The following PhD vacancies and research topics within the School of Life Sciences were compiled in November 2013 and were correct at the time of publication.

For further guidance on pursuing a PhD in any of these areas, please consult the School of Life Sciences website or contact the relevant members of academic staff as listed below.

Biochemistry

The control of transcription by mitogens during embryogenesis and oncogenesis

Supervisor:  Peter Shaw (peter.shaw@nottingham.ac.uk)

My group studies how transcription factors activate gene expression in response to extracellular signals. For example, cell proliferation and embryogenesis are controlled by growth factors that coordinate gene expression programmes over time and throughout a developing embryo. Mitogenic factors use the Ras/MAPK cascade to up-regulate G1 cyclins and other cell cycle genes promoting cell division. The pathway is crucially important, not least because it is subverted by oncogenes in all human cancers.

Several ETS family transcription factors activate their target genes in response to Ras/MAPK signalling. For example, the MAPK ERK phosphorylates Elk-1, which then activates c-fos, Egr1 and a number of other ‘early response’ genes. Our recent work has shown that Elk-1 is not only phosphorylated by ERK, it also recruits the kinase to target promoters, whereupon ERK phosphorylates subunits of the core co-activator complex (Mediator) associated with RNA polymerase II. Phosphorylation of Mediator is important for its function, because a mutation that prevents phosphorylation of Mediator subunit MED14 reduces Elk-1 dependent transcription.

We wish to learn how phosphorylation of MED14 and other Mediator subunits influences its function. We plan to explore the effect of ERK phosphorylation on conformational change, subunit interactions and their stability within Mediator. Moreover, we need to establish which phases of the transcription cycle, such as elongation, re-initiation, or post-transcriptional events are influenced by Mediator phosphorylation. Conceivably ERK phosphorylation increases the responsiveness of Mediator to other transcriptional regulators, thereby contributing to feed forward control of developmental events.

Growth factors that induce ERK activity determine embryonic stem cell (ESC) self-renewal and drive tumour cell proliferation. In this context, ERK phosphorylation may prime Mediator to select transcription factors that regulate subsequent steps of the cell cycle, committing cells to mitosis instead of differentiation. A similar mechanism may operate in tumour cells. We are currently offering projects on the role of Mediator phosphorylation during cell cycle progression in ESCs and tumour cells.
Arrdc2 and its role in cell signalling and intracellular protein trafficking

Supervisor: Simon Dawson (simon.dawson@nottingham.ac.uk)

We have discovered a novel protein, arrdc2, which is a member of the recently described α-arrestin family of proteins. α-arrestins, of which there are at least six proteins in the human genome, are thought to be evolutionarily older than their more famous α-arrestin cousins and share many of the same structural features. Despite the similarities, little is known about the functions of the α-arrestins although increasing data is being described which suggests that the α-arrestins may play roles in both receptor-mediated cell signalling and intracellular protein trafficking processes.

We have shown that arrdc2 interacts with members (the NEDD4 sub-group) of the ubiquitin-protein ligase (E3) family of proteins and is ubiquitylated. We wish to understand the consequences of the observed interaction and the role of arrdc2 ubiquitylation in both the context of defined cell signalling pathways and intracellular protein trafficking. This will be achieved using fluorescence microscopy, gene reporter assays, genetic knockdown experiments and biochemistry experiments.

Transposon: from biotech tools to epigenetics and development

Supervisor: Ronald Chalmers (ronald.chalmers@nottingham.ac.uk)

Transposons are selfish DNA elements that become amplified as they move from one location in the genome to another. They thrive in all branches of the tree of life and are therefore probably very ancient. About 50% of the modern human genome has its origins in the activity of transposons. Consequently, transposons are intimately involved in many aspects of our biology. The best example is perhaps the transposon ancestry of the vertebrate adaptive immune system. We study several aspects of transposition, including the molecular mechanism of recombination, the development of tools for biotechnology and the epigenetic interactions between a transposon and its host. Our work is interdisciplinary, involving the techniques of biochemistry, genomics, transcriptomics and systems biology.

Understanding disease mechanisms in disorders of the bone and brain

Supervisor: Rob Layfield (robert.layfield@nottingham.ac.uk)

Work in my lab has a particular focus on a protein called p62 and the processes it controls. Mutations in the p62 protein are a common cause of the bone disorder Paget's disease and we continue to research precisely how they impact on protein structure and function. Very recently p62 mutations have also been identified in a subset of patients with the neurodegenerative disorders amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD).
Why some patients present with an osteoclast phenotype but others with a neuronal phenotype is a critical question which we are addressing.

**Regulation of a Crucial Mitotic Kinesin**

Supervisor: Claire Friel ([claire.friel@nottingham.ac.uk](mailto:claire.friel@nottingham.ac.uk))

My group is interested in the control of chromosome segregation, which is crucial in eukaryotic cell division. We have a particular focus on the role of microtubule depolymerising kinesins. The mitotic centromere-associated kinesin (MCAK), a member of the kinesin 13 family, is essential during mitosis: both in generating the force to separate sister chromatids and in ensuring correct segregation of chromosomes by correcting inappropriate kinetochore-microtubule attachments. The aim of the proposed work is to discover how mitotic cofactors regulate MCAK’s activity as a microtubule depolymerase. Using fluorescently labelled microtubules and time-lapse microscopy, we will measure the rate of microtubule depolymerisation by MCAK in the presence of its various regulatory cofactors. Further, to uncover the molecular mechanism of observed effects, microtubule depolymerisation will be evaluated in terms of nucleotide turnover, using transient kinetic methods, and in terms of microtubule binding, using total internal reflection fluorescence (TIRF) microscopy.

**Molecular Biology of DNA Repair: Hel308/HelQ helicases**

Supervisor: Edward Bolt ([ed.bolt@nottingham.ac.uk](mailto:ed.bolt@nottingham.ac.uk))

We investigate chromosome re-arrangements and repair of DNA damage, using molecular biology techniques alongside proteomics. This project focuses on the DNA repair enzyme Hel308/HelQ, which is emerging as an important factor in promoting genome stability in archaea and eukaryotes and is a part of a protection system against some cancers. The project includes elucidating helicase/translocase mechanisms and how Hel308/HelQ interacts with DNA replication and recombination factors. Work in my laboratory is part of wider collaborations in The UK, Croatia and Germany in which we contribute biochemical analysis of protein structure and function.

**Function and mechanism of multidrug efflux pumps in cancer cell biology**

Supervisor: Ian Kerr ([ian.kerr@nottingham.ac.uk](mailto:ian.kerr@nottingham.ac.uk))

We are interested in a group of proteins – the ATP binding cassette (ABC) transporters. Several of these proteins have the ability to pump out a very wide range of substrates from human cells. This is known as multidrug efflux. Some of the human ABC transporters are involved in the resistance of cancer cells to chemotherapy because of this multidrug efflux activity. My group is
interested in how these proteins work – in other words the structural and mechanistic details of multidrug transport, and we have a number of different projects that to investigate this. We also have collaborations with another group (Dr Beth Coyle) which is interested in the contribution of these pumps to brain tumour drug resistance in children, and joint projects with this group are a possibility.

Cell and Developmental Biology

The role of survivin in cell survival and cancer

Supervisor: Sally Wheatley (sally.wheatley@nottingham.ac.uk)

Survivin is a small pro-survival protein normally only expressed during G2 and M-phases of the cell cycle. However, its expression is deregulated in all cancers, and its overabundance protects cells against apoptosis and irradiation. Although predominantly cytoplasmic in interphase, survivin is also found in the nucleus and mitochondria. To achieve its multiple roles survivin interacts with many proteins: in mitosis, it targets the essential “chromosomal passenger complex” (CPC) to the centromere. By collaborating with aurora-B kinase and the spindle checkpoint, survivin ensures chromosomes are correctly aligned at the cell centre prior to cell division, and that the genome is transmitted accurately from one generation to the next. Other survivin-interactors include microtubules, XIAP; exportin, beclin and LC3B and it is phosphoregulated by many kinases, including aurora-B, cdk1 and plk1. Overall the goal of my lab is to understand how survivin impacts on human health, through analysis of its molecular function in mitosis, apoptosis and autophagy.

Def6 and swap70 proteins and their roles in cell shape, movement and fate during zebrafish embryogenesis

Supervisor: Fred Sablitzky (fred.sablitzky@nottingham.ac.uk)

We have discovered a protein, def6 that functions as a novel type of guanine nucleotide exchange factor for Rho GTPases (1). Using morpholino-mediated knockdown experiments combined with marker gene expression studies we determined that def6 plays a fundamental role in zebrafish development regulating convergent extension cell movement during gastrulation. We showed that def6 acts downstream of Wnt5b in the non-canonical Wnt signalling pathway (2). Def6 and its only parologue swap70 share a unique domain arrangement that is highly conserved through evolution (3). We now want to determine in more detail the function of def6 and swap70 proteins to further dissect molecular pathways regulating cell movements, shape and fate. The objective of the research project is to determine the
molecular network of def6 and swap70 function using loss- and gain-of-function analysis, in vivo imaging, time-lapse microscopy, in situ hybridisation and comparative data analysis.

**In cell analysis of myosin Va function in intracellular transport**

Supervisor: **Alistair Hume** ([alistair.hume@nottingham.ac.uk](mailto:alistair.hume@nottingham.ac.uk))

In order that the cells of our body function correctly they must establish and maintain a complex arrangement of specialised internal structures (organelles). The function of organelles is essential for life e.g. energy production. Transport and communication between organelles is a fundamental and essential physiological process. In line with the importance of organelle transport blocks and other defects in these processes result in many common human diseases such as Cystic Fibrosis, hypercholesterolemia, neuro-degeneration and some forms of cancer.

To allow organelle transport, cells have evolved complex (protein-based) machinery that can move material between different organelles and areas of the cell. One class of proteins required for this are motor proteins that convert chemical energy, from food, into movement and transport cargo along subcellular protein ‘tracks’ known as the cytoskeleton. This project aims to understand in greater detail how one of these motors, MyosinVa (MyoVa), functions in intracellular transport.

**Using the fly to study cancer**

Supervisor: **Marios Georgiou** ([marios.georgiou@nottingham.ac.uk](mailto:marios.georgiou@nottingham.ac.uk))

Tumour cell invasion and metastasis are the major cause of mortality in human cancers. However, we know relatively little about the biology that underlies the important transition to malignancy - when cancer cells gain the ability to leave their tissue of origin and spread through the host. We have developed a combination of tools that enable us to study tumour cell invasion in the living fruit fly (Drosophila melanogaster). Now, using the back of the fly (the dorsal thorax) we are able to combine powerful Drosophila genetics and excellent cell biology to image mutant cells as they become invasive, in high temporal and spatial resolution, in the hours and days following tumour induction.

This novel in vivo system combines Drosophila genetic tools to express GFP-fusion proteins specifically in well-spaced epithelial cells in the fly dorsal thorax, allowing us to study epithelial cell shape in detail. Through the use of the Flp/FRT system we are able to generate tumours specifically within this tissue and observe the behaviour of the epithelium when introducing small clones of mutant tissue. Using the MARCM technique we are able to specifically label individual mutant cells, allowing for a detailed analysis of cancer cell morphology, dynamics and behaviour following transformation.

By studying tumour suppressor genes and oncogenes that have been implicated in tumour progression, we hope to make a significant contribution to cancer research. However, we will
additionally be looking to identify novel genes that promote or inhibit tumour progression and invasion, using a genetic screen. We will also be addressing other aspects of tumour progression, including cell-cell adhesion, tissue architecture and the tumour microenvironment.

**Providing insights into the molecular understanding of heart development and the formation of congenital heart defects**

Supervisor:  **Siobhan Loughna** ([siobhan.loughna@nottingham.ac.uk](mailto:siobhan.loughna@nottingham.ac.uk))

My lab is interested in understanding how the heart develops and then goes wrong to give rise to congenital heart defects, which are the most common defects in new born babies. The techniques we use are molecular, developmental and cell biology techniques, such as gene knockdown technology, in vivo manipulation, cell culture, in situ hybridisation, immunofluorescence, electron microscopy and mutational analysis. One research area is the analysis of novel genes that play critical roles in heart development, and which when aberrantly expressed can lead to heart defects. Another area of interest is a technique we use to create a model for heart enlargement (cardiomyopathy) and the formation of a ventricular septal defect (a common congenital heart defect).

**Mechanisms behind fetal vascular dysfunction in diabetic pregnancies**

Supervisor:  **Lopa Leach** ([lopa.leach@nottingham.ac.uk](mailto:lopa.leach@nottingham.ac.uk))

The central research focus of our group is to understand the mechanisms regulating two key functions of human blood vessels: permeability and angiogenesis. We are specifically interested in the role of junctional adhesion molecules and how their impairment can lead to placental and fetal vascular dysfunction in pregnancies complicated by diabetes mellitus. We use the extra-corporeally perfused term placenta and isolated human endothelial cells as complementary experimental models. This allows a powerful integration of physiology, confocal imaging and molecular biology. We also have a human in vitro model of the outer-retinal barrier which allows studies into neo-vascularisation, a complication of age-related macula degeneration. We are currently looking at transmigration behaviour of stem cells acquired from the human placenta and cord and how they affect endothelial barrier function.
Genetics

www.nottingham.ac.uk/life-sciences/research/genetics.aspx

Bioinformatic Studies of Mobile DNAs in Vertebrates

Supervisors: John Brookfield (john.brookfield@nottingham.ac.uk)
Olivier Hanotte (olivier.hanotte@nottingham.ac.uk)

44% of the human genome, and similar proportions in other vertebrate species, consists of mobile DNAs or their inactive descendants. These are scattered throughout genomes as a result of their past or present mobility, and many have been characterised as “junk DNA”. These DNAs are capable of spreading through genomes by replication transposition, and their copy numbers can increase to hundreds of thousands or millions, even if they convey no benefits to their hosts. However, while these sequences seem to start their lives as parasitic DNAs, they may subsequently evolve functions that are adaptive for the host. There exist powerful statistical tests, examining sequence conservation, which can identify whether a now-inactive copy of a previously mobile sequence family is now conferring any adaptive benefit on its host. The project will consist of applying bioinformatics analyses to whole genome information from wild and domesticated species of vertebrates, including variation within- and between-species, to establish whether interspersed repetitive sequences make a major contribution to adaptation and adaptive change.

Behavioural ecology of nesting in Wheatears (Oenanthe)

Supervisor: Kate Durrant (katie.durrant@nottingham.ac.uk)

Many, if not all, species of wheatear carry stones to build a nest platform during the breeding season. There are many hypotheses regarding this behaviour. These include nest support, use in thermoregulation, weatherproofing, as an anti-predation device and as a sexually-selected display of quality. We have discovered that nest sites and platforms are reused between seasons in the white-crowned black wheatear (Oenanthe leucopyga). Stones appear to be accumulated over the years, raising interesting questions over site inheritance and parasite control. It is also inherently valuable to study desert species, as most work has been performed on temperate woodland species and knowledge on the evolutionary pathways and strategies required to survive in arid lands is missing. The aim of this project would be to investigate the function of the platform and carrying behaviour in the field in a comparative study between genera and within Oenanthe leucopyga, building on previous work.

Insect-plant relationships
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Supervisor:  Francis Gilbert (francis.gilbert@nottingham.ac.uk)

We are interested in the dependences of plants on insects and vice versa, with both pollination and herbivory interactions. We work in South Sinai (Egypt) and in the UK on various systems, including the chemical ecology of Sinai asclepiads and the population biology and genetics of the insects and associated plants of the Lamiaceae and Boraginaceae. A further interest is in the role of grazing by insects and livestock in maintaining plant diversity in the Sinai mountains. The aim of the work in Sinai is both academic and practical since our work underpins the management plans of the St Katherine Protectorate.

Genetic diversity and adaptation of indigenous livestock from the tropics

Supervisor:  Olivier Hanotte (olivier.hanotte@nottingham.ac.uk)

Indigenous livestock of the tropics carry unique genetic adaptation allowing them to survive and to remain productive under the challenges of natural selection. Particularly important are their adaptation to climatic stress and infectious parasitic diseases. Our ongoing research program has two main objectives: 1. to genetically characterize the diversity of indigenous livestock genetic resources, including understanding its origin, its geographic distribution and its history (cattle, sheep, goat dromedary, buffalo and/or chicken); 2. to identify genetic signature of selection (e.g. heat tolerance/susceptibility and livestock diseases). Genetic characterization is performed through sequencing of mitochondrial DNA and genome-wide SNP genotyping, while NGS approaches and HD SNP chip genotyping are used for the identification of signatures of selection and candidate chromosomal regions and genes for adaptive traits. Research outputs aim to contribute to the conservation and sustainable utilisation, including improvement of productivity, of indigenous livestock to the benefit of farmers’ communities.

Evolution and development of left-right asymmetry/colour polymorphism

Supervisor:  Angus Davison (angus.davison@nottingham.ac.uk)

We are applying next generation sequencing methods to investigate two fascinating and long-standing problems in evolutionary and developmental biology. In the first project, we are investigating the evolution and development of left-right asymmetry. The ultimate aim is to understand how “chirality” is determined at the molecular level, then extrapolate this to include the means by which variation in sequence, and dominance relations between alleles, contributes to the evolution of new chiral morphs. In the second study, we are interested in how conspicuous colour polymorphisms evolve, a question that relates to the much wider issue of how the genome responds to disruptive or balancing selection. The fast moving nature of these projects makes it difficult to give a precise project. However, I envisage that the student will use Illumina RAD genotyping runs, along with RNA Seq methods and BAC mapping to further home in on the genes in question. He/she may also develop new species/models to study,
enabling deeper comparative analyses. The student will receive training in standard molecular lab methods, next generation sequencing and bioinformatic methods.

**Evolutionary genetics of arachnids and their endosymbiotic bacteria**

Supervisor: **Sara Goodacre** ([sara.goodacre@nottingham.ac.uk](mailto:sara.goodacre@nottingham.ac.uk))

Spiders, ticks and other arachnids are known to be infected with a range of endosymbiotic bacteria that are transmitted from mother to offspring. The effects of individual infections on their arachnid hosts are not well understood, but similar bacteria lead to significant reproductive and behavioural changes in other arthropod hosts. This project will characterise the genetic diversity of microbial infections in individual arachnid hosts using molecular techniques and investigate their effects on host biology under laboratory conditions.

**Characterising the transcriptome of social Stegodyphus spiders - understanding invertebrate post-transcriptional control mechanisms.**

Supervisors: **Sara Goodacre** ([sara.goodacre@nottingham.ac.uk](mailto:sara.goodacre@nottingham.ac.uk))  
**Keith Spriggs** (Pharmacy, [keith.spriggs@nottingham.ac.uk](mailto:keith.spriggs@nottingham.ac.uk))

Untranslated regions of eukaryotic genes regulate protein expression through post-transcriptional mechanisms such as microRNAs, ribosome recruitment and poly-adenylation. However, almost nothing is known about the nature of untranslated regions in spiders (Araneae), a group that is the focus of studies into potentially useful proteins such as venom and silk. The aims of this bioinformatic project are to examine newly sequenced spider transcriptome sequences (and genomic sequences where possible) in order to identify and characterise regulatory elements in untranslated regions and to characterise mobile genetic elements such as transposons. In addition to broadening our knowledge of mechanisms for regulating gene expression, this work will also have likely application in the optimisation of synthetic silk and venom expression systems.

**Individual fitness in spatially-structured plant populations**

Supervisor: **Markus Eichhorn** ([markus.eichhorn@nottingham.ac.uk](mailto:markus.eichhorn@nottingham.ac.uk))

Individual plants in natural populations are typically clustered at small scales. The position of a plant within an aggregation has numerous implications for competition with conspecifics and interactions with pollinators and herbivores. In this project we will use a combination of observational and experimental approaches to investigate the impacts of population spatial structure on plant properties, and assess whether plants are able to make adaptive adjustments in response to their neighbourhoods. This will involve assessing spatial variation in flower
morphology, seed characteristics or relative investment in vegetative versus reproductive tissues. Initial censuses will map distributions of naturally-occurring plants and their traits, followed by experimental plantings with predetermined patterns to investigate their impacts.

Project time will be divided between experimental work and the field, with approximately 12 months fieldwork over three years. A suitable candidate will have strong interests in either plant ecology/botany or mathematical modelling.

**Sequence variation underlying human neuropsychiatric and neurodegenerative diseases**

Supervisor: Helen Knight ([helen.knight@nottingham.ac.uk](mailto:helen.knight@nottingham.ac.uk))

This is the decade of the ‘brain’ and this is also the decade of advancements in ‘genomic technologies’. This project aims to use cutting edge sequencing technologies to understand susceptibility to human disorders of the brain. The project will use a combination of bioinformatics and statistical tools with molecular biology techniques to investigate how sequence variants, including deleterious mutations, within genes encoding proteins needed for neuronal transmission differ between populations of healthy and non-healthy individuals. Identified risk variants may also be assessed for correlations with phenotypic data such as cognitive performance and biochemical measures. The findings of such studies should improve our understanding of how genetic architecture relates to biological and pathophysiological processes which contribute to expression of disease - a key topic in current academia.

**Characterisation of genomic copy number variation in chickens**

Supervisor: John Armour ([john.armour@nottingham.ac.uk](mailto:john.armour@nottingham.ac.uk))

Domestic chickens are of major importance in the world’s food supply, but the study of genetic variation in chickens is generally underexplored. Recent whole-genome studies have demonstrated that in addition to substantial substitutional (SNP) variation, there is widespread variation between chickens in the copy number of many genes. Some of these examples of copy number variation (CNV) involve genes of the immune system, most strikingly in the major histocompatibility complex (MHC) on chromosome 16. In this project, the student would develop methods for characterising CNV of chicken genes, beginning with candidates from the MHC, but also including other candidate genes of functional interest from elsewhere in the chicken genome. Typing methods would then be applied to DNA from well-characterised chickens from around the world, and where appropriate correlated with important phenotypes like disease resistance.

**DNA Replication and Repair in Archaea**
Archaea are the third domain of life, they live in harsh environments that pose enormous challenges for growth and DNA repair. Most archaea are difficult to cultivate and so little is known about these fascinating organisms. At first glance, archaea appear similar to bacteria they are small, unicellular and lack organelles. However, archaea share many aspects of their molecular machinery with eukaryotes, in particular the mechanisms for DNA replication and repair. We are studying these processes in archaea using a combination of cell biology, genetics and biochemistry.

**Genome Replication and stability in model organisms**

**Supervisor:** Conrad Nieduszynski (conrad.nieduszynski@nottingham.ac.uk)

We study genome replication in a range of model organisms, including the budding yeast Saccharomyces cerevisiae. All the steps of genome replication are similar between yeast and humans. Therefore advances we make working with yeast will be informative for future studies with human cells and treatment of patients. Failures in the processes of DNA replication lead to genetic instability and diseases such as cancer and congenital disorders. Specifically we are interested in understanding the cellular control of the initiation and termination of DNA replication. We are studying these processes using a combination of cell biology, genetics, genomics and bioinformatics.

**Immunity**

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**Molecular basis of allergic sensitisation; an integrated mathematical-experimental approach**

**Supervisors:** Amir Ghaemmaghami (amir.ghaemmaghami@nottingham.ac.uk)  
Bindi Brook (bindi.brook@nottingham.ac.uk)

Allergy remains a global health issue with substantial health implications. Despite recent advances in patient care the morbidity and mortality of allergic diseases particularly allergic asthma has remained high. This is mainly due to inadequate and symptomatic nature of current treatments and the complex pathophysiology of allergic diseases.

Allergen exposure and sensitisation are key events in triggering ‘allergic cascade’ which leads to Th2 cell polarisation, IgE antibody production, mast cell sensitisation and triggering that collectively underpin most pathologies in allergic diseases. Allergen sensitisation is typically
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initiated by the recognition of allergens by antigen presenting cells, such as dendritic cells (DCs).
DCs have been shown to play a key role in the induction and re-elicitation of Th2-mediated inflammation in allergic diseases. However, the molecular processes underpinning these events have remained elusive. We argue that better understanding of early events at the interface of allergens and antigen presenting cells could pave the way for the rational design of novel intervention strategies that can target early stages of disease development. Using human cells in vitro (instead of animal models) provide many advantages in terms of the biological relevance however in vitro models lack the complexity of whole organisms and do not reflect the full spectrum of cell-cell and cell-matrix interactions.

In this application we propose to use a combination of in silico and experimental models to investigate the molecular basis of allergic asthma. To achieve this we will combine state-of-the-art multi-scale mathematical modelling techniques with an experimental platform based on a biomimetic 3D immune-competent model of human lung epithelium. The mathematical model will inform further optimisation of the tissue model and account for the lack of interaction at ‘whole organism’ level in an in vitro model. Crucially, the project provides multidisciplinary training opportunities in the interface of biological (cell and molecular immunology and tissue modelling) and mathematical sciences allowing the student to develop a deep understanding of and the ability to use mathematical models to improve understanding of biomedical phenomena.

Unraveling the host-parasite interface in African trypanosomes
Supervisor: Catarina Gadelha (catarina.gadelha@nottingham.ac.uk)

The surface membrane is the point of interaction between a cell and its surroundings. This interface is the site of many essential cellular functions such as nutrient uptake, secretion and sensing the environment. The surfaces of parasites, however, have an extra level of constraint: they must perform these vital tasks whilst avoiding recognition and elimination by the host. For African trypanosomes – lethal protozoan organisms endemic to some of the poorest countries of sub-Saharan Africa – cell surface composition is essential to the parasite’s strategy of immune evasion, survival and disease transmission. However, very little is known about the proteins that reside at this interface. This severely hampers the development of drugs or vaccines against human African trypanosomiasis and related diseases. This project will use advanced cell biology, biochemistry and molecular techniques to investigate surface membrane function, molecular components and biogenesis at the trypanosome host-parasite interface. In doing so, it will identify exposed essential proteins that are potential vulnerabilities for the development of new treatments.

Understanding cell division and developmental biology of malaria parasite
Supervisor: Rita Tewari (rita.tewari@nottingham.ac.uk)
Malaria is an infectious disease that threatens 40% of total world’s population, the majority living in developing countries. There are ~500 million clinical cases and 1 million deaths per year mostly of children (http://www.who.int/topics/malaria/). The disease is caused by an apicomplexan protozoan parasite of the genus Plasmodium that is transmitted by the bite of an infected female Anopheles mosquito. Our research is mainly aimed to understand the molecular pathways that are involved in malaria parasite development and differentiation, cell division, and parasite interactions with both mammalian and vector host.

We are interested in studying number of gene families that regulate the process of cell division and signalling pathways during parasite development. We use molecular, genetic, cell biology, biochemistry, proteomics and reverse genetics approaches to study the function of regulatory protein families like kinases, phosphatases, cell division proteins and armadillo repeat proteins in malaria parasite biology. For all these studies we use rodent malaria model Plasmodium berghei that is easily amenable to reverse genetic studies and whole life cycle of parasite can be studies both in mammalian host and vector mosquito.

Microbiology

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Autotransporter secretion from Pseudomonas aeruginosa

Supervisor: Kim Hardie (kim.hardie@nottingham.ac.uk)

All the autotransporters characterized to date are virulence factors. Pseudomonas aeruginosa is an important opportunistic pathogen that is a particular problem to sufferers of cystic fibrosis (CF) and people with wounds. It is classed as a superbug because of the incidence of infections it causes in hospitals and the intrinsic resistance it has to the currently available antibiotics. The functions of the autotransporter proteins and how they contribute to the pathogenicity of P. aeruginosa have not been well studied. In our lab, we have just published the functional characterisation of one Autotransporter which we have called AaaA. Although we know it is an arginine-specific aminopeptidase that helps cause chronic skin wound infections, we do not know how it is able to do this, or what it’s substrate is. We are investigating these aspects and also aim to characterize its role within infections of the skin and CF lung.

Novel ways to decrease the spread of superbugs

Supervisor: Kim Hardie (kim.hardie@nottingham.ac.uk)

Infection costs money, decreases quality of life, and often causes death. Superbugs frighten people and threaten the benefit of Hospitals. The recent swine and bird flu’s highlight the
impending dangers of pandemics. The single most effective way to decrease infection rates is to wash hands well and at appropriate times. We plan to harness children’s enthusiasm to learn with an attractive, interactive toy that will teach them how to wash their hands properly. The lesson will last a lifetime, and the powerful pestering by children will spread the word. The improved cleanliness of the public will reduce cross infection in the community, and lessen the introduction and spread of infection in hospitals. The project will involve going into schools and hospitals to trial a novel intervention we have designed to educate children how to wash their hands (the Glo-yo, described recently in Journal of Hospital Infections, http://glo-yo.co.uk/). Our novel molecular detection technology will also be employed and part of the project will be to assess its usefulness for diagnosis and monitoring.

Functional characterization of selected meningococcal autotransporter proteins

Supervisor: Neil Oldfield (neil.oldfield@nottingham.ac.uk)

Neisseria meningitidis is a Gram-negative bacterium which can cause devastating outbreaks of meningitis and septicaemia. Meningococci elaborate numerous cell-surface and secreted virulence factors which facilitate colonization of, persistence in, and damage to, the host. One important class are the autotransporter (or type V secreted) proteins. Eight autotransporter proteins have been identified in meningococci, five of which were first discovered in our laboratory. This project will focus on the autotransporters IgA1 protease; App; MspA and NalP. These are secreted proteases which cleave various bacterial surface and/or host cell proteins, but their exact repertoire of targets and therefore precisely how they contribute to pathogenicity are still unclear. This project will be to investigate host cell receptors, uptake pathways, proteolytic targets, signalling events and phenotypic changes mediated by the autotransporters to provide new insights into pathogenesis. This will provide training in tissue culture, confocal microbiology, flow cytometry, protein biochemistry and molecular microbiology.

The evolution of microbial diversity and virulence in the cystic fibrosis lung

Supervisor: Steve Diggle (steve.diggle@nottingham.ac.uk)

The Cystic Fibrosis (CF) lung presents a complex polymicrobial ecology, which complicates treatment. The most commonly associated CF pathogen is Pseudomonas aeruginosa. It is now well established that P. aeruginosa strains isolated from CF patients are diverse at both the genetic and phenotypic level. It is less known what impact this diversity has on the evolution of virulence and disease states. The aims of this project are (a) to provide new insights as to how and why diversity evolves within a single species bacterial population; (b) to determine how diversity within populations impacts on the susceptibility to antibiotics and (c) determine how diversity during infection impacts on patient health and clinical practice. The project offers training in laboratory and clinical microbiology, microbial genetics, next generation sequencing, bioinformatics, molecular biology and evolutionary biology. Our group (www.stevediggle.com)
has strong partnerships with Evolutionary Biology groups in Oxford and Edinburgh providing ample opportunity for novel collaborative research.

**Biology and genetics of reproduction in filamentous fungi**

Supervisor: **Paul Dyer** ([paul.dyer@nottingham.ac.uk](mailto:paul.dyer@nottingham.ac.uk))

Filamentous fungi are of importance in the food, industrial and medical sectors and have important roles in the ecology of natural ecosystems. This project aims firstly to gain knowledge relating to the physiological and molecular-genetic mechanisms controlling reproduction in fungi. This is especially as applied to the evolution and regulation of sexual reproduction in ascomycete fungi such as Aspergillus and Penicillium species, and also lichen-forming fungi. It is hoped that an improved understanding of mechanisms underlying sex and mating will lead to new strategies for strain improvement and the control of fungal diseases. Secondly, this project aims to use the sexual cycle to study the biology of genetic traits of interest relating to fungicide resistance, food production and production of industrial metabolites of interest. A combination of classical microbiology and genetics and modern molecular and genomic techniques are being used in these investigations.

**Stress and drug resistance in the yeast model**

Supervisor: **Simon Avery** ([simon.avery@nottingham.ac.uk](mailto:simon.avery@nottingham.ac.uk))

This project is focused on understanding the effects of stress on cells, with emphasis on toxic metals, oxidants and antimalarial drugs. We study yeasts like Saccharomyces cerevisiae, which is an ideal eukaryotic model for characterizing stress-effects at the whole-cell and molecular levels. This project will concentrate on stressor- or drug-induced oxidative stress as the main toxicity mechanism. This area is of particular interest considering the associations of oxygen free radicals with pathogen resistance, drug mode-of-action, cancer, aging and a host of other degenerative conditions in humans. The project will include analyses of the variability in stress responses seen among individual cells within populations. Cell individuality is a highly topical area being investigated by a number of laboratories across the world.

**Integration of quorum sensing signalling into bacterial regulatory networks**

Supervisors: **Miguel Cámara** ([miguel.camara@nottingham.ac.uk](mailto:miguel.camara@nottingham.ac.uk))
**Paul Williams** ([paul.williams@nottingham.ac.uk](mailto:paul.williams@nottingham.ac.uk))
**Stephan Heeb** ([stephan.heeb@nottingham.ac.uk](mailto:stephan.heeb@nottingham.ac.uk))

The regulation of biofilm formation, swarming and the biosynthesis of virulence factors in Pseudomonas aeruginosa (PA) is controlled through the production and release of diffusible...
chemical signals termed quorum sensing (QS) signal molecules (QSSMs). The PA QS system consists of two N-acyl homoserine lactone (AHL) regulatory circuits (termed las and rhl) linked to a 2-alkyl-4(1H)-quinolone (AQ) circuit. LasR and RhlR are both LuxR-type transcriptional regulators which activities depend respectively on the AHLs N-(3-oxododecanoyl)-L-homoserine lactone (3OC12-HSL, synthesized by LasI) and N-butanoyl-L-homoserine lactone (C4-HSL, produced by RhlI) to drive the expression of virulence determinants. In addition to the AHLs, PA produces AQs, two of which (PQS and HHQ) are involved in the control of gene expression. These QS systems are tightly integrated within other regulatory networks in PA which include two-component systems and post-transcriptional regulators. The aims of this project will be to investigate novel mechanisms by which these additional regulatory systems interact with QS-mediated control of virulence in this bacterium. The project will provide extensive training in molecular biology, microscopy and analytical biochemistry techniques.

**Characterisation and exploitation of novel antimicrobial targets in Pseudomonas aeruginosa**

Supervisors: Miguel Cámara (miguel.camara@nottingham.ac.uk)  
Paul Williams (paul.williams@nottingham.ac.uk)  
Stephan Heeb (stephan.heeb@nottingham.ac.uk)

As part of a large collaborative antimicrobial discovery programme we have identified a number of key genes required for full virulence in the bacterial pathogen Pseudomonas aeruginosa (PA). Some of these genes were already known for being central regulators of the quorum sensing regulatory circuits while others still remain to have more precisely their functions and modes of action elucidated. We have seen that the disruption of some of these genes render PA biofilms more susceptible to the action of antibiotics. The aims of this project will be: (i) to identify novel inhibitors of the quorum sensing systems in PA and (ii) to unravel the functions and modes of action of some of the newly identified genes with a view to establish the basis of novel treatments which can eventually be used, in combination with currently available antimicrobials, to treat PA infections. The project will provide extensive training in molecular biology, microscopy and analytical biochemistry techniques.

**The role of bacterial surface proteins in meningococcal pathogenesis**

Supervisor: Karl Wooldridge (karl.wooldridge@nottingham.ac.uk)

Neisseria meningitidis (the meningococcus) is usually a harmless commensal bacterium which colonises the human nasopharynx. For reasons that are poorly understood the organism occasionally invades the mucosa of the upper respiratory tract and invades the bloodstream, from where it can cause systemic infection; it is also capable of breaching the blood-brain barrier (BBB), which is normally impenetrable to most bacterial pathogens, where it can cause meningitis. We are currently investigating the role of a number of bacterial surface proteins...
which bind to receptors in human cells. We have shown that one such protein, the non-integrin laminin receptor, is targeted by the meningococcus as well as other bacteria capable of breaching the BBB and causing meningitis. The interactions of bacterial proteins with host cell receptors are believed to play important roles in disease. The student would work as part of a team investigating various aspects of this host-pathogen interaction.

**ABO blood group antigens are levers for adherence of Campylobacter**

Supervisor: **Dlawer Ala'Aldeen** ([daa@nottingham.ac.uk](mailto:daa@nottingham.ac.uk))

Campylobacter species are the commonest reported bacterial causes of gastroenteritis in the UK and industrialized world. The bacteria colonise the small intestine of the human host, before colonizing and invading in the colon. This study focuses on bacterial adhesion molecules and the way they cooperate to establish efficient attachment to human enteric surfaces that can successfully withstand strong external forces that acts upon bacteria.

The ABO (or ABH) and Lewis Blood group Antigens (BgAg) have been epidemiologically associated with susceptibility to several infectious agents. Recent studies showed that adherence of Campylobacter to epithelial cells can be partially inhibited by fucosylated sugar components of human breast milk, which were later identified as human BgAgs H1 and H2. Preliminary work in our research group confirmed that C. jejuni specifically binds all human BgAgs. The corresponding adhesins were identified and shown to undergo post-translational modification (i.e. glycosylation). The aim of this study is to understand better the role of bacterial glycosylation in the attachment process, to identify the binding sites of specific adhesin–receptor bonds, to investigate the biomechanical properties of the adhesins and to identify immunodominant peptide(s) within each adhesin which may be targeted by the human immune system.

**Specific interaction of human cytokines with Escherichia coli modulates bacterial behaviour**

Supervisor: **Jafar Mahdavi** ([jafar.mahdavi@nottingham.ac.uk](mailto:jafar.mahdavi@nottingham.ac.uk))

The effects of uropathogenic E. coli on the host have been explored at length: E. coli exerts its pathogenicity through both its virulence factors and the inflammatory immune response that it triggers in the host. What remains to be considered, however, is how this cytokine-orchestrated immune response in turn influences E. coli infection. The binding of human cytokines to Gram-negative pathogens via unknown receptors localised to the bacterial surface has been documented.

This study will investigate the role of (a) key receptor(s) in the interaction between E. coli and cytokines associated with uropathogenic E. coli infection (i.e. IL-8, IL-6, IL-4 and TNF-α and IFN-γ). Identification of receptors is crucial for an understanding of the host/pathogen
relationships. It is hypothesised that this interaction will trigger modulation in the expression of E. coli virulence factors such as exotoxins, adhesins, type III secretion system effector proteins, as well as capsule production and flagella motility.

Future work will explore the physiological relevance of this phenomenon to both host and pathogen and the response of a wider range of E. coli virulence factors will be examined. Ultimately, this work will be extended to in vivo studies, with possible bearings of the design of novel future pharmaceuticals.

Developing bacteriocins as alternatives to antibiotics against Clostridium difficile infection

Supervisor: Sarah Kuehne (sarah.kuehne@nottingham.ac.uk)
Chris Penfold (chris.penfold@nottingham.ac.uk)

Clostridium difficile-associated diarrhoea (CDAD) is currently the most frequently occurring nosocomial infection in many hospitals worldwide and imposes a substantial financial burden on health-care systems. Indeed, in 2011, C. difficile killed nearly six times as many people in the UK as MRSA. C. difficile infection (CDI) occurs following the disruption of the normal gut microflora, most often as a consequence of antibiotic treatment. The spectrum of disease ranges from asymptomatic carriage to a fulminant, relapsing, and increasingly fatal colitis. Currently treatment options are limited to very few antibiotics which are under threat from the emergence of resistant strains. New countermeasures are urgently required, and we are investigating the use of bacteriocins as therapeutic alternatives. Bacteriocins are narrow spectrum protein antibiotics that rapidly kill closely related species and have recently been shown to be produced by Clostridium spp. with activity against a range of C. difficile isolates. The aim of this project is to identify bacteriocins produced by Clostridia and other endospore forming bacteria isolated from environmental samples and test biological activity of producing strains against a range of clinically relevant C. difficile isolates. We will then characterise each bacteriocin further, investigating the mode of action and methods of entry.

Pyocins as alternatives to antibiotics against Pseudomonas aeruginosa infections

Supervisor: Chris Penfold (chris.penfold@nottingham.ac.uk)

Pyocins are bacteriocins produced by Pseudomonas aeruginosa to kill closely related strains of the same species during times of environmental stress. There are three types of pyocin: (i) type R and (ii) F pyocins resemble phage particles in structure and kill bacteria by depolarisation of the cytoplasmic membrane, (iii) S type pyocins proteins that kill sensitive bacteria by degrading their DNA. Recently, we have used PCR to determine the distribution of pyocin types within laboratory strains and clinical isolates of Pseudomonas aeruginosa. Using biological activity assays and DNA mutagenesis we have defined the sensitivity and resistance profiles of all
isolates against other isolates and have shown that inhibition of growth of one isolate by another isolate is related to pyocin type. In this project, we will determine the role of pyocins in shaping interactions of different isolates of Pseudomonas aeruginosa in liquid culture and biofilms. Pseudomonas aeruginosa is very capable of forming biofilms as a means of cell to cell communication and protection of individual cells against environmental hazards. Pseudomonas aeruginosa exists in the lungs of sufferers of cystic fibrosis as organised biofilm structures which hinder antibiotic therapies. We will test the impact of pyocins on the stability of individual cells within the biofilm structure and assess the opportunities for pyocin therapy against Pseudomonas aeruginosa in biofilm.

Uncovering Yersinia spp. virulence mechanisms

Supervisors: Steve Atkinson (steve.atkinson@nottingham.ac.uk)  
Paul Williams (paul.williams@nottingham.ac.uk)

The Gram-negative bacterial human pathogens belonging to the group Yersinia regulate key virulence descriptors, such as biofilm formation, cell aggregation, motility and type three secretion as a population-wide response through the production and transduction of diffusible chemical signals. At the molecular level this process, usually referred to as quorum sensing (QS), consists of two regulatory circuits (ypsR/I and ytbR/I) which depend on N-acylhomoserine lactones (AHL) as the signal. The relationship between the QS system and these important markers for virulence is complex and to date we have uncovered a temperature-dependent network of integrated control circuits. The project aims to continue this work to examine in more detail how Yersinia pseudotuberculosis, Yersinia enterocolitica and Yersinia pestis regulate their virulence mechanisms as a product of cell density. The project will provide extensive training in molecular genetics, microbiology, microscopy and biochemistry techniques.

Regulation of quorum sensing-dependent type three secretion in Y. pseudotuberculosis

Supervisors: Steve Atkinson (steve.atkinson@nottingham.ac.uk)  
Paul Williams (paul.williams@nottingham.ac.uk)

Through genetic mutation of the quorum sensing (QS) loci of Y. pseudotuberculosis we have shown that QS impacts on virulence in this pathogen by regulating several temperature dependent interconnected pathways which includes the expression of the type three secretion (TTS) system. The TTS system enables the invading pathogen to produce a surface nanomachine analogous to a hypodermic needle which injects a number of effector proteins into the host defense cells where they subvert the host cell metabolism, triggering apoptosis. Two regulatory proteins, YmoA and VirF act as checkpoints in the control of the production of the needle and effectors. Given that QS is involved in the regulation of TTS this project aims to examine whether there is a regulatory relationship between QS, VirF and YmoA. To achieve this
we will use molecular techniques to construct bioluminescent reporter gene fusions to examine gene expression. The project will provide extensive training in molecular genetics, microbiology, microscopy and biochemistry techniques.

**Small regulatory RNAs in the human pathogen Clostridium difficile**

Supervisor:  **Klaus Winzer** ([klaus.winzer@nottingham.ac.uk](mailto:klaus.winzer@nottingham.ac.uk))

The ‘superbug’ Clostridium difficile is the major cause of antibiotic-associated diarrhoea and severe inflammation of the colon. In the UK, deaths caused by this bacterium have quadrupled in recent years and the emergence of new, hypervirulent strains is of particular concern. Despite its medical importance, very little is known about the regulatory networks that are operating in C. difficile, and almost nothing about the roles played by small regulatory RNAs (sRNAs). sRNAs have been found in the genomes of many other bacteria where they have important functions in the regulation of cellular processes such as sporulation, quorum sensing, metabolism, and virulence (toxins). Unravelling the sRNA regulatory network in C. difficile would be an important step toward understanding how this pathogen survives in the gut environment and causes disease. As part of a previous PhD project, we have identified 260 putative sRNAs using a combination of bioinformatic and experimental approaches. We now wish to explore the role and mode of action of a number of highly expressed sRNAs in more details.

**Discovery of novel bacterial virulence factors and their roles in host-pathogen interactions**

Supervisor:  **Alan Huett** ([alan.huett@nottingham.ac.uk](mailto:alan.huett@nottingham.ac.uk))

Secreted bacterial effector proteins allow bacterial pathogens to manipulate, subvert and invade host cells to establish and maintain an intracellular niche. Discovery of new effector proteins is challenging since there are no known conserved signal sequences or motifs which are required for effector secretion.

Using a combination of cutting-edge microscopy, cell biology and molecular techniques we will discover and analyse novel bacterial effector proteins and their roles in infection and disease.

This project will involve cloning of bacterial genes, high-throughput transfection of human cell lines, automated image capture and the analysis of multi-colour images to identify novel bacterial effector proteins. Candidate proteins will then be confirmed and their functions elucidated using state-of-the-art molecular and cell biology methods.

These methods and techniques are broadly applicable to many bacterial pathogens and host cell processes, but current interests focus upon pathogenic Escherichia coli, Chlamydia trachomatis and host cell autophagy.
Neuroscience

www.nottingham.ac.uk/life-sciences/research/neuroscience.aspx

Chronic pain: the impact of early life experience upon life-long processing of noxious stimuli

Supervisor:  Gareth Hathway (gareth.hathway@nottingham.ac.uk)

We study the way in which early-life events can influence the way in which the nervous system processes and reacts to painful stimuli throughout life. The early postnatal period represents a time in which significant changes are occurring within the central and peripheral nervous systems. Clinically children in hospital undergo repeated painful procedures. This adversely impacts upon the development of pain processing systems yet this pain is often inadequately controlled due to our lack of understanding of the way in which pain is processed differently in children and neonates when compared to adults. We utilise in vivo, ex vivo and in vitro approaches to study the neurobiology of pain processing. The aim of the project is to identify key developmental processes that are central to the normal development of pain processing and which are fundamentally altered by pain in early life.

Role of micro-RNAs in the regulation of axonal function and connectivity in cortical neurons

Supervisor:  Federico Dajas-Bailador (f.dajas-bailador@nottingham.ac.uk)

The ability to think, move, or sense the environment depends on the correct formation and subtle changes of neuronal circuits and their billions of connections. In essence, this connectivity is dependent on neuronal polarization, a process by which neurons develop a long axon and multiple dendrites.

The regulation of axonal growth presents the neuron with important logistical problems derived from the fact that axons can travel great distances to find their targets. For this, the concept of axonal mRNA localization and regulated translation at developing axon growth cones and synapses has gained increased acceptance. Our recent work has discovered how small non-coding RNAs (microRNAs) can control the local translation in the axon of key components of the cytoskeleton and thus regulate axonal growth and branching.

Now, the use of microfluidic chambers has allowed us to determine the microRNA content of the axon using next-generation sequencing. The aim of this research project is to identify the cellular function of some of these newly identified axonal microRNAs, providing training in general cell biology skills, neuron primary cultures, imaging techniques and bioinformatics. We
believe this is an exciting and novel project that will address a crucial scientific question in the field of molecular neuroscience.

**Neurotrophic regulation of peripheral nerve function: implications for somatosensory responses in vivo**

Supervisor: **Victoria Chapman** ([victoria.chapman@nottingham.ac.uk](mailto:victoria.chapman@nottingham.ac.uk))

Our research investigates the peripheral and central processing of acute painful inputs and chronic pain responses. Behavioural and electrophysiological methods are used, often with pharmacological interventions, to study pain mechanisms in models of inflammatory, neuropathic and osteoarthritic pain.

The development and maintenance of healthy peripheral nerves, specifically C-fibres and Adelta-fibres, is essential for the detection of painful stimuli and also to ensure that an appropriate response is mounted to this injury, for example a short-term inflammatory response to prevent further injury. Neurotrophic factors, such as nerve growth factor (NGF) have well-established roles in the development and maintenance of peptidergic C-fibres and the detection and response to painful stimuli. This research project will address the hypothesis that the balance between levels of proNGF and NGF, and activation of the receptors p75, sortilin and TrkA, determines the extent of beneficial versus detrimental effects on healthy sensory nerve function.

**The ubiquitin proteasome system and neurodegenerative disease**

Supervisor: **Lynn Bedford** ([lynn.bedford@nottingham.ac.uk](mailto:lynn.bedford@nottingham.ac.uk))

The mechanisms that cause neurones to die in neurodegenerative diseases such as Alzheimer’s and Parkinson’s diseases remain unclear. The ubiquitin proteasome system is essential for the degradation of unwanted intracellular proteins. We are using a unique in vivo genetic mammalian model of 26S proteasome dysfunction in neurones to investigate mechanisms involved in neurodegeneration. The early stages of neurodegeneration are thought to involve progressive protein and functional changes in synapses, before neuronal death. Synapses are essential to neuronal function – they are the means by which neurones in the brain communicate. In this project we wish to investigate the protein changes in synaptosomes during progressive neurodegeneration following 26S proteasome dysfunction. Our work will identify mechanisms associated with disease progression and therefore highlight potential avenues for therapeutic intervention in human disease.

**Epigenetic mechanisms underlying the positive effects of exercise on mental wellbeing and adult neurogenesis**
Supervisor: Maria Toledo-Rodriguez (maria.toledo@nottingham.ac.uk)

Our research interests focus on understanding resilience to psychiatric disease at the cellular and molecular level. Currently we study the epigenetic mechanisms underlying the positive effects of exercise on neurogenesis and mental health. It has been shown that exercise improves and prevents not only physical but also mental disease (e.g. depression, anxiety or dementia). The long-term effects of exercise on cognition are partly mediated by an increase in adult neurogenesis. Adult neurogenesis is a complex process where each step (proliferation, survival, differentiation) is regulated by epigenetic modifications. The objective of this project is to determine the epigenetic network underlying the increase of survival of new neurons in the hippocampus following long-term exercise. This project will provide training in different molecular biology techniques (bisulfite sequencing, Chip, QPCR, cloning), histology, microscopy and behavioural characterization. The insights from this project could lead to novel therapies to prevent psychiatric disease and/or improve mental health.

Ionic mechanisms of hypoglycaemic neuropathy in sciatic nerve

Supervisor: Angus Brown (a.m.brown@nottingham.ac.uk)

We have previously established that glycogen is present in sciatic nerve, the first such description. The glycogen acts selectively to protect large myelinated A fibres during aglycaemia, but smaller unmyelinated C fibres do not benefit from the presence of glycogen. However once glucose and glycogen have been depleted during aglycaemia pathology inevitable occurs, although the mechanism(s) is unknown. Preliminary data shows that the injury that is imposed on the nerves is dependent upon the presence of extracellular Ca2+, strongly suggesting that movement of Ca2+ from the extracellular space to the intracellular axonal compartment pre-empts the injury process. Depletion of ATP is a consequence of exhaustion of energy substrates and leads to axon membrane depolarization, which is turns leads to activation of voltage gated Ca2+ channels. Given the contrasting expression of ion channels between unmyelinated fibres, where the channels are distributed evenly over the axolemma, and myelinated fibres, where the ion channels are focally expressed at the nodes we hypothesize that there are differing routes of Ca2+ influx into the two types of axon. We plan to use electrophysiology and imaging techniques in combination with specific pharmacological compounds to identify the routes of Ca2+ influx in A and C fibres of sciatic nerve.

The impact of drug treatments on hippocampal neurogenesis and memory

Supervisor: Peter Wigmore (peter.wigmore@nottingham.ac.uk)

New nerve cells are continuously produced in the hippocampus throughout life in a process called adult neurogenesis. The generation of these cells is required for the consolidation of short to long term memories. Adult neurogenesis requires the proliferation of neural stem cells
residing in a specialised location, the sub granular zone, adjacent to the dentate gyrus within the hippocampus. Drugs or environmental influences can increase or decrease hippocampal neurogenesis with effects on memory. Patients who have been treated with chemotherapy frequently complain of persistent memory problems. We have demonstrated, using a rodent model, that chemotherapy causes a decline in spatial memory and that this is associated with a persistent reduction in cell proliferation in the sub granular zone. In contrast chronic antidepressant treatment increases hippocampal neurogenesis and memory. Pre-treatment with antidepressants protects the hippocampus from the anti mitotic effects of chemotherapy and the associated decline in memory. We are currently investigating the effects of chemotherapy and antidepressants on neural stem cell proliferation in vivo and in vitro together with the associated behavioural changes.

In vivo modelling of Stroke

Supervisor:  Rebecca Trueman (rebecca.trueman@nottingham.ac.uk)

Our lab group works on stroke and treatments for this common disease. We study how different factors such as high blood pressure or infection affect the outcome of the stroke. The group has links with leading clinicians in the stroke field, as well as other preclinical researchers. We use in vivo models and sensitive behavioural tests; combined with physiological measurements, state of the art MRI, immunohistochemistry and molecular biology, to examine mechanisms or test potential therapeutics.

Within our lab group you would learn a number of skills, including behavioural assessment, surgery, immunohistochemistry and molecular techniques.

Pharmacology and Physiology

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Impact of dietary meal pattern and composition on risk factors for obesity and cardiovascular disease in people

Supervisor:  Ian Macdonald (ian.macdonald@nottingham.ac.uk)

Regular eating patterns, including consumption of breakfast, appear to be linked to improved insulin sensitivity, blood lipid profiles and ad libitum food intake. There is also some evidence that omitting breakfast is accompanied by reduced insulin sensitivity and increased energy intake later in the day. The mechanisms of these effects have not been identified and the present studentship will investigate the effect of dietary composition (varygin fat, carbohydrate
and protein) on the impact of breakfast and of regular eating patterns on appetite, metabolic responses and body weight in healthy volunteers.

Human Metabolic Physiology Projects

Supervisor:  **Francis Stephens** ([francis.stephens@nottingham.ac.uk](mailto:francis.stephens@nottingham.ac.uk))

Influence of nutrition and exercise on the metabolic and molecular regulation of the integration of carbohydrate, fat and amino acid metabolism in human skeletal muscle in health, disease, and ageing. Techniques include use of in vivo stable isotopic tracers and measures of whole-body calorimetry, insulin sensitivity, and composition, combined with muscle biopsy analyses.

Factors underlying the induction of peripheral insulin resistance

Supervisor:  **Tim Constantin-Teodosiu** ([tim.constantin@nottingham.ac.uk](mailto:tim.constantin@nottingham.ac.uk))

Our research aims at identification of molecular and biochemical signalling pathways that underlie human muscle insulin resistance and muscle atrophy following trauma (surgery), immobilisation, inflammation and chronic high-dietary fat intake. Our research interest can be also viewed as an integration of in vivo whole body functional measurements with in vitro metabolic, proteomic, genomic, and mitochondrial measurements (rates of ATP production), and bioinformatics.

Studying the Pharmacology of G protein coupled receptor dimers using fluorescence imaging

Supervisor:  **Nick Holliday** ([nicholas.holliday@nottingham.ac.uk](mailto:nicholas.holliday@nottingham.ac.uk))

G protein coupled receptors (GPCRs) mediate cell-cell communication by a wide range of chemical messengers, and so are key targets for drug discovery. Recent discoveries highlight that GPCR function can be manipulated by receptor dimerisation, but the impact of this process on pharmacology has been challenging to investigate. This project will use fluorescence complementation approaches to trap and identify precise combinations of GPCR dimers by confocal imaging. This will allow quantitative study of their responses to different receptor ligands by a range of techniques, including high content imaging and analysis. By focusing on peptide or nutrient GPCRs relevant to appetite control and gut-pancreas-brain communication, the project findings will have broader relevance to tackling the health challenges of diabetes and obesity.

Adverse actions of psychoactive drugs on pancreatic beta-cell function
Supervisor: **Paul Smith** ([paul.a.smith@nottingham.ac.uk](mailto:paul.a.smith@nottingham.ac.uk))

Recent meta-analyses of clinical data indicate that certain classes of widely prescribed psychoactive drugs may increase the risk of type 2 diabetes mellitus (T2DM). The utilization and oxidation of glucose is fundamental to its stimulation of insulin secretion from the endocrine pancreas. Indeed, we have recently discovered that this bioenergetic pathway within the pancreatic beta-cell is an off-target for certain drug drugs which will adversely affect their function. By using a combination of molecular pharmacology, electrochemistry, electrophysiology and fluorescent techniques we aim to identify the specific molecular targets and pathways by which some drugs can adversely affect beta-cell function. Moreover through comparative cellular physiology we aim to determine why, and under what conditions, makes the pancreatic beta-cell so uniquely susceptible to such drugs and how this may be alleviated.

**G protein- coupled receptor pharmacology**

Supervisor: **David Kendall** ([dave.kendall@nottingham.ac.uk](mailto:dave.kendall@nottingham.ac.uk))

Our interests lie in the pharmacology of G protein-coupled receptors and in how they can be exploited in the development of new drugs and in using existing drugs, including those previously used for other purposes, to treat disease. We have a particular focus on cannabinoid receptors and opioid receptors and are working with pharmaceutical companies to design and test compounds that could be of benefit in the treatment of chronic pain, depression, anxiety, stroke and neurodegenerative disorders. A recent development is in the investigation of the possibilities for using cannabinoid drugs to treat skin pigmentation disorders. We use a variety of in vitro and in vivo pharmacological approaches, making use of expertise in modern methods of cell signalling and animal disease models, often in collaboration with other School colleagues.

**Role of hydrogen sulphide production in the regulation of airway smooth muscle tone**

Supervisor: **Richard Roberts** ([richard.roberts@nottingham.ac.uk](mailto:richard.roberts@nottingham.ac.uk))

We have recently demonstrated that hydrogen sulphide (H2S) is synthesised within the airways in the lungs. H2S synthesis in the airways occurs through activation of the enzymes cystathionine β lyase, cystathionine β synthase, and mercaptopyruvate sulphurtransferase (MPST). We have found that MPST expression and activity in the airways can be altered by inflammatory mediators. Our recent studies indicate that MPST may be located in the mitochondria in the airways and this mitochondrial source of H2S may play a role in the regulation of airway tone, possibly through effects on the epithelial cells. Therefore the aims of this project are to determine whether H2S can be produced in the mitochondria in the airways, to determine whether inflammation upregulates MPST in the mitochondria, and to determine whether mitochondrially-derived H2S plays a role in the regulation of airway tone by epithelial cells. This project will involve the use of pharmacological and biochemical techniques.
Local regulation of blood vessel contractility by purines, pyrimidines and hydrogen sulphide

Supervisor: Vera Ralevic (vera.ralevic@nottingham.ac.uk)

Our main research interest is in mechanisms of local control of blood vessel contractility, with focus on the roles of purine and pyrimidine nucleosides/nucleotides and their receptors, and on the novel gasotransmitter hydrogen sulfide. The work is, therefore, of potential relevance for the understanding and treatment of cardiovascular diseases. Purines and pyrimidines cause blood vessels to contract or relax via actions at cell surface P2 receptors, and we have preliminary evidence for a novel role of the P2Y14 receptor, a recently discovered P2 receptor, in regulation of vascular contractility. This project is concerned with the characterisation of cardiovascular P2 receptors, using pharmacological and molecular techniques, and will investigate their vasomotor roles and also their potential roles in vascular inflammation. A separate project involves characterisation of the actions of hydrogen sulfide in blood vessels, its role in hypoxic vasoconstriction/vasorelaxation and its protective role in endothelial injury. This project will also use a pharmacological and molecular approach.

Natural toxins and their synthetic analogues as tools to study ion channels and as potential drugs and pesticides

Supervisor: Ian Mellor (ian.mellor@nottingham.ac.uk)

Brief description: The project will use a combination of electrophysiological techniques such as voltage-clamp and patch-clamp with molecular biology and protein expression to understand how natural toxins and their synthetic analogues act on ion channels in the nervous system. The project will study the modes and sites of action of the toxins and assess their suitability for development as novel therapeutic agents or pesticides. The project could also be directed towards the study of existing drugs and pesticides in order to better understand their modes and sites of action or to investigate problems in their use such as insecticide resistance. These studies also reveal much about the structure and function of ion channels.

Central and peripheral control of body weight in a seasonal model of adiposity

Supervisor: Fran Ebling (fran.ebling@nottingham.ac.uk)

Seasonal cycles of body weight provide a natural model system to understand the control of energy intake and expenditure. Our studies in the Siberian hamster suggest that a change in the hypothalamic availability of thyroid hormone is the key determinant of annual weight loss and gain. Uptake of thyroid hormone into the hypothalamus from the peripheral circulation occurs largely through tanycyte cells lining the third ventricle. Tanycytes express deiodinase
enzymes so they control the local concentrations of thyroid hormones in the hypothalamus. Short autumn/winter photoperiods upregulate type III deiodinase mRNA in tanycytes, which reduces the availability of biologically active thyroid hormone in the hypothalamus. This is associated with reduced appetite and increased catabolism of intra-abdominal fat reserves, resulting in body weight loss. Our research seeks to understand the cellular and molecular actions of thyroid hormone in the brain as this may identify novel targets for long term pharmacological manipulation of body weight. We also have a major interest in the actions of FGF21 in seasonal cycles as treatment of hamsters with a FGF21 mimetic also affects deiodinase expression in the hypothalamus, and is likewise associated with reduced appetite and weight loss.

**Enzymes as targets for drug discovery, target validation and as biomarkers**

**Supervisor:** Steve Alexander ([steve.alexander@nottingham.ac.uk](mailto:steve.alexander@nottingham.ac.uk))

Over recent years, we have generated, developed and established a wide range of assays for different enzyme activities. In particular, we have enzyme assays for metabolism of the endocannabinoids (anandamide and 2-arachidonoylglycerol), nucleosides and nucleotides (adenosine and ATP), gasotransmitters (nitric oxide and hydrogen sulphide), adenyllyl and guanylyl cyclases and phospholipase C. The assays differ dependent on application. Some assays are targetted at investigating biochemical and pharmacological mechanisms of activity; some are used to quantify activities ex vivo and some are used to generate high-throughput screening assays. This project will explore the use of fluorescently-tagged irreversible enzyme inhibitors to quantify multiple enzyme activities in a complex mixture to correlate enzyme function with disease and/or pharmacological/therapeutic intervention. The potential application of this technique for novel drug discovery will also be evaluated.

**Drug Metabolism and Toxicity**

**Supervisor:** Patrick Barton ([patrick.barton@nottingham.ac.uk](mailto:patrick.barton@nottingham.ac.uk))

The role of the membrane bound drug transporters such P-glycoprotein, OATP1B1, OAT1 and OAT3 are known to have a significant impact of the kinetics, disposition and toxicity of many drugs in humans. The interaction of drug molecule with these transporters expressed in cellular systems is an effective way to quantify the influence these have on areas such as human clearance, access to sites of action such as the CNS and potential toxicity.

I am interested to understand the role transporters proteins, together with metabolic enzymes, in a range of cellular systems and use the data generated to predict clearance and disposition as well as potential toxic outcomes in humans. These in-silico prediction systems such as in-vitro/ in-vivo extrapolation (IVIVE), Physiologically Based Pharmacokinetics (PBPK) and Quantitative Structure Activity Relationships (QSAR) utilize the cellular in-vitro data to provide a
mechanistic insight into the role of transporters proteins and facilitate a better understanding of human kinetics and toxicity of potential new drugs.

**Synthetic Biology**

**Designing of novel biosensors using synthetic biology approaches**

Supervisor:  
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Infectious diseases are still a major cause of death, disability and social and economic upheaval accounting for more than 11.9 million deaths a year worldwide. Current efforts concentrate on the development of novel antimicrobial and therapeutic strategies. However, early interventions based on state-of-the-art diagnostic strategies and novel treatments that will accelerate the detection and management of bacterial infections is paramount to substantially reduce the impact of infectious diseases. Many bacterial pathogens produce signature signal molecules to control their virulence by a process known as quorum sensing (QS). Our laboratory has years of expertise studying these signalling processes and in designing biosensors for their detection. However, these biosensors are usually not sensitive enough to detect the very low levels of these molecules in human samples, especially during the early stages of infection. We have recently been using synthetic biology strategies with the aid of molecular biology and computational modelling approaches to design sophisticated synthetic circuits which can sense with increased sensibility the signature molecules and amplify the responses to low signal levels. These strategies are leading to many applications, some of which will have clinical outcomes. The aim of this project is to recycle some of these engineered circuits for the design of highly sensitive biosensors which can be used to detect early stages of infection through the detection of QS molecules and trigger a genetically-controlled biological response which will additionally result in a reactive first line of defence against the invading pathogen. The project will provide extensive training in molecular biology, synthetic biology, computer modelling, microscopy and analytical biochemistry techniques.

**Engineering microbes to produce fuels and chemical commodities**

Supervisor:  
**Klaus Winzer** ([klaus.winzer@nottingham.ac.uk](mailto:klaus.winzer@nottingham.ac.uk))

There is strong interest in producing fuels, chemicals, and materials from renewable non-food resources. In our group, we use advanced synthetic biology and metabolic engineering approaches to implement novel metabolic pathways leading from feedstocks such as cellulose and syngas to desirable biofuels and chemical commodities, such as butanol, isoprene, and alkanes. We have a number of different PhD projects available and make use of a variety of microbial chassis (e.g. Clostridium, Cupriavidus, Geobacillus) depending on the metabolic routes
to be implemented. We have strong partnerships with groups in the Bioenergy/Renewables sector in Europe, the US, China and India, providing ample opportunity to take part in international conferences, workshops, and exchange programmes.

**Chemical Commodity Production using Steel Mill Gas-Eating Microbes Engineered by Synthetic Biology**

**Supervisor:** Nigel Minton ([nigel.minton@nottingham.ac.uk](mailto:nigel.minton@nottingham.ac.uk))

The environmental damage being caused by the indiscriminate use of fossil fuels for chemical manufacture, energy generation and transportation threatens the very future of our planet. Attention has focussed on converting plant biomass into chemicals and fuels through microbial fermentation. However, developing economic processes is proving challenging. An alternative approach is to use gas fermenting microbes that are able to grow on SynGas (CO and H2) derived from sustainable resources, such as biomass and domestic/ agricultural wastes or steel mill off-gas. The studentship will implement process improvements through the identification of new microbial chassis, or the modification of existing chassis, that are able to produce a broader range of chemical commodities. They will assemble the necessary tools (parts and modules) and strategies that can be used in the selected microbes to implement synthetic routes to product formation using synthetic biology approaches.

**Novel Routes to Cancer Therapy using a Clostridial Spore Delivery System**

**Supervisor:** Nigel Minton ([nigel.minton@nottingham.ac.uk](mailto:nigel.minton@nottingham.ac.uk))

The search for effective means of selectively delivering high therapeutic doses of anti-cancer agents to tumours has in the last decade explored a variety of ingenious and increasingly complex biological systems. Invariably, such systems have been found wanting. In contrast, the ability of intravenously injected clostridial spores to infiltrate and thence selectively grow in the oxygen depleted regions of solid tumours appears a totally natural phenomenon, requiring no fundamental alterations, and is exquisitely specific. The student will take a synthetic biology approach to endow the clostridial delivery vehicle with the necessary bioparts and modules for the production of a range of anti-tumour agents capable of selectively affecting tumour cell growth.

**Biological engineering parts of the human gut micro-biome to combat Clostridium difficile infection**

**Supervisor:** Sarah Kuehne ([sarah.kuehne@nottingham.ac.uk](mailto:sarah.kuehne@nottingham.ac.uk))
Clostridium difficile is the major cause of hospital associated diarrhoea and imposes a substantial financial burden on health-care systems worldwide. C. difficile infection (CDI) occurs following the disruption of the normal gut micro-flora, most often a consequence of antibiotic treatment. Currently treatment options are limited to very few antibiotics which are under threat from the emergence of resistant strains. Alternative countermeasures are urgently required. This project aims to develop novel therapies for controlling CDI through biological engineering of specific components of the healthy human micro-biota.

**Biologically engineering of the thermophilic chassis to produce advanced biofuel**

Supervisor: Ying Zhang (ying.zhang@nottingham.ac.uk)

Concerns overs the finite nature of fossil fuels and the environmental damage their usage causes has led to a focus on the production of chemicals and fuels using microbial chassis and renewable feedstocks. Thermophilic chassis have a number of attractive features for the envisaged processes. Of paramount importance is that the enzymes employed in the implemented synthetic pathways function effectively at high temperature. In this project we will mine the genomes and metagenomes of thermophilic bacteria for appropriate components and evolve thermostable enzymes from mesophilic bacteria (by directed evolution) for use in a thermophilic chassis The metabolic profiles of fermenting strains will be analysed using LC/MS (and "son" real time, live cell NMR) to identify and develop superior or novel strains for industrial use.

**Synthetic biology approaches to reduce effluent disposal costs and environmental impacts of the alcohol industry**

Supervisor: Ying Zhang (ying.zhang@nottingham.ac.uk)

Alcoholic beverage production processes result in vast amounts of wastewater which is difficult to treat due to its acidity and high organic matter content. A novel approach to clean-up is to utilise the acid and the organic compounds as a feedstock for biological routes to high valued chemical commodities. The project will use synthetic biology approaches to both improve the substrate range of the chosen microbial chassis and extend its product profile. Biological parts and modules will be designed and iteratively tested to produce the eventual process organism useful in the treatment of the effluents from breweries, distilleries and soft drinks manufacturers.