The following PhD vacancies and research topics within the School of Pharmacy 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 Pharmacy website or contact the relevant members of academic staff as listed below.

**Advanced responsive polymers for drug delivery**

Supervisor: Cameron Alexander ([cameron.alexander@nottingham.ac.uk](mailto:cameron.alexander@nottingham.ac.uk))

Materials that can respond to stimuli are of interest as carriers that can protect drugs during transport in the body yet release the drugs where and when they are most needed. We are investigating new ways by which these materials can respond to biological signals and are developing polymers that can release drugs, biopolymers and complex macromolecular therapeutics such as nucleic acids following these stimuli.

**Synthetic polymer-cell interactions**

Supervisor: Cameron Alexander ([cameron.alexander@nottingham.ac.uk](mailto:cameron.alexander@nottingham.ac.uk))

The interactions of polymers with both bacterial and mammalian cells are important in disease processes and in regenerative medicine. We are looking at how synthetic polymers bind to cells in suspension and at surfaces, and future projects in this area will consider changes in cell biology (gene expression, protein and polysaccharide production) as a consequence of polymer-cell recognition.

PhD projects in both these areas are highly multidisciplinary, involving synthetic organic, medicinal and polymer chemistries combined with biophysical studies of polymer-biopolymer and polymer-cell interactions. Through collaborations with other groups we also evaluate drug, biopolymer and gene release efficacy in cell culture, and assess cell behaviour, signalling and gene regulation in response to polymer interactions.

**The development of surface engineered biomimetic systems for drug delivery/tissue-engineering**

Supervisor: Morgan Alexander ([morgan.alexander@nottingham.ac.uk](mailto:morgan.alexander@nottingham.ac.uk))

We are developing novel polymeric surfaces for drug-delivery, tissue-engineering and cellular therapy. The research programme will involve the synthesis and surface-chemical characterization of polymer systems, where we apply our understanding of the influence of surface structure on cellular biology. The surface sensitive techniques applied include scanning
probe microscopy, contact angle, X-ray photoelectron microscopy and time-of-flight secondary ion mass spectrometry.

High throughput nanoscale arrays for screening polymer antimicrobial properties

Supervisor: Morgan Alexander (morgan.alexander@nottingham.ac.uk)

Microbial infections are a growing problem in healthcare, with examples including methicillin-resistant Staphylococcus aureus (MRSA) and Clostridium difficile (C. diff.). The production of polymers which exhibit strong anti-microbial properties represents a significant challenge, the achievement of which has significant implications for producing safer medical devices (catheters, stents, implants etc) and in other healthcare settings. This project aims to screen a wide range of chemically different polymers to develop materials which exhibit strong anti-microbial properties and can be used in the next generation of biomedical devices.

The award of a recent £1.4 million grant from the Wellcome Trust (Prof Davies, Prof Williams & Dr Alexander at Nottingham, Profs Langer & Anderson at MIT) has enabled the LBSA to invest in a state of the art array printer, capable of printing controlled arrays using a wide variety of polymers. The project will involve characterising the anti-microbial properties of these arrays using surface analytical techniques, fluorescence microscopy, microbial cell culture methods and chemometric methods.

Prospective candidates should have a good (2:1 or above) degree in a relevant subject area (e.g. pharmacy, materials science, biological sciences, chemistry) and meet the University requirements for English (an IELTS score of 6 with no less than 5.5 in any element or equivalent accepted qualification). This position is available to a self-funded student. Assistance with securing any awards, bursaries etc may be available.

Development and application of novel quantitative metabolomic profiling methods to human and bacterial metabolism studies

Supervisor: David Barrett (david.barrett@nottingham.ac.uk)

This challenging project will involve the development of quantitative metabolomics methodology using state-of-the-art Ultra Performance Liquid Chromatography (UPLC) linked to Orbitrap and ion trap mass spectrometry (MS). The student (biochemical and/or analytical background preferred) will apply the novel methodology to the analysis of (a) metabolites in human disease human (with Medicine and Health Sciences collaborators) or (b) in several bacterial species (with Centre for Biomolecular Sciences). In addition to UPLC-MS analysis, authentic standards and databases will be used to identify a complete profile of metabolites in the biological samples with a focus on identification of bioactive lipids.
Raman microscopy for characterising solid dosage forms

Supervisor:  Jonathan Burley  (jonathan.burley@nottingham.ac.uk)

Drug and excipient distribution in tablets underpins their therapeutic performance. New developments in Raman microscopy/spectrometry allow a full and detailed chemical mapping of a tablet to be performed in 7-10 minutes. This project will involve looking at real-world examples, including problematic formulations, with a view to improving the design of old and new medicines.

Solid drug forms in tablets

Supervisor:  Jonathan Burley  (jonathan.burley@nottingham.ac.uk)

Securing the supply of medicines and understanding factors which can affect their performance.

Transmission Raman Spectroscopy (TRS) is an emerging area of analysis which has a number of key benefits over other state of the art methods. It is non-destructive, fast (seconds or less), quantitative, can penetrate up to 50 mm of opaque material (e.g. tablets), and provides easy-to-interpret data. It is one of only two techniques which can potentially be used to analyse tablet content in a non-destructive manner (near infra-red spectroscopy is the other). This project will look at using TRS to identify quality-critical parameters in tablets, including: drug degradation, amorphous content, polymorphic make-up, drug content, counterfeit or not, etc.

Intermolecular forces in pharmaceuticals from thermal expansion measurements

Supervisor:  Jonathan Burley  (jonathan.burley@nottingham.ac.uk)

This project will investigate the potential of rapid, automated measurements of the thermal expansion of pharmaceuticals for determining the forces which hold the molecules together. X-ray powder diffraction will be the main method used, and calculations and Raman spectroscopy will also be employed. This is a totally new approach to the long-standing problem of measuring forces between molecules. In simple terms, strong bonds between molecules should give low thermal expansion, whereas weak bonds will lead to large thermal expansion. New developments in experimental equipment allow these measurements to be made very rapidly.

Making and stabilising amorphous formulations

Supervisor:  Jonathan Burley  (jonathan.burley@nottingham.ac.uk)
One of the main reasons a new drug fails to make it to patients is solubility. This project will look at new ways of formulating drugs as the amorphous form, to improve solubility and potentially bioavailability. If successful, one of the key bottlenecks for new medicine development will be removed.

New drugs are usually crystalline when made and purified. By converting them to an amorphous form their apparent solubility can be increased by several orders of magnitude. Current state of the art methods form creating amorphous materials involve heat or solvent or both (e.g. spray drying, melt extrusion). This project will look at the use of solvent-free cryomilling to make new medicines; a wide variety of analytical techniques will be employed. Outputs may include new rapid-release medicines and treatments.

**Chemical synthesis and biological studies of the proteasome inhibitor argyrin A and analogues thereof**

Supervisor:  **Weng Chan** ([weng.chan@nottingham.ac.uk](mailto:weng.chan@nottingham.ac.uk))

Unique naturally occurring macrocyclic peptides are important chemotypes for the exploration of new therapeutic agents. A number of such unique peptides will be considered. In order to establish robust synthetic chemistry to macrocyclic peptides, this project will involve the chemical synthesis of the argyrin A and analogues thereof. This is will be achieved using a combination of modern solid-phase peptide synthesis and macrocyclisation strategies. New unique pseudoaromatic amino acid analogues will be synthesised and incorporated into the peptide framework. We would then determine the capacity of these macrocyclic peptides to inhibit proteasome-regulated processes, in the context of tumour growth suppression.

**Novel enabling chemical methods to macrocyclic peptides and chemical probes**

Supervisor:  **Weng Chan** ([weng.chan@nottingham.ac.uk](mailto:weng.chan@nottingham.ac.uk))

Unique naturally occurring macrocyclic peptides are important chemotypes for the exploration of new therapeutic agents for the treatment of carcinoma and bacterial infection. Inspired by naturally occurring templates such as argyrin and solonamide, this project will entail the development of novel macrocyclic peptide. Using modern synthetic organic chemistry, new aromatic amino acid analogues will be synthetised via chiral auxillary agents and palladium-catalysed cross-coupling reactions. These unique amino acid building blocks will then be incorporated into a peptide framework, which will be assembled by modern solid-phase peptide synthesis strategies. The project will also entail the design and chemical synthesis of probes responsive to hydrogen peroxide, as a reporter on the cellular ‘reactive oxygen species’ status.
**Early stage health economic modelling to assess the cost-effectiveness of tools for stratifying breast cancer patients for anthracycline and herceptin treatment**

**Supervisor:** Li-Chia Chen ([li-chia.chen@nottingham.ac.uk](mailto:li-chia.chen@nottingham.ac.uk))

Preliminary results have indicated about 60 patients per million population present with HER2-positive breast cancer per year, and these patients are routinely treated with Anthracycline in conjunction with Herceptin. The annual drug acquisition / prescribing cost per patient for Anthraclycline and Herceptin is £1,240 and £25,000 respectively.

Although Anthracycline treatment is routinely used in conjunction with Herceptin for these patients, less than 50% will respond to Anthracycline and Herceptin and only 40% to anthracycline therapy alone. This unsuccessful treatment represents a significant level of over-medication and unnecessary suffering to patients. The drug costs alone to the NHS totals £4.9 M for Anthracyclines and £73 M for Herceptin. Furthermore, cardiac toxicity is a major problem with both drugs and is particular problematic when these are used in combination (over 10% of patients are forced to stop this potentially curative treatment due to this side effect).

Previous studies conducted by the research team have identified two genetic biomarkers (SPAG5 and T128) that can predict the treatment efficacy of Antracycline and Herceptin. To evaluate the cost-effectiveness of developing the tools for stratifying breast cancer treatments based on those two biomarkers, an economic modelling will be conduct to incorporate the current best evidence on clinical efficacy, patient safety, and utility data, and the benefits of optimising medicine utilisation will also be evaluated. The research approaches include systematic review and meta-analysis, secondary database analysis and economic modelling.

**High throughput nanoscale arrays for screening stem cell interactions with polymeric biomaterials for tissue engineering applications**

**Supervisor:** Martyn Davies ([martyn.davies@nottingham.ac.uk](mailto:martyn.davies@nottingham.ac.uk))

There is considerable interest in the use of stem cells for tissue engineering applications for artificial organs. One of the key issues is the selection of the material used for the scaffold that supports suitable stem cell adhesion, growth and proliferation. Recently we have worked with collaborators at MIT to develop a high throughput screening method that rapidly assesses the interaction between stem cells and large polymer library arrays. This project will continue this work to explore the relationship between the surface physicochemical properties of the polymer materials and the stem cell interactions as part of the quest for the ultimate goal, a bioreponsive surface that exhibits ideal properties to facilitate stem cell proliferation for the next generation of tissue engineered organs.

The award of a recent £1.4 million grant from the Wellcome Trust (Prof Davies & Dr Alexander at Nottingham, Profs Langer & Anderson at MIT) has enabled the LBSA to invest in a state of the art array printer, capable of printing controlled arrays using a wide variety of polymers. The
PhD Vacancies 2014

School of Pharmacy

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Understanding the Protein Kinase C delta pathway in disease

Supervisor: Lodewijk Dekker (lodewijk.dekker@nottingham.ac.uk)

The Protein Kinase C delta (PKC-δ) pathway has been associated with various disease states, including inflammation and stroke and malignant diseases such as breast cancer. To understand underlying mechanisms, it is important to know the exact molecular targets of this kinase, which are currently poorly characterised. We aim to identify PKC-δ-mediated phosphorylation events. A dominant negative strategy complemented by chemical genetics approaches will be employed to manipulate PKC-δ enzyme activity in cell models. Phosphorylated proteins will then be isolated and separated using chromatography and gelelectrophoresis. Proteins will be identified by means of mass spectroscopy methods. The results will lead to better understanding of the PKC-δ pathway in disease and potentially identify novel targets for pharmacological intervention.

mRNA metabolism as a target for anti-inflammatory drugs

Supervisor: Cornelia H. de Moor (cornelia.de_moor@nottingham.ac.uk)

Chronic inflammatory diseases include afflictions such as rheumatoid arthritis, inflammatory bowel disease and asthma. In addition, inflammation has also been shown to play a role in several types of cancer and was recently linked to aging and coronary heart diseases. Therapeutic choices for inflammatory disease are limited to the non-steroid anti-inflammatory drugs (NSAIDS), which inhibit prostaglandin synthesis by cyclooxygenases, and corticosteroids, which act as repressors of inflammatory gene transcription. Both types of drugs have reduced effectiveness with long term usage, do not work in certain patients and can have serious side effects. Anti-inflammatory drugs that work on different principles could therefore significantly benefit a large number of patients with a variety of ailments.

Inflammatory gene transcription is mediated by the translocation of the transcription factor NFκB to the nucleus, which induces the transcription of inflammatory genes, including cytokines, chemokines, cyclooxygenases and transcription factors. The expression profile of these genes has recently been demonstrated to depend heavily on the stability of their mRNAs. Many of the
key regulatory mRNAs were shown to be expressed transiently because of their instability, rather than due to transcriptional down regulation. Therefore, agents that specifically target these efficiently transcribed, unstable mRNAs could have a high potential as anti-inflammatory drugs.

In the De Moor laboratory, we have recently identified a new class of anti-inflammatory drugs that act at the post-transcriptional level. In this project you will use medium and high throughput assays to identify more potent compounds working by this novel mechanism and study their effectiveness and metabolism in cells and animals.

**Manipulation of the ubiquitin system by human papillomavirus**

**Supervisor:** Ingrid Dreveny ([ingrid.dreveny@nottingham.ac.uk](mailto:ingrid.dreveny@nottingham.ac.uk))

Human papillomavirus (HPV) transforming proteins play key roles in the development of certain types of cancer. These proteins influence human regulatory pathways to the advantage of the virus by interacting with and manipulating the function of human proteins to evade immune detection and degradation. The project will investigate the interaction of HPV transforming proteins with human deubiquitinating enzymes and provide training in a wide range of molecular biology, biochemical and structural biology techniques (including cloning, protein expression, purification and X-ray crystallography). Understanding the molecular basis of these interactions is vital for the development of novel therapeutic agents.

**Development of a protein array technology for the diagnosis of allergies and the study of the immune response in schistosomiasis**

**Supervisor:** Franco H. Falcone ([franco.falcone@nottingham.ac.uk](mailto:franco.falcone@nottingham.ac.uk))
**Additional Supervisor:** Marcos J.C. Alcocer ([marcos.alcocer@nottingham.ac.uk](mailto:marcos.alcocer@nottingham.ac.uk))

**External Collaborators:**
- W. Evan Secor, Centers for Disease Control and Prevention (CDC), Atlanta
- Colin Fitzsimmons and David Dunne, University of Cambridge
- Guilherme Oliveira, FioCruz/Center for Bioinformatics Belo Horizonte, Brazil

We are looking for a highly motivated, enthusiastic and team-orientated individual interested in bridging allergy and parasitological research. The project is aimed at developing a protein array-live cell technology which can be used to immunoprofile the immune responses to environmental antigens or allergens. The technology is based on our recent proof-of-concept work [1] which was awarded a Da Vinci Health Technology Innovation Network Prize in the Category ‘Breakthrough Technologies’ in 2008.
We are particularly interested in its exploitation for identification of immune responses associated with protection against infection or re-infection with schistosomes in the context of vaccine development, and as a better tool for diagnosis of sensitization to environmental allergens.

This position is available to a self-funded student. Assistance with securing any awards, bursaries etc can be offered. Applicants will have a 1st or upper second class degree (or equivalent level) in biology, chemistry, biochemistry or a related discipline and a strong interest in parasitology, allergy research, modern proteomic technologies, and meet the University requirements for English (an IELTS score of 6 with no less than 5.5 in any element or equivalent accepted qualification). Training will be provided in key experimental and bioinformatic approaches such as recombinant DNA techniques (cloning, PCR, in vitro translation), protein array technology and data analysis.


Development of a protein array or microfluidics technology for the diagnosis of allergies in humans and companion animals

Supervisor: Franco H. Falcone (franco.falcone@nottingham.ac.uk)
Additional Supervisor: Marcos J.C. Alcocer (marcos.alcocer@nottingham.ac.uk)

We are looking for a highly motivated, enthusiastic and team-orientated individual interested in developing cutting edge allergy diagnostic technologies. The project is aimed at developing a protein array- or microfluidics-live cell technology which can be used to immunoprofile the immune responses to environmental antigens or allergens. The technology is based on our recent proof-of-concept work [1] which was awarded a Da Vinci Health Technology Innovation Network Prize in the Category ‘Breakthrough Technologies’ in 2008.

This position is available to a self-funded student. Assistance with securing any awards, bursaries etc can be offered. Applicants will have a 1st or upper second class degree (or equivalent level) in biology, chemistry, biochemistry or a related discipline and a strong interest in immunology, allergy research, modern proteomic technologies, and meet the University requirements for English (an IELTS score of 6 with no less than 5.5 in any element or equivalent accepted qualification). Training will be provided in key experimental and bioinformatic approaches such as recombinant DNA techniques (cloning, PCR, in vitro translation), cell culture, protein array technology and data analysis.

New antibiotics for the treatment of Helicobacter pylori infection

Supervisors:  Peter Fischer (peter.fischer@nottingham.ac.uk)  
                Dave Barrett (david.barrett@nottingham.ac.uk)

Helicobacter pylori is the main cause of peptic ulceration and gastric adenocarcinoma, the latter being the second largest cause of cancer deaths worldwide. Successful treatment prevents ulcer recurrence, and reduces the risk of gastric cancer. However, treatment is complex and resistance to antibiotics in current use is increasing fast. The project aims to design and test new antibiotic prodrugs with improved gastric bioavailability.

Prodrug candidates will be synthesised and their physicochemical properties assessed using established methodology. Metabolic and hydrolytic stability will be assessed using incubations with appropriate biological preparations and existing bioanalytical methods. Anti- H. pylori activity will be tested against multiple clinical strains.

The project is of an interdisciplinary nature and will provide students with training in the areas of medicinal chemistry and bioanalysis, as well as microbiology in collaboration with the Nottingham Digestive Diseases Centre Biomedical Research Unit.

How chromatin regulators read the epigenetic language

Supervisor:  David Heery (david.heery@nottingham.ac.uk)

We study the structure and function of epigenetic regulators of gene expression using biochemistry, cell biology, chromatin IP, chip-Seq and structural biology. Several projects are available to study the structure and function of the Histone Acetyltransferases MOZ/MYST3 and MORF/MYST4. We recently solved the crystal structure of the MYST3 Double PHD domain in complex with histone tails (Dreveny et al, Submitted). Remarkably we discovered for the first time that MYST3 can induce a-helical structure of the tail which enables it to read and catalyse histone acetylation and methylation signals. Projects are available to study this domain structure in MYST4 and related proteins.

What is the regulatory role of the lncRNA (Bgl3) in the human globin gene locus?

Supervisor:  David Heery (david.heery@nottingham.ac.uk)

Foetal γ-globin genes are repressed soon after birth and replaced by expression of the adult δ-globin and β-globin genes. This is achieved by chromatin looping of an enhancer to the relevant proximal promoters. We have shown that repression of the γ-globin genes involves the developmental regulatory zinc finger protein BCL11A, and its binding partner, the nuclear receptor COUP-TFII (Chan et al.Nucleic Acids Research 2013; In Press). However, these repressors also block a neighbouring non-coding transcript (or lncRNA) termed Bgl3. The aim of
the project is to establish how Bgl3 transcription is regulated and discover proteins that can bind Bgl3 RNA. We hope to uncover novel mechanisms regulating globin genes. This would have therapeutic implications for sickle cell disease, globinopathies and cancers in which BCL11A is mutated.

**MOZ TIF2 function in acute myeloid leukaemia**

Supervisor:  **David Heery** ([david.heery@nottingham.ac.uk](mailto:david.heery@nottingham.ac.uk))

MOZ/MYST3 is a histone acetyltransferase that is important for the development of haematopoietic stem cells. However, with recurrent chromosomal translocations in acute myeloid leukaemia patients express a fusion protein (MOZ-TIF2) which is sufficient to cause AML in animal models (Kindle et al., MCB 2005; Collins et al., JBC 2006; Kindle et al Leukaemia, 2010). We have used chromatin Immunoprecipitation coupled with Next Generation Sequencing techniques to identified gene targets of MOZ in the K562 cell line. The project would aim to use RNA seq to identify genes that are misregulated by MOZ TIF2. The project will include molecular and cell biology, siRNA techniques, lentiviral expression of MOZ-TIF2 and NGS techniques. Some background in any of these techniques would be desirable.

**Nuclear receptor/cofactor interactions**

Supervisor:  **David Heery** ([david.heery@nottingham.ac.uk](mailto:david.heery@nottingham.ac.uk))

We have shown that the helical signature sequence LXXLL mediates interactions of Nuclear receptors and their many cofactors and that these interactions are essential for gene regulation (Heery et al., Nature 1997). Recent work from the lab has discovered novel highly selective sequences (FSXXLXXL) in some regulators that allow them to bind a subset of Nuclear receptors known as TLX, PNR and the COUP-TFs (Chan et al., Nucleic Acids Res 2013, In Press). Several projects are available to investigate the structure and function of Nuclear receptor / Coregulators using, yeast two hybrid, proteomics and structural biology. For example now discoveries on the interaction of the retinal specific PNR are of potential relevance in understanding diseases involving sight loss via retinal degeneration. Other cancer -related projects under this theme also available.

**Investigation of the factors required for regulation of hepatitis C virus by microRNA-122.**

Supervisor:  **Catherine Jopling** ([catherine.jopling@nottingham.ac.uk](mailto:catherine.jopling@nottingham.ac.uk))

Hepatitis C virus (HCV) is a positive sense RNA virus that establishes persistent infections in the liver that may eventually result in cirrhosis or hepatocellular carcinoma. MicroRNAs are short,
non-coding RNA molecules that are major regulators of gene expression in a broad range of eukaryotes. A liver-specific microRNA, miR-122, binds directly to hepatitis C virus (HCV) RNA and positively regulates viral replication. The mechanism by which this regulation occurs is not yet clear. This project will investigate the protein factors required for the regulation of HCV by miR-122 in order to improve understanding of this important regulatory process.

Self-assembly of prodrugs for intra-tumoral delivery

Supervisors: Maria Marlow (maria.marlow@nottingham.ac.uk)  
Barrie Kellam (barrie.kellam@nottingham.ac.uk)  
Tracey Bradshaw (tracey.bradshaw@nottingham.ac.uk)

Securing the supply of medicines and understanding factors which can affect their performance.

Higher dose administration of a toxic chemotherapeutic directly into a tumour site (intratumoral delivery) is an obvious and alternative treatment to systemic delivery. Localised intra-tumoral delivery will reduce systemic exposure and hence reduce the potential for side effects. There is also the potential to form a depot for sustained release.

The Project will involve taking an existing chemotherapeutic and creating a prodrug that will self-assemble to form a physical gel in-situ upon injection into a tumour. The sol to gel transition will either be achieved by modification of the pH or temperature and could take advantage of the acidosis within the tumour. Introduction of a wide range of physicochemically distinct groups to metabolically liable tether points will be evaluated via parallel synthesis to afford a diverse library for gelation assessment. Once the conditions for gelation have been identified, the physical properties and bonding modes within the gels will be characterized. Enzymatic conversion of the prodrug to the drug will also be evaluated in vitro. Finally the project will use an appropriate preclinical cancer model (e.g subcutaneous xengraft) to evaluate the localised and systemic delivery. Research training will be broad based in that it will combine synthetic, physical chemistry, formulation science and cancer biology. This studentship will also provide an insight into designing and developing a drug product/therapy for oncology.

The kinetics of induction of immune regulatory networks by parasitic nematode infection

Supervisor: David Pritchard (david.pritchard@nottingham.ac.uk)

The project will explore the induction of immune regulatory networks following graded infection with the immune suppressive nematode parasite Heligmosomoides polygyrus. Candidates will ideally already have funding, and experience in immunology. The project represents a unique opportunity to bridge gaps in our knowledge regarding the kinetics of infection with parasites.
required to induce effective immune suppression, knowledge which will then be applied to experimental therapeutic infections of humans, to treat allergic and autoimmune disease.

Formulation characterization and screening using advanced scanning probe microscopy

Supervisor: Clive Roberts (clive.roberts@nottingham.ac.uk)

Atomic force microscopy and nanothermal microscopy can provide nanoscale resolution of the properties of formulation materials. We have shown many examples of applying these techniques to help develop oral and inhalation based medicines. Supported by complimentary techniques such as DSC, XRD, X-ray photoelectron microscopy and time-of-flight secondary ion mass spectrometry you will apply the latest advanced probe microscopy techniques to characterize a new generation of biopharmaceutical formulations.

Predicting the mass manufacturability of formulations based upon nano and micro scale measurements

Supervisor: Clive Roberts (clive.roberts@nottingham.ac.uk)

There is considerable interest in developing new strategies to select appropriate lead molecules based not only on their therapeutic profile but also the ability to develop them into a viable medicine that can be manufactured. Very many compounds fail at this point. This PhD will address this key issue.

The quantitative spatial and chemical analysis of formulations at the micron scale is now routine, using approaches such as infra-red and Raman spectroscopy and imaging. In recent years some nanoscale analyses using the probe microscopes have also become commonplace. This includes, for example the measurement of morphology, surface energy, elastic modulus and adhesion phenomena from nanoscale regions and frequently from single particles. You will build on this background to develop strategies for lead compound selection based upon nanoscale analysis.

We have developed a significant range of approaches and publication firsts in the application of nanoscale analysis of pharmaceuticals. Much of this work has been done in close collaboration with industry. You will employ a range of analytical techniques but in particular scanning probe microscopes, such as atomic force microscopy and nanothermal analysis.

Prospective candidates should have a good (2:1 or above) degree in a relevant subject area (e.g. pharmacy, materials science, physics, chemistry) and meet the University requirements for English (an IELTS score of 6 with no less than 5.5 in any element or equivalent accepted qualification).
Regenerative medicine applications of drug delivery

Supervisor:  **Kevin Shakesheff** ([kevin.shakesheff@nottingham.ac.uk](mailto:kevin.shakesheff@nottingham.ac.uk))

This project concerns the clinical translation of new drug delivery technologies in the field of bone repair. The Nottingham team have invented a new class of pharmaceutical systems called “injectable bone”. This system allows drugs to be delivered locally within a site of injury. The project will provide training in protein drug delivery, tissue engineering and polymer science.

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

Supervisor:  **Keith Spriggs** ([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 polyadenylation. However, almost nothing is known about the nature of untranslated regions in spiders (Araneae), a group that is the focus of studies into industrially and medically useful proteins such as venom and silk. The aims of this bioinformatic project are to examine newly sequenced spider transcriptome sequences (and, where possible, genomic sequences) 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.

Overcoming cancer cell resistance to the chemotherapy drug Irinotecan

Supervisor:  **Keith Spriggs** ([keith.spriggs@nottingham.ac.uk](mailto:keith.spriggs@nottingham.ac.uk))

The topoisomerase inhibitor Irinotecan is frequently used in the treatment of colon cancer. Irinotecan is a prodrug and is converted to its active form by carboxylesterase enzymes. Cancer cells can develop resistance to Irinotecan by down-regulating carboxylesterase activity, thereby reducing levels of active drug. This project will use cell culture models of cancer to investigate ways in which we can reduce or reverse Irinotecan resistance. For example, aspirin (which itself has been shown to have anti-cancer properties) is inactivated by the same carboxylesterases that activate irinotecan: aspirin is expected to be more toxic to cells that have adapted to Irinotecan by down-regulating carboxylesterases. In addition, treatment with aspirin or similar compounds is expected to reverse the selective pressure on Irinotecan treated cancer cells to down-regulate carboxylesterases. We are also interested in understanding the mechanisms by which Irinotecan cancer cells adapt, as it is not currently known at what level of gene expression (e.g. chromatin remodelling, transcriptional repression, splicing, mRNA processing and export, translational repression, post-translational
modification or protein turnover) the observed down-regulation occurs. The project will involve training in cell biology and molecular biology techniques.

**Design and development of paradoxical nanostructures for smart materials**

**Supervisor:** Phil Williams ([phil.williams@nottingham.ac.uk](mailto:phil.williams@nottingham.ac.uk))

It is possible to conceive materials that show paradoxical behaviour when stressed; springs that shorten when pulled, cylinders that thicken when stretched, etc. In this project we will use modern computational simulation techniques to design and refine molecular architectures that show such behaviours. This work will involve the use of the University's multi-thousand processor high performance computer to undertake molecular dynamics simulations, bioinformatic techniques of sequence, structure and function database searching, and theoretical and analytical approaches to create generally applicable rules for the design of novel materials with unique properties. Such materials may have application in the creation of new types of sensors, fail-safe systems and mechanical devices, to name but a few.

**Phylomechanics: The evolution of the mechanical properties of proteins**

**Supervisor:** Phil Williams ([phil.williams@nottingham.ac.uk](mailto:phil.williams@nottingham.ac.uk))

Proteins have evolved with specific function, some of which is mechanical in nature: cell adhesion proteins, muscle proteins, mechanoreceptor proteins all have to withstand mechanical stress. The mechanical properties of proteins have, therefore, evolved. Many questions can be asked of this evolution; what are the driving forces? Do force-bearing proteins share common ancestry? Can the effect of mutation be predicted? In this project we will develop our use of computational and bioinformatic tools for the rapid analysis of protein mechanical properties for the exploration of evolutionary links in mechanical function; phylomechanics. The project will apply computational tools being developed in our laboratories across protein structural databases using the University's multi-thousand processor high performance computing systems. The outcomes of the project will increase our understanding of evolution, protein folding and degenerative disease.

**Development of small-molecule inhibitors of enzymes involved in post-transcriptional gene regulation**

**Supervisor:** Sebastiaan Winkler ([sebastiaan.winkler@nottingham.ac.uk](mailto:sebastiaan.winkler@nottingham.ac.uk))

Potent, selective and cell-permeable inhibitors of enzymes are powerful tools for the study of protein function. Because such chemical probes share many characteristics with therapeutic
drugs, they can play important roles in the validation of potential therapeutic targets and early-stage drug discovery.

This project will focus on the development of screening assays, and the subsequent identification of drug-like inhibitors of enzymes involved in post-transcriptional gene regulation. An example of an enzyme involved in this pathway is Caf1/CNOT7, a Mg(II)-dependent ribonuclease enzyme, which is a potential therapeutic target for the treatment of osteoporosis. The project will involve the expression and purification of recombinant proteins, automated screening of compound libraries, and the biochemical and cellular characterisation of drug-like inhibitors.

**Role of BTG1 and BTG2 in acute lymphocytic leukaemia and diffuse large B-cell lymphoma**

Supervisor:  **Sebastiaan Winkler** ([sebastiaan.winkler@nottingham.ac.uk](mailto:sebastiaan.winkler@nottingham.ac.uk))

Acute lymphocytic leukaemias (ALL) and diffuse large B-cell lymphomas (DLBCL) often contain small deletions of or point mutations in the highly related BTG1 or BTG2 genes. However, it is not clear how mutations in BTG1 and BTG2 contribute to tumourigenesis.

This project aims to gain further understanding regarding the contribution of BTG1 and BTG2 to tumour development. This will be investigated by knockdown of BTG1 and BTG2 mRNA in B cell lines in combination with the expression of mutant BTG1 and BTG2. The effects on gene expression as well as cellular proliferation and differentiation will be investigated by a variety of modern techniques, including real-time quantitative PCR, flow cytometry and fluorescence microscopy.