Research Experience Placements 2019

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Dr Andrew Povey	Mechanisms of toxicity induced by nitrosation of □-methylaminoalanine
Dr Glen Martin and Professor Andrew Renehan	Do the relationships between body mass index and waist circumference on cancer incidence differ by comorbidity?
Dr Hui Guo	Investigation of causal mechanisms of cardiovascular disease
Dr Igor Chernyavsky and Professor Oliver Jensen	Microstructural determinants of human placental health: an image-based modelling approach
Dr Ingo Dierking	Mimicking nerve fibres with nanotubes, graphene oxide and liquid crystals
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Dr Adam McMahon and Dr Michael Fairclough	Optimisation of the synthesis of the PET radioligand [11C]PK11195.
Dr Michael O'Toole, Dr Alex Casson and Rebecca Morton	The Pocket Therapist: real-time responsive mode therapy using mobile platforms and smart sensors.
Professor Paul Popelier	Rigorous atomistic modelling of peptide structure.
Professor Stuart Allan	Investigating the role of α-defensins in thrombo-inflammation: A potential target for treating ischaemic stroke?

Supervisor Details	**Dr Andrew Povey** **0161 275 5232** apovey@manchester.ac.uk https://www.research.manchester.ac.uk/portal/en/researchers/andrew-povey(c82675ab-0c63-402f-80c4-10aa8c67cd9c).html
Project Title	**Mechanisms of toxicity induced by nitrosation of -methylaminoalanine**
Project outline	Aim: To test the hypothesis that nitrosation of -methylaminoalanine results in both primary and secondary nitrosamines that are genotoxic. -methylaminoalanine (BMAA) is an amino acid analogue that is suspected to cause the central nervous system pathological conditions, amyotrophic lateral sclerosis and parkinsonism-dementia complex (1). The mechanisms of these effects have yet to be defined. We have shown that BMAA can be nitrosated in vitro forming a DNA damaging agent that is toxic to cultured human neuroblastoma cells (2). However, BMAA has both a primary and secondary amino groups, and while DNA damage is a consequence of primary amine nitrosation and spontaneous breakdown of the product, it is not clear if cellular toxicity is a result of secondary amine nitrosation and subsequent catabolism by cellular mixed function oxidases to yield a different genotoxic agent. BMAA will be nitrosated as previously (2) and assessed for DNA damaging capacity before and following activation by mixed function oxidases provided by a commercially available human liver cell-free supernatant. DNA damage will be monitored as single strand breaks introduced into supercoiled bacterial plasmid DNA, which changes its electrophoretic mobility in agarose gels. The possible nature of the damage, which may give clues to the biological effects of BMAA, will be investigated using various damage processing and detecting proteins. To examine cell killing, cultured human liver cells, which express some of the likely mixed function oxidases, will be exposed to increasing doses of nitrosated BMAA and survival determined using microtitre plate growth assays. The studies should provide a better understanding of BMAA toxicity and will provide a wide range of chemical, molecular biological and cell biological wet lab experience. 1Bradley et al 2013 Amyotroph Lateral Scler Frontotemporal Degener. 14:325-33; 2Potjewyd et al 2017 Neurotoxicology 59;105-109.

Supervisor Details	**Dr Glen Martin and Professor Andrew Renehan** **0161 275 0179** glen.martin@manchester.ac.uk andrew.renehan@btinternet.com https://www.herc.ac.uk/ https://www.research.manchester.ac.uk/portal/glen.martin.html
Project Title	**Do the relationships between body mass index and waist circumference on cancer incidence differ by comorbidity?**
Project outline	There is a relationship between body mass index (BMI) and waist circumference (WC), with increased cancer risk, but their joint contributions are unknown. We are currently investigating the combined relationships between BMI and WC on cancer incidence. However, there might be heterogeneity in such a relationship across subgroups of individuals. Specifically, cancer incidence may naturally differ across individuals with

	different co-existing conditions, meaning individual-level comorbidity patterns might be informative. This complex inter-relationship has recently been highlighted for individuals who smoke; while mean BMI is generally lower in smokers versus non-smokers, among heavy smokers, WC is (paradoxically) substantially elevated. Therefore, this project will begin to investigate whether the combined relationships between BMI and WC on cancer incidence differ across patients with different comorbidities (diabetes and diabetes severity will be a focus). The prospective student could get 'hands-on' experience of analysing a large cohort of > 25,000 participants from the EPIC-Heidelberg cohort, where BMI and WC have been measured repeatedly every 3 years over 15 years from study entry. This project will feed into a wider programme of work, where we hypothesise that the identification of risk factors that inhibit the earlier detection of cancer will allow the development of prediction models that can target screening programmes in an adaptive way. **Objectives** **1: What is the current evidence surrounding the relationships between repeated BMI or WC measurements on cancer incidence, across different comorbidity patterns?** Here, the student will undertake a systematic literature review. **2: Begin to explore common comorbidity patterns in the EPIC-Heidelberg cohort, and investigate relationships between BMI and WC on cancer incidence within said patterns.** The completion of this objective will depend on project time-scales and the students own interests. This project would suit students with an interest in applying informatics or statistics to real-world health data.

Supervisor Details	**Dr Hui Guo** **0161 306 8003** hui.guo@manchester.ac.uk https://www.research.manchester.ac.uk/portal/hui.guo.html
Project Title	**Investigation of causal mechanisms of cardiovascular disease**
Project outline	Cardiovascular disease (CVD) is one of the main causes of mortality. Genetic risks and other risk factors have been investigated in many genome-wide association studies. However, it is difficult to draw causal conclusions from these studies which are observational. Mendelian randomization (MR), regarded as a quasi-randomized experiment, is designed to examine if an exposure causes an outcome, where exposure associated genetic variants are regarded as proxies of the exposure. This approach aims to use summary statistics, to make causal inference between the exposure and the outcome in observational studies. In this project, we aim to make use of publicly available summary statistics from large-

	scale genome-wide association studies (e.g. UK Biobank) and apply the state-of-the-art MR methods, to investigate the underlying causal mechanisms of CVD. In particular, we will look into putative causal factors, which helps targeting the right biomarkers and developing treatments for CVD prevention.

Supervisor Details	**Dr Igor Chernyavsky and Professor Oliver Jensen** **0161 306 3640** **Igor.Chernyavsky@manchester.ac.uk Oliver.Jensen@manchester.ac.uk** **http://www.maths.manchester.ac.uk/~ojensen/ http://math-biophys.info**
Project Title	**Microstructural determinants of human placental health: an image-based modelling approach**
Project outline	A complex multiscale relationship between the structure and function is common in many human organs (such as the brain, lung, liver and placenta), and many diseases are associated with an imbalance in the relationship. This summer project aims to develop new tools to characterise solute transport in complex biological media, using the human placenta as a motivation and primary application. The human placenta is a critical life-support system for the developing fetus. The supply of oxygen and nutrients has to be well orchestrated within a complex fetal vascular network packed in irregular trees and surrounded by maternal blood flow, thus forming a disordered double-porous medium. Placental insufficiency could result in stillbirth or premature delivery (affecting tens of thousands of all pregnancies in the UK alone), as well as in a higher risk of cardiovascular, metabolic and neurological disorders later in adult life with significant costs to society and healthcare. At the same time, the human placental arrangement is unique, having no close analogues in other species, so theoretical modelling is of particular value. However, the complexity of placenta prevents direct analysis and simulation at the organ level, and there is a lack of established mathematical tools to manage the complexity. The project methodology will include basic statistical shape analysis and modelling of transport in porous materials, informed by unique 3D X-ray micro-tomography datasets acquired in Manchester (which span the spatial scales of 10 microns to 10 mm). The expected outcome will be better understanding of placental structure in health and disease, contributing to a long-term roadmap of developing computer-assisted diagnostics and therapies for placental fitness. The project will suit a student taking an undergraduate degree in applied mathematics, physics, bioengineering or a related area who has enthusiasm to apply their skills to a challenging biomedical application.

Supervisor Details	**Dr Ingo Dierking** **0161 275 4067** **Ingo.dierking@manchester.ac.uk** **https://softmatter-dierking.myfreesites.net/**
Project Title	**Mimicking nerve fibres with nanotubes, graphene oxide and liquid crystals**
Project outline	In healthy nerve fibres, axons are surrounded by layers of Myelin sheath forming Schwann cells. Many of these surround the whole fibre which can then transport information quickly between nodes of Ranvier, thus from one dendritic neuron to another. We anticipate to mimic this situation though self-organized growth; one dimensional conductive nanowires, surrounded by a lyotropic liquid crystal. Nanowires in water will act as axions. These will be nucleation centres for the growth of Myelin figures, when lecithin and CTAB (cetyl-trimethylammonium-bromide) are added to the solution. The Myelin figures are self-assembled double layers which arrange into concentric cylinders, surrounding the artificial axon. They are spontaneously formed lyotropic liquid crystalline structures which occur as a function of amphiphilic concentration in water. Damaged nerve cells are responsible for diseases like multiple sclerosis or neuromyelitis optica. They are caused by demyelination of the nerve fibres, damaging or destroying the myelin sheath and exposing the nerve fibre, leading to slow and disrupted information flow. With respect to strengthen the myeline sheath surrounding the nanowire-axon, we will further add small concentrations of two-dimensional graphene oxide (GO) to the so far discussed solution. Graphene oxide is electrically insulating and flexible to bending, yet strong when pulled. GO is chemically compatible with water, forming lyotropic liquid crystals themselves. It is anticipated that the graphene oxide will be incorporated into the myeline structure giving it additional strength. The investigations on mimicking nerve cells may thus provide fundamental insight into possible curing mechanisms of nerve diseases. Objectives: (1) to produce samples of artificial nerve cells by varying concentrations of nanowires, amphiphilic compounds and graphene oxide in water. (5 weeks) (2) to characterize their formation and integrity via microscopy methods. (2 weeks) (3) to perform electric conductivity experiments on selected samples to study effects of added graphene oxide. (3 weeks)

Supervisor Details	**Dr Samuel Jones and Dr Celina Jones** **Samuel.jones-4@manchester.ac.uk** **Celina.jones@manchester.ac.uk** **0161 306 2359, 0161 306 5749** **www.broadspectrumantivirals.com**
Project Title	**Applying an antiviral finish to textiles**
Project outline	This project will focus on the development of antiviral fabrics. Development of such fabrics are of critical importance for the prevention of cross-contamination between infected individuals and healthy patients. Specifically in a hospital setting antiviral fabrics (curtains, bedding, clothing) could help reduce the significant problem of rotavirus and norovirus transmission. Antiviral fabrics may also be of use in protecting nurses and doctors who respond to viral outbreaks. Within The School of Materials at The University of Manchester there is a unique diversity of specialisms, offering an undergraduate student the opportunity to

	participate in a uniquely interdisciplinary project. This particular project will explore the potential of applying antiviral finishes to textile materials. Previous work with medical textiles has demonstrated the possibilities of applying textiles finishes to give fabrics anti-bacterial, anti-microbial or anti-fungal properties. Typically this involved the use of biocides or silver ions, but research has investigated the use of colorants with antimicrobial properties as an alternative. The use of these colorants combines two production processes; colouration and improved functional properties of the textile material. This project builds on recent work on biocompatible extracellular broad-spectrum antiviral materials that have been shown to destroy viruses on contact *i.e.* are virucidal. The aim of this project is to explore the application of a new *antiviral* finish (based on these new virucidal materials), which will destroy the virus on contact with the textile material. This work could lead to fabrics capable of protecting users from viral infections and reducing the spread of rotavirus and norovirus within hospitals. **Aim:** To apply antiviral molecules, (created from the antiviral material with a traditional textile colorant or crosslinker) to textile substrates and to test the antiviral properties of the new material. **Objective 1** – explore attachment techniques for attaching new antivirals to textile substrate. **Objective 2** –determine the antiviral properties of the new antiviral textile substrate against a range of viruses.

Supervisor Details	**Dr Adam McMahon and Dr Michael Fairclough** **Adam.mcmahon@manchester.ac.uk Michael.fairclough@manchester.ac.uk** **0161 275 0026, 0161 275 0034**
Project Title	**Optimisation of the synthesis of the PET radioligand [11C]PK11195.**
Project outline	The University of Manchester has recently opened its state of the art PET/MRI scanning suite: combining the quantitative molecular imaging modality of positron emission tomography (PET) with the high resolution, soft tissue contrast imaging of magnetic resonance imaging (MRI) to investigate the mechanism and treatment of disease. The Wolfson Molecular Imaging Centre (WMIC) supports the important research performed at the PET/MRI suite through the manufacture of PET radioligands for imaging myriad biological processes and diseases. One such PET radioligand, [^{11}C]PK11195, binds to the 18 kDa translocator protein (TSPO) which is upregulated in activated microglia; [^{11}C]PK11195 PET is used to image TSPO *in-vivo* for a number of neuro-inflammation studies. The production of [^{11}C]PK11195, carried out on a specialised automated radiochemistry platform, is particularly time sensitive considering the short radioactive half-life of carbon-11. Routine [^{11}C]PK11195 production occurs at the WMIC for on-site clinical PET scanning; in order to supply clinically relevant doses to the satellite PET/MR site in central Manchester a consistently high radiochemical yield is vital and ensures the generation of

	high quality images from the PET/MR. This data will be used to enhance understanding of neuro-inflammation in various disease areas including neuro-oncology , Alzheimer's disease and Huntington's disease and will be a valuable tool for patient stratification. The aim of this clinically important project which is in alignment with the strategic theme of inflammation within the University faculty is to optimise [^{11}C]PK11195 radiosynthesis. This will be done by investigating a number of components that affect reaction kinetics including the influence of solid surface interactions as well as solvation in order to supress side reactions. Yields of [^{11}C]PK11195 will be monitored by analytical techniques including HPLC and LCMS. The student will receive training in radiochemistry and have the opportunity interact with clinicians and researchers at WMIC and the PET/MR facility.

Supervisor Details	**Dr Michael O'Toole, Dr Alex Casson and Rebecca Morton** **michael.otoole@manchester.ac.uk** **alex.casson@manchester.ac.uk** **0161 306 4801** **https://www.research.manchester.ac.uk/portal/alex.casson.html**
Project Title	**The Pocket Therapist: real-time responsive mode therapy using mobile platforms and smart sensors.**
Project outline	We propose a new device to support therapeutic interventions for mental health and neurodevelopmental disorders, specifically emotional regulation, by delivering therapy to a mobile platform at a time of most need, responsive to the emotional state of the service user. The concept is to use a series of discrete and unobtrusive smart sensors to measure the user's physical and autonomic responses, such as heart-rate, perspiration, voice-modulation, muscle tension, movement, etc. The measurements are then used to profile their emotional state – whether they are angry (red), anxious or worried (yellow), low or depressed (blue) or optimum, relaxed or regulated (green) – and send a prompt or message to their mobile device reminding them of the strategies or actions they have agreed with their therapist in advance. The student's project will be to investigate and report on the technical feasibility of this proposition at its earliest phase prior to preparing an MRC DPFS or similar application. It will build on an EEG smart therapeutics platform currently being created by CI Casson (MRC CiC, and EPSRC mental health technologies funded), and complement the EPSRC funded "Wearable clinic" project led by HeRC, which follows Clintouch and has Serious Mental Illness as one of the use cases. The student will: (1) Literature survey: Establish whether similar systems exist and (if found) critique the technology and efficacy. Identify relevant significant standards, regulations, and approvals. (2) Technical survey:

	Identify and review suitable architectures, data and security protocols, sensors, hardware, and components for the system, with costs models where appropriate. (3) Specifications and Proposals: Based on literature and technical surveys, present a set of detailed proposals, specifications and top-level schematics and designs for the system. (4) Provisional prototyping: Should time permit, conduct some prototyping on parts of the system and author quick-start guides for future researchers.

Supervisor Details	**Professor Paul Popelier** **pla@manchester.ac.uk** **0161 306 4511** **http://www.qct.manchester.ac.uk/**
Project Title	**Rigorous atomistic modelling of peptide structure.**
Project outline	**Background:** Understanding the detailed behaviour of (oligo)peptides in aqueous solution in a correct, complete and fundamental way remains a huge challenge still today. In particular, no structural information is available on the very onset in the nucleation event of the small protein Amyloid β, which is thought to cause Alzheimer's disease. In other words, the 3D topology and size of the primary nucleus of amyloid fibril formation is unknown. An understanding of the nucleation mechanism is vital to design drugs that actually work. The unsatisfactory state of affairs is due to two major factors: (i) standard experimental tools of structural biology (NMR, CD, IM-MS, crystallography) fail to probe this early stage successfully, while (ii) molecular simulation by means of standard force fields provide very inconsistent structural and dynamical information, with huge differences depending on which version is used. **Aims and objectives :** Thus, there is an urgent need to make solid progress in the construction of a completely new force field that is much more reliable than current force fields. This is exactly what has happened in our research lab, where a novel force field called FFLUX is being developed to model peptides in a more realistic way. FFLUX avoids the classical combination of bonded potentials (ball and spring, angle, torsion) and non-bonded potentials (point charge electrostatics, Lennard-Jones). Instead, FFLUX uses so-called topological atoms, which are malleable boxes trained (by a machine learning method called kriging) to adapt their energy to a previously unseen environment. In this project the student will build on the success of the recent milestone of FFLUX rapidly and correctly predicting the energies of minimum geometries of polyalanine. There is one main ambitious goal: create a kriging model for a fragment of the 42-residue Amyloid β peptide and use it to study its potential energy surface. If achieved, this would correspond to a step change in force field design.

Supervisor Details	**Professor Stuart Allan** **0161 275 5255** **stuart.allan@manchester.ac.uk** **https://www.bmh.manchester.ac.uk/research/domains/neuroscience-mental-health/stroke/** **https://www.research.manchester.ac.uk/portal/stuart.allan.html**
Project Title	**Investigating the role of α-defensins in thrombo-inflammation: A potential target for treating ischaemic stroke?**
Project outline	Human neutrophil peptides (HNPs), also known as α-defensins, are potent anti-microbial molecules released by neutrophils in response to infection. Elevated levels of HNPs are also observed during sterile inflammation and have been implicated in inflammatory cardiovascular diseases such as atherosclerosis and coronary artery disease. In vitro experiments have suggested that HNPs may influence coagulation, endothelial reactivity, platelet aggregation and cytokine production. Despite the known involvement of these thromboinflammatory pathways, the direct contribution of HNPs to stroke pathophysiology has not been investigated. This project aims to identify the brain-specific thromboinflammatory changes induced by HNPs. Firstly, we will culture brain microvascular endothelial cells (BMVECs) under static conditions, treat the cells with HNPs and use immunocytochemistry to quantify levels of VWF and P-selectin release and upregulation of cell adhesion molecules (E-selectin, PECAM-1, ICAM-1 and VCAM-1). Cells will then be grown under physiological flow conditions and used to visualise, in real time using confocal microscopy, HNP-induced changes to platelet-platelet, platelet-endothelium and leukocyte-endothelium interactions. Secondly, donor human platelets will be treated with HNPs and platelet aggregation, in response to a range of agonists, will be measured using light transmission aggregometry. Finally, we will culture microglia, the brain resident immune cells, and we will measure any differences in pro-inflammatory cytokine production upon HNP treatment by ELISA and western blot. We hypothesise that HNPs will enhance platelet aggregation, promote recruitment of leukocytes at the endothelium and increase the release of pro-inflammatory cytokines demonstrating, for the first time, their role in thromboinflammation in the vasculature and tissues of the brain. These findings will be used as a rationale for future grant applications to investigate the effect of HNPs on stroke pathophysiology in vivo. Ultimately, we hope to identify HNPs as a novel, and potentially druggable, target in the treatment of ischaemic stroke.