Dr Astrid Iversen, Human Immunology Unit, Nuffield Department of Clinical Medicine

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Project title: Increasing and shaping the HIV epitope-specific CTL response through antigen processing optimized DNA vaccine constructs.

Project description: The best hope for ending the human immunodeficiency virus (HIV-1) pandemic is the development of a safe and effective protective vaccine. Unfortunately, HIV has proved very different from those viruses for which effective immunizations already exists. Key obstacles are: (i) the extreme viral variation both within and between patients, (ii) the integration and persistence of the virus in the human genome, and (iii) the heavily glycosylated outer viral coat, which partly conceal sites that could induce protective antibodies. The recent failure of a cytotoxic T-cell (CTL)-based major vaccine trial demonstrated that conventional preventive vaccine strategies do not generate CTL responses that lower viral load and/or protect against infection; indeed the trial showed that vaccinated persons had an increased risk of acquiring HIV. We here propose to generate a therapeutic vaccine, which would help focus the immune response towards major variants of CTL epitopes restricted by the most common HLA alleles in a given population. Such CTL responses could force HIV to evolve into a less fit variant of the virus, which as a consequence would lower the viral load, and lead to benefits for the infected individual as well as reduce the risk of...
transmission.
We have described the evolution of an HLA-A2 restricted epitope (SL9) in HIV p17 Gag and identified common epitope variants, which the virus acquires over time in most infected individuals (Iversen, AKN et al, Nature Immunol, 2006). Moreover, we found that individuals harboring virus with CTL-escape mutations had lower average viral loads in plasma than persons carrying wild-type virus.

We here propose to use our understanding of the evolution and processing of SL9 in p17 Gag to generate a proof-of-concept therapeutic vaccine, which would help focus the immune response towards major epitope variants of SL9, restricted by the most common HLA allele in Caucasians, HLA-A*02. We will design long peptides encompassing combinations of the most common SL9 epitope variants using our already defined antigen processing parameters to optimize epitope production. These peptides will subsequently be analyzed using our already established antigen processing assays (Tenzer, S et al, in prep) and will potentially be optimized further by re-design of the peptides and further in vitro antigen processing analysis. Based on these results we will design DNA constructs containing various combinations of the CTL epitope variants in both their natural HIV genomic context and in the optimized processing context. Expression of the epitopes and CTL recognition by T-cell clones recognizing well-defined epitope variants will be analysed in vitro. If optimized constructs give rise to greater/better CTL responses, the next key step will be to evaluate the potential of these constructs to induce CTL responses and drive HIV evolution. To this end, we will use a recently developed humanized mouse model available at the WIMM and an infectious HIV clone carrying the wild-type SL9 epitope sequence.

Supervisor: Dr Paul Bowness, Human Immunology Unit, Nuffield Dept of Clinical Medicine

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Project title: Monocyte function in Ankylosing Spondylitis

Project description: Ankylosing Spondylitis (AS) is a common inflammatory rheumatic disease of unknown aetiology thought to be due to aberrant immune function. We hypothesize that heightened immune activity of monocytes is critical to the pathogenesis of AS. The student will determine the proteome of monocytes and T cells from blood and joints of patients with AS, and then determine the immunological function and consequences of the altered protein expression, using biochemical, Mass Spectrometry (MS) and cellular immunological techniques. Our own group has previously identified an aberrant homodimeric form of HLA-B27, that is expressed by myelomonocytic cells and is also recognized by Leukocyte Immunoglobilin-like receptors (LILR) human monocytes (ref 1, as well as lymphocytes). Together these data make a compelling case for detailed study of monocytes and their lineage in AS. We have carried out a preliminary proteomic study of AS monocytes, which has shown upregulation of several proinflammatory pathways, including Integrin, TLR, Vascular Endothelial Growth Factor and Ubiquitin Proteosome pathways (ref 2).

The aims of this project are: 1. To determine the number and phenotype of peripheral
blood monocytes in AS patients. 2. To measure the ability of AS monocytes to present antigens and to stimulate T and NK cells ex vivo. 3. To determine the effect of HLA-B27 expression and of salmonella sp. infection on monocyte protein expression (using monocyte cell lines, human monocytes ex vivo, and monocyte stem cells). 4. To determine the effect of HLA-B27 and of salmonella sp. infection on monocyte function. The PhD will using FACS-based and functional assays of human cells and cell lines. There will be training in cellular and molecular immunology. This project also provides exposure to and training in proteomic techniques, as part of an ongoing collaboration with the group of Benedikt Kessler (within the NDM).

The student will also attend a Basic Methods and Techniques course which runs over 24 weeks at the beginning of the first year. Training in the laboratory will include: basic laboratory methods, tissue culture, T cell cloning, T cell assays, molecular biology, biochemistry and flow cytometry. Within the human immunology group there are twice weekly lab meetings compulsory weekly immunology seminars, and an informal non-compulsory journal club for students and junior postdocs only.

Pathology

**Supervisor:** Dr Ervin Fodor, Sir William Dunn School of Pathology

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**Project title:** The role of host factors in influenza virus replication

**Project description:** The natural hosts of influenza A viruses are aquatic birds. On rare occasions these viruses may be transmitted to humans, adapt to the new host and then give rise to an influenza pandemic. Evidence is increasing that the viral RNA-dependent RNA polymerase, an enzyme that is responsible for the transcription and replication of the viral RNA genome, is a major determinant of host range. This suggests that the activities of the RNA polymerase during the viral replication cycle are regulated by interactions with host factors. However, the identity of these host factors remains unknown and the molecular mechanisms involved need to be determined. The principal aim of the proposed project is to elucidate the molecular mechanism of transcription and replication of the influenza virus RNA genome by the viral RNA polymerase, a complex of three subunits, PB1, PB2, and PA. The RNA polymerase synthesizes three types of viral RNAs in the nucleus of infected cells. The negative-sense genomic vRNA is transcribed into capped and polyadenylated mRNA (transcription) and replicated through a complementary RNA (cRNA) intermediate to produce more vRNA (replication). We are interested in determining the role of host factors that participate in the regulatory processes involved with these transcriptional events. There is a particular interest in host factors involved in the nuclear import and the assembly of the RNA polymerase complex and in its interactions with the host RNA polymerase II transcriptional machinery. Further interests include the characterization of host responses to viral infection triggered by the expression of the viral RNA polymerase. This includes the mitochondrial
localization of the PB2 subunit of the viral RNA polymerase and its potential involvement in regulating innate immune responses via its interaction with the mitochondriald antiviral signalling protein (MAVS). We use a wide variety of techniques, including classical biochemical approaches, bio-imaging, and state-of-the-art mass spectrometry as well as virological methods, including reverse genetics, to study virus-host interactions.

Key references:

Supervisor: Dr David Greaves, Sir William Dunn School of Pathology; A*Star collaborator: Dr Subhra Kumar Biswas

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Project title: Novel anti-inflammatory pathways that regulate macrophage activation and inflammatory cell recruitment

Project description: Inflammation is a localised, response to injury or infection characterised by the sequential release of inflammatory mediators and the recruitment of circulating leukocytes. Recruited leukocytes become activated at the site of inflammation and release further pro- and anti-inflammatory mediators. Sites of acute inflammation are characterised by the rapid recruitment of neutrophils whereas sites of chronic inflammation are characterised by the continuing recruitment of monocytes that differentiate into macrophages. Macrophage activation is a hallmark of many forms of chronic inflammation including atherosclerosis and rheumatoid arthritis.

My laboratory is studying the role played by a family of inflammatory mediators called chemokines in the recruitment and activation of macrophages in chronic inflammation. We have developed methods to reduce CC chemokine activity in vivo (1) and we are developing new reagents to block activation via the CX3CR1 chemokine receptor which has been implicated in the development of atherosclerotic lesions (2). Recently we have identified a novel endogenous anti-inflammatory pathway that regulates inflammatory cell recruitment and activation via a G-protein coupled receptor called ChemR23. These studies have identified targets for the development of novel anti-inflammatory drugs and implicated cysteine proteases in the resolution of inflammation (3).

Applicants should have a genuine interest in inflammation biology and/or innate immunity. The successful applicant will develop a specific research project in the area of regulation of leukocyte recruitment or the resolution of inflammation.
**Supervisor:** Professor Neil Barclay, Sir William Dunn School of Pathology; A*Star collaborator: Professor Alex Law

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**Project title:** Molecular analysis of regulation of leukocyte activity

**Project description:** Leukocytes are subject to exquisite control so that they can initiate the appropriate immune response against a pathogen, for the optimum duration, at the correct site and at an optimal level to prevent it leading to autoimmunity and other side effects. Interactions between proteins at the surface of leukocytes play a key role in this. This project will apply newly developed techniques to build on our expertise in identifying and characterising these surface interactions [1-4]. During lymphocyte activation reagents that will alter the redox potential are produced and we have shown that newly developed sensitive mass spectrometry can detect surface proteins that have disulphide bonds that are susceptible to reduction. The hypothesis is that changes in redox potential provide a rapid sensitive way to control immune reactions and there are data to support this idea. We have predicted that many proteins will contain labile disulphide bridges in addition to those within the domains that are inaccessible to reducing reagents without denaturation. In addition our collaborator in Singapore (Alex Law) has already shown that the activity of a major class of membrane proteins – the integrins - is affected by removal of key disulphide bridges [5]. The project will develop the methodology to ensure we identify all susceptible proteins and then investigate different cell types and see if these changes occur during immune responses by using quantitative mass spectrometry. The biochemical studies will be complemented by functional studies to determine the affects of modification of disulphide residues on the activity of individual proteins. If this is an important mechanism in immune regulation, these labile disulphides may be targets for immune therapy.

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**Supervisor:** Professor William James, Sir William Dunn School of Pathology; A*Star collaborator: Dr Subhra Kumar Biswas

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**Project title:** Characterization of macrophage-specific expression sites in the human genome using a novel hit-and-run iPS-induction vector

**Project description:** The regulation expression of "normal" genes and of artificial transgenes in human macrophages is governed by a complex mix of transcriptional regulatory elements and epigenetic factors. These have not been well-explored, and yet are crucial for a proper understanding of HIV pathogenesis, in addition to many other questions relating to human disease and defence. We have developed two cutting-edge technologies that, amongst other things, offer us the possibility of examining these processes in mechanistic detail. First, we have developed a system for routinely and
efficiently producing authentic human macrophages from embryonic stem cells for the facile genetic modification of macrophages (Karlsson et al., 2008). Second, we have developed a system for generating human induced pluripotent stem (iPS) cells from adult somatic tissues, using an improved, transient expression system that leaves no permanent genetic trace in the iPS cell (unpublished). Using these two techniques, the project will create target recombination sites in human iPS cells at chromatin positions that are associated with high-level expression in adult human macrophages. The chromatin dynamics of these sites will then be characterized during the in vitro process of hemopoiesis, and the information gained used to generate macrophages expressing genes of therapeutic or analytical interest in relation to HIV pathogenesis.


**Physics**

*Supervisor:* Dr Achillefs Kapanidis, Department of Physics

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**Project title:** Single-molecule studies of transcription factors in stem cells

**Project description:** The Kapanidis lab (Gene machines’ group) studies the mechanisms and interactions of DNA/RNA polymerases and transcription factors; the main tools of the group are single-molecule fluorescence imaging and biochemistry. The specific project will build on a recently established collaboration between the Kapanidis group and the group of Dr Sohail Ahmed (Institute of Mol Medicine, Biopolis). Specifically, we are studying the interactions and localization of stem-cell-related transcription factors Sox2 and Oct4 using single-molecule fluorescence methods. Sox2 and Oct4 are two transcription factors central for early development and the maintenance of pluripotency in embryonic stem (ES) cells; it has also recently been shown that simple transduction of these two proteins in cells can revert differentiated cells (such as skin cells) into embryonic stem cells. However, the mechanisms of action of the two transcription factors is unclear. Moreover, although the profile and concentration of transcription factors is important for cell differentiation, the actual copy numbers are largely unknown. Finally, although Chip-ChIP data are available for hundreds of promoters occupied by these two transcription factors, the cellular localisation patterns for the transcription factors is unknown (besides the fact that active genes are located close to nuclear pore complexes and the nuclear envelope).

The proposed work seeks to address these gaps in our knowledge using single-molecule fluorescence detection methods developed and/or implemented in the Kapanidis group. We will examine the interaction of Sox2 and Oct4 with promoter DNA, as well as their copy number in cell lysates using alternating laser excitation spectroscopy (ALEX) and
total-internal-reflection fluorescence (TIRF); and we will use super-resolution fluorescence imaging methods (with a resolution of 10-20 nm, an order of magnitude better than diffraction-limited fluorescence imaging) to localize and count Sox2 and Oct4 molecules in cells at various stages of the cellular differentiation. Projects will involve a variety of techniques including molecular biology, biochemistry, cell biology, single molecule fluorescence imaging and advanced image analysis.

**Supervisor:** Dr Stephen Tucker and Dr Mark Wallace, Department of Physics and Department of Chemistry  
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**Project title:** Single molecule studies of ion channels

**Project description:** The Tucker lab is focused on understanding the intimate relationship between ion channel structure and function. The objectives are to understand how and why ion channels do what they do i.e. to understand their molecular mechanism of operation at an atomic level as well as understanding their role in physiology and disease. In collaboration with Dr Mark Wallace in the Department of Chemistry we have begun to use single molecule imaging techniques to address some of the questions. The aim is to use fluorescent markers to monitor the structural changes which occur during channel gating and to measure these movements at the same time as measuring the electrical activity of a single ion channel. This will enable us to address questions about the gating mechanism which are not possible to monitor when studying averaged signals from large populations of channels. Projects could potentially involve a variety of techniques including molecular biology, biochemistry, single molecule fluorescence and electro-physiology.

**Physiology, Anatomy and Genetics**

**Supervisor:** Dr Stephen Goodwin, Department of Physiology Anatomy & Genetics  
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**Project title:** Genes, Circuits and Behaviour: Structure/function analyses of the neural circuitry controlling sexual behaviour in Drosophila

**Project description:** Our laboratory uses the fruit fly, Drosophila melanogaster, to study the genetic, developmental, and neural mechanisms that underlie sex-specific behaviours in higher animals. In particular, the elaborate courtship ritual performed by the male fly has provided remarkable insights into how the neural circuitry underlying sexual behaviour, which is largely innate in flies, is built into the nervous system during development, and how this circuitry functions in the adult. Innate behaviours refer to the actions of an animal that manifest themselves without prior experience, and thus by
implication are genetically inherited. Yet how does gene expression control the development and function of the nervous system so that a gene's action influences some discernible aspect of behaviour? We are studying how the Drosophila transcription factor genes fruitless and doublesex act within the complex and highly organized network of transcription factors to orchestrate the developmental events necessary for sex-specific behaviours and physiology, and the broader lessons this can teach us about the mechanisms underlying the development of sex-specific neural circuitry.

Our work is supported by the Wellcome Trust, the Biotechnology and Biological Sciences Research Council (BBSRC, UK) and the Royal Society.

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**Supervisor:** Professor David Paterson, Department of Physiology Anatomy and Genetics  
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**Project title:** Gene transfer strategy using viral vectors to study the regulation of cardiac excitability  
**Project description:** David Paterson leads a research team in the area of cardiac neurobiology. They are interested in how both branches of the cardiac autonomic nervous system communicate at the end organ level and whether oxidative stress plays a role in uncoupling pre-synaptic and post synaptic signalling. The endogenous gas nitric oxide is now thought to be a key intermediary in cardiac inter/intracellular signalling, where it has been shown to regulate several ion channels that control cardiac excitability. His group has developed a method for targeting the enzyme involved in making nitric oxide using a gene transfer approach involving cell specific viral vectors to study the physiology of this messenger in normal and diseased hearts. Current projects involve investigations looking at abnormal calcium regulation coupled to defective nNOS signalling that may underlie cardiac sympathetic hyper-responsiveness caused by hypertension. Impaired neurohumoral activation (as seen in hypertension) is a negative prognostic indicator for sudden cardiac death and a strong independent predictor of mortality. Our work and that of others has recently established that nitric oxide (NO) inhibits cardiac sympathetic activity. A reduction in NO bioavailability in hypertension caused by oxidative stress impairs cyclic nucleotide signalling and contributes to sympathetic hyper-responsiveness. Overexpression of nNOS into cardiac sympathetic nerves induced by cell specific adenoviral gene transfer can rescue this effect. We now propose to investigate whether hypertension causes abnormal calcium signalling due to impaired NO-cGMP coupling that leads to enhanced noradrenaline release in normotensive aged matched control rats. Specifically, (i) we will determine if impairment of the NO-cGMP pathway disrupts cardiac sympathetic calcium regulation in the adult spontaneously hypertensive rat (SHR), (ii) establish whether calcium regulation is impaired in neonatal sympathetic nerves from the SHR before the development of hypertension itself, thereby being an early neural marker of the disease; and (iii) test whether targeted nNOS gene transfer to cardiac sympathetic neurons can rescue the calcium impairment and abnormal neurotransmission.
Supervisor: Dr Shankar Srinivas, Department of Physiology Anatomy & Genetics
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Project title: Investigating cell fate and movement in peri-implantation mammalian embryos

Project description: Mammalian embryogenesis is a tremendously dynamic process and is characterized by dramatic changes in the positions of cells and tissues. Our overall objective therefore is to characterize the movement of cells during development and to map their ‘fate’ – the tissues or regions of the fetus they give rise to over the course of development.

This project will focus specifically on the process of anterior patterning in the early embryo. A special collection of cells referred to as the AVE is responsible for specifying the position of the future anterior. This project will use a wide range of techniques (such as time-lapse microscopy of fluorescently labeled embryos, transgenic techniques, molecular biology and confocal imaging and 3D reconstructions) to study the movement, lineage and fate of AVE cells in normal and genetically mutant embryos.

Supervisor: Professor Chris Ponting, Department of Physiology Anatomy & Genetics
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Project title: Identification of genes and pathways underlying neurological diseases

Project description: Neurological disorders, both developmental (e.g. learning disability) and late-onset (e.g. Alzheimer's disease), affect several hundred million people worldwide and place a huge burden on global health care in both developed and developing countries. Spontaneous mutations, such as rare copy number variants (CNVs), are frequently associated with common neurological disorders including learning disability, autism and schizophrenia. CNV screening in clinical practice, however, is limited because pathological CNVs cannot be distinguished routinely from common, apparently benign CNVs, and because genes underlying patients' phenotypes remain largely unknown. Detecting causative genetic variation is further complicated by overlapping symptoms between, and varying symptoms within, neurological disorders. Until the genetic and other causative elements underlying these disorders are revealed, accurate diagnosis and insights into the etiology of neurological disease that might lead to treatment are severely limited. We have developed a bioinformatics approach to identify genes whose variants underlie patients' phenotypes. This approach has been applied successfully to patient cohorts for learning disability, autism and developmental delay. With the diminishing cost of CNV detection, the results from genetic screens of new cohorts are being reported with increasing frequency, generating a wealth of new
data ready for further analysis. This project will further refine approaches to identifying causative gene alleles. A wealth of data is readily available to associate the disruption of a particular molecular function or cellular pathway with clinical observations; in short, to forge links between genotype and disease phenotype. One specific aim will be to incorporate new data sources and to develop the existing statistical method into a systems-based approach. By integrating CNVs with these data we shall begin to build up a picture of which biological pathways, networks and processes contribute to different neurological diseases and to stratify patient cohorts in spectrum disorders, such as autism. We shall also reveal the commonalities that underlie what were previously thought of as distinct disorders, such as learning disability and Alzheimer's disease. Candidates for this PhD position should be enthusiastic, computer literate and open to learning computational approaches to biological analysis. They should also be comfortable with statistics and interested in the applications of genomics in medicine. However, the Ponting group provides an excellent training environment in computational methods, statistics and genome biology.

Supervisor: Dr Francis Szele, Department of Physiology, Anatomy and Genetics
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Project title: Molecular Regulation of Subventricular Zone Cell Migration in Adult Neurogenesis

Project description: The adult brain subventricular zone (SVZ) consists of stem and progenitor cells that generate thousands of migratory neurons on a daily basis. As such, it is an excellent system for studying fundamental questions in developmental neurobiology and for harnessing endogenous cell replacement approaches. The stem cells are astrocyte-like and bear processes that encircle and provide “tubes” for “chains” of contiguous migrating neuroblasts. The migratory neuroblasts in turn find their way in the rostral migratory stream (RMS) by 1) interacting with astrocyte processes, and 2) extending their own motile filopodial-bearing processes in order to make migratory decisions. The Szele lab has developed 2-photon microscopy of slices from GFP+ transgenic mice to visualize these processes in real-time. We are expanding our technical armamentarium by crossbreeding and generating bi- and tri-coloured mice that label stem, progenitor and neuroblast cells. These animals will be widely useful to developmental neurobiologists for in vivo, slice and neurosphere approaches. The student’s DPhil project will use one of the lines to simultaneously visualize the processes of astrocytes (Nestin-GFP mice) and migratory neuroblasts (Dcx-RFP mice) with 2-photon microscopy. It is known that Cdc42 modulates Slit-Robo signaling in the SVZ, one of the key determinants of cell migration decisions. However many other cytoskeletal and signaling components that play a role in other migratory cells have not been examined in the SVZ. In this dissertation project we will test the hypothesis that IRSp53 mediates leading process morphology in SVZ cells, and thus migration, via Cdc42. We will also examine the role of N-WASP and Mena in SVZ neural migration. Thus we hope to use advanced imaging of migration to ask mechanistic questions in SVZ cell migration.
**Supervisor:** Dr Richard Wade-Martins  
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**Project title:** Molecular mechanisms of Parkinson's disease

**Project description:** Parkinson's disease (PD) is a movement disorder and the second most common neurodegenerative disease. The critical observation in PD neuropathology is the selective loss of the dopaminergic neurons of the substantia nigra pars compacta which accumulate cytoplasmic inclusions called Lewy bodies composed mainly of the protein alpha-synuclein. Recent genome-wide association studies identify the gene encoding alpha-synuclein (SNCA) as the most important genetic factor underlying PD. The Wade-Martins laboratory has several projects ongoing using neuronal cell culture and transgenic mouse models to understand the very earliest pathological pathways in PD with a focus on understanding the molecular basis of PD and the role of alpha-synuclein in dopamine homeostasis. Dr Wade-Martins heads the Oxford Parkinson Disease Centre (OPDC), established in 2009 funded by the award of the £5 million Parkinson's Disease Society Monument Trust Discovery Award to Oxford. We will use the unique interdisciplinary research environment within Oxford to establish a leading centre focused on understanding the earliest pathological pathways in PD. Internationally-recognised scientists with strengths in genetics and genomics, transgenic rodent models, in vivo neuroanatomy and neuropharmacology of the basal ganglia, magnetic resonance imaging (MRI), and analysis of protein biomarkers, will work closely with experts in the clinical epidemiology and clinical neurology of PD. Applications from graduate students interested in all aspects of Parkinson's disease are welcome to undertake a range of interdisciplinary projects under joint supervision by OPDC investigators.

**Supervisor:** Professor Gero Miesenböck, Department of Physiology, Anatomy & Genetics  
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**Project title:** How to Learn from a Mistake

**Project description:** We have recently given flies memories of a bad experience they never had. By activating just 12 nerve cells with an optical 'remote control', we have taken the first steps towards defining the precise neuronal circuitry that underlies an important form of adaptive intelligence: the ability to learn from a mistake.

Even the simplest animals have to modify their behaviour in a changing environment in order to survive. Fruit flies navigate a world of smells in which they learn to find food and sex, and avoid danger. Normal flies can be quickly trained to avoid odors that they previously favoured if they receive an electric shock each time they encounter the odor. This form of learning can only take place, however, if a part of the fly's brain called the
mushroom body receives inputs carrying the neurotransmitter dopamine.

We were able to remote-control when dopaminergic cells fired by using a laser that flashed each time the fly strayed into a particular odor. This procedure conditioned the flies to avoid the odor as effectively as electric shock, but only when four particular dopamine-producing cell clusters were active. Only one of these, known as PPL1, sent connections to the relevant cells of the mushroom body. We thus suspect that this cluster of 12 cells emits the signals that train the fly to associate the odor with something bad.

Now we hope to find the cells that lie upstream of PPL1 neurons and calculate some prediction of reward or punishment. We aim to uncover the mechanism used to make this calculation, and to find out whether it resembles the temporal difference algorithm developed by computer scientists working on machine learning more than 20 years ago.

We are also keen to discover what happens in the mushroom body when the contents of memory are updated. The ability to write behaviourally relevant memories at will, simply by activating a small set of dopaminergic neurons, opens the possibility of watching the processes of memory formation and recall directly, by peering into the living brain with a microscope.

Psychiatry

*Supervisor:* Dr Robert Rogers, Department of Psychiatry

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*Project title:* The project involves brain imaging experiments and drug studies in order to learn more about the neural basis of socially cooperative behaviour and the impact of impaired social function in psychiatric disorders.

*Project description:* Neurotransmitters such as serotonin play an important role in social behaviour. We have been investigating the role of these systems in social cooperative behaviour using game-theoretic models of social exchanges. We have already shown that temporary disruption of serotonin transmission in healthy volunteers impairs the expression of socially cooperative behaviour during performance of an iterated Prisoner's Dilemma game, possibly by diminishing the reward value of longer-term reciprocal social interactions (see Wood et al, 2006). We wish to extend this work by examining the role of other neurotransmitter systems in learning socially cooperative behaviour, use fMRI to identify the neural sites where neurotransmitters act to influence social cooperation, and to extent this work to clinical populations such as those with depression in order to understand how such disorders are associated with social withdrawal. This project will be co-supervised by Professor Phil Cowen of the Department of Psychiatry.
**Radiation Oncology and Biology, Grey Institute of**

| **Supervisor:** Dr Thomas Brunner, Grey Institute of Radiation Oncology and Biology |
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**Project title:** Tumour-stroma interactions in pancreatic carcinoma  
**Project description:** A number of tumours provides a large stromal component in tumour masses (e.g. breast, colon, prostate, lung, pancreas). We are studying this interaction in pancreatic carcinoma where a specific cell type, pancreatic stellate cells (PSC), are responsible for the extremely rich stromal component of pancreatic ductal adenocarcinomas (PDAC). We are investigating the contribution of PSC to the therapeutic resistance of PDAC. To this end we use co-culture methods in vitro and co-injection methods in vivo of PDAC and PSC. In addition, we inhibit PSC function in orthotopic tumours. In all of the models we investigate the influence on radiation resistance and investigate signaling cascades. In the in vivo models we also analyse vascular changes in the tumours depending on the function of PSC. This is done pathohistologically as well as with small animal imaging methods. We predict to better describe the biological consequences of PSC in PDAC and to target these with small molecular inhibitors.

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**Project title:** DNA damage dependent ARF signalling and cancer  
**Project description:** The ARF (Alternative Reading Frame) gene encoded by the INK4A-ARF (CDKN24) locus on human chromosome 9p21 is frequently deleted in many tumours, including cutaneous malignant melanoma, which is an extremely aggressive and often fatal cancer. The ARF tumour suppressor function is assigned to its ability to interact and inhibit E3 ubiquitin ligases Mdm2 and Mule that are involved in regulation of p53 and Mcl-1 proteins and thus controls cell cycle progression and apoptosis. Correspondingly, ARF knockout mice develop increased rates of cancers (reviewed in [1]). ARF mainly resides in the nucleolus, forming a complex with another nucleolar protein nucleophosmin (NPM), however, in response to DNA damage this complex is disrupted and ARF is released into the nucleoplasm and cytoplasm [2] and inhibits Mdm2, thus allowing cells to accumulate p53, delaying cell progression and allowing repair of damaged DNA [3]. At the same time, inhibition of Mule by ARF results in an accumulation of Mcl-1 and induction of apoptosis if DNA damage is too substantial [4]. These data suggest that ARF plays a central role in early detection and signalling of DNA damage, although the molecular mechanism involved is unknown. An understanding of the role of ARF at the early stages of the stress response potentiates development of new approaches to specifically target cancer cells deficient in ARF. This project will address the molecular mechanism regulating release of ARF in response to DNA damage. It will involve biochemical characterization of ARF-protein complexes as well as
identification and characterisation of other ARF related mechanisms and proteins contributing to sensing and signalling DNA damage.

**Supervisor:** Dr Tim Humphrey, Grey Institute of Radiation Oncology and Biology

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**Project title:** Chromosome Stability and Cancer

Research team led by Dr. Tim Humphrey

Most human cancers are genetically unstable and exhibit heterogeneous chromosomal rearrangements, which can result in loss of heterozygosity and/or oncogene activation. Understanding how such rearrangements arise and how they are suppressed in normal cells is a central to cancer research. Current evidence suggests that DNA double-strand breaks (DSBs) arising from either exogenous or endogenous events are early contributors to tumorigenesis. However, the molecular mechanisms underlying break-induced genomic rearrangements, and how such mechanisms are normally suppressed, are currently poorly understood. Using the genetically amenable fission yeast *Schizosaccharomyces pombe*, in which DNA damage responses are evolutionarily conserved, we have recently identified a novel mechanism by which a site-specific DSB can result in a heterogeneous spectrum of genomic rearrangements including genome-wide copy number variation. The aim of this PHD project will be to further characterize this mechanism of break-induced genome instability, and to identify genes that prevent such events from occurring in normal cells. Novel genes and pathways will be examined both in yeast and mammalian cells to determine their possible roles in tumorigenesis and tumour suppression. Techniques will include genetics, molecular biology and biochemistry.

**Supervisor:** Dr Eric O’Neill, Grey Institute of Radiation Oncology and Biology; A* link to Professor David Lane

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**Project title:** The role NPM-p14ARF signalling in p53 stabilisation, senescence and tumour survival

**Project description:** Tumour suppressors play an important role in regulation of unlicensed cellular growth by oncogenic mutations such as RASv12. Loss of tumour suppression is a key step in the progression of oncogene driven cells to a neoplasia. The p53 gene is frequently mutated, or regulation lost, resulting in a failure to prevent such oncogenic events. Recently we have uncovered a novel regulatory pathway that promotes p53 activity through an alternative pathway to ATM and involving DNA-PK and DNA damage induced phosphorylation of NPM and nucleolar release of p14ARF. In the initial promotion of growth induced by RASv12, PI3K (a kinase related to DNA-PK) is hyper-activated and subverts the DNA-PK DNA damage constitutively stabilising p53.
This is one potential mechanism of an oncogene driven senescence response. Escape from senescence requires circumventing p53 activity, when this occurs by mutations of the p53 DNA binding domain it can lead to a dominant negative effect on wild type p53 or the related family members, p63 and p73. In this case, RASv12 promotes stabilisation of mutated p53 which appears to contribute to the resistance of RASv12 driven tumours to DNA damaging chemotherapy and radiotherapy.

The long term goal of this project is to resensitise RASv12 driven tumours to DNA damaging therapy by intervention strategies aimed at destabilising mutant p53. The key points of this project will be;

- The initial aim is to verify the regulation in the senescence response and the molecular mechanism of how RASv12 signalling leads to regulation of NPM and p14ARF.
- Do tumour derived mutations in NPM affect p53?
- Are wild type and mutant p53 stabilities differentially affected by NPM and p14ARF?
- Can the pathway be targeted with novel agents (e.g. PI3K inhibitors) to affect the stabilisation of mutant p53?

**Vaccinology, Jenner Institute**

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**Project title:** Designing and testing more potent vaccines

**Project description:** Traditional vaccines are made from killed or inactivated pathogens and only a very small number of subunit vaccines derived from pathogen components have been licensed. However, the availability of full sequences of the genomes of most infectious pathogens and of new viral vectors now make possible a new generation of vectored vaccines that will address not only difficult global diseases such as HIV, malaria and tuberculosis but also the immunotherapy of viral infections and cancer.

We have developed numerous improved adenoviral vectors that generate very powerful antibody and T cell responses when used in optimised immunisation regimes. Some of these are of chimpanzee origin and avoid the problem of widespread immunity to human adenoviruses. Others express novel adjuvants in addition to a pathogen gene, enhancing further the potency of these novel vaccines. Clinical trials are in progress of several of these new approaches targeting the most virulent malaria parasite *Plasmodium falciparum*.

The DPhil project will involve generation of vaccines comprising newly available vectors and a series of promising vaccine candidate antigens from the *P. falciparum* genome. These will be tested in malaria models for safety, immunogenicity and efficacy. The functional activity of the induced immune responses will be assessed both by growth inhibition assays and by polyfunctional flow cytometry. The most promising candidates
will progress towards clinical trials at the vaccine centre in Oxford.

**Zoology**

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*Project title:* Phylodynamic analysis of antigenic and genetic evolution of Influenza A  

*Project description:* Human influenza viruses - of which type A is the most virulent - infect 3-5 million people worldwide each year, resulting in more than 250000 deaths. It is now clear that the continual antigenic change of influenza A, which enables the virus to evade host immune responses, results from a complex and poorly-understood interplay of genetic and epidemiological processes. Although genomic and immunological data are abundant, there is a critical lack of quantitative models for data analysis. This project will develop an innovative evolutionary model to analyse the joint antigenic and genetic evolution of influenza A. The model will likely be based on ‘strong selection’ coalescent theory and incorporate viral population structure arising from both geography and antigenic type. As previously demonstrated, such models can be implemented in a statistical inference framework in order to estimate key parameters from empirical genetic data. The aim is to estimate, for the first time, parameters such as the ratio of antigenic to genetic change, local effective population sizes, and lineage migration rates, and thereby begin to build a rigorous quantitative understanding of influenza A behaviour.

*Supervisor:* Professor Angela McLean (Zoology) and Professor Rodney Phillips (Clinical Medicine), The Institute for Emerging Infections  
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*Project title:* Mathematical Models of the Emergence of New Infections of Humans  

*Project description:* The evolution of infectious diseases poses real problems for mankind. Many infections are developing resistance to drugs and vaccines that were once highly effective. At the same time entirely new infections are emerging from reservoirs in wild animals that were previously unknown. The study of pathogen evolution is a highly quantitative, interdisciplinary subject and a DPhil in this topic offers training in mathematical and statistical modelling coupled with exposure to problems of immediate significance for human well-being.

Angela McLean and Rodney Phillips are Co-Directors of The Institute for Emerging Infections, a founding Institute of the James Martin 21st Century School. The mission of the Institute for Emerging Infections is to understand the underlying processes that drive the emergence and spread of novel human infectious diseases. A multi-disciplinary
A team of biologists, mathematicians and clinicians are studying recently emerged infections and using the knowledge thus gained to anticipate challenges that will be posed by novel emergent infections in the 21st century.

Candidates should have a first degree in a highly quantitative subject and a strong interest in the biology of infectious disease.