Research Experience Placements 2020

Supervisor	Project Title (further details below)
Dr Aleksey Yerohin	Development of multifunctional (biocompatible and corrosion resistant) coatings for next generation of resorbable implant applications
Dr Alissa Ferry	The investigation of pupil dilation responses as an early biomarker of Alzheimer's Disease.
Dr Antje Heinrich	Examining the suitability of the reading span task to measure cognitive ability associated with speech-in-noise perception
Dr Beatriz Mingo	Halloysite Nanotubes with enlarged lumen for controlled release of biomedical agents on PEO coatings
Dr Ceri Ellis	Infants temperament in Neurofibromatosis type 1
Dr David Jenkins	Identifying trends in publically available health data.
Prof James O'Connor and Dr Denis Alferez	Characterisation of Hypoxia levels in Patient Derived Xenograft models of Triple Negative Breast Cancer
Prof Garth Cooper	Role of localized vitamin B5 deficiency in cerebral demyelination and neurodegeneration
Dr Grazyna Lipowskaw-Bhalla	Characterisation of immune environment in murine solid tumours following radiotherapy and immunotherapy treatments
Dr Hervé Boutin	Are the protein synthesis regulatory pathways altered in the transgenic rat model of Alzheimer's disease TgF344-AD?
Dr Jason Taylor	Towards Early Detection of Dementia with Functional Neuroimaging: Automatic Classification of Patients and Controls using Machine Learning
Dr Lucy Higgins	Defining placental dysfunction by angiogenic marker status: what is the relationship between angiogenic markers and underlying placental pathophysiology?
Dr Matthew Sperrin	Handling uncertainty correctly in risk prediction
Dr Darren Plant (Megan Sutcliffe)	Quantifying interleukin-7 plasma concentrations in patients with rheumatoid arthritis who have been treated with a tumour necrosis factor inhibitor therapy.
Dr Michael Harte	Investigating markers of inflammation in Alzheimer's disease post-mortem tissue.
Prof Paul Popelier	Rigorous atomistic modelling of peptide structure
Dr Stephen Fowler	Development of a screening method to differentiate Carbapenemase-producing Enterobacteriaceae cultures using volatile metabolites

Supervisor Details	**Dr Aleksey Yerohin** **Enquiries:** aleksey.yerokhin@manchester.ac.uk +44 161 306 2405
Project Title	Development of multifunctional (biocompatible and corrosion resistant) coatings for next generation of resorbable implant applications
Project outline	Magnesium, as an element naturally present in the human body, has shown great potential for the next generation of resorbable implant materials due to key advantages, such as biocompatibility and biodegradability, high strength-to-weight ratio and stiffness similar to that of the human bone. However, the high chemical activity and poor corrosion behaviour of magnesium results in an early deterioration in the mechanical properties and accumulation of hydrogen bubbles around the implants, impeding (and ultimately preventing) the healing process. An appropriate surface treatment is therefore needed to increase corrosion resistance of Mg in biological environment and increase its bioactivity. Plasma Electrolytic Oxidation (PEO) is an environmentally-friendly technique used to form ceramic-like coatings that contain oxides of both parent metal and electrolyte constituents, offering high corrosion resistance and mechanical protection to the metal substrate. Importantly, the coating properties can be easily tailored by altering the process parameters, thus catering difference application. The objective of this work is to develop dense PEO coatings on Mg containing bioactive Ca/P compounds to achieve the biocompatibility of the coatings as well as a high corrosion resistance. The work consists of the following parts: • Electrolyte and sample preparation. (1 week) • Voltammetric studies of anodic behaviour of Mg alloy substrates in Ca and P containing electrolytes. This will provide an understanding of the passivation behaviour of individual electrolyte constituents, contributing to the final electrolyte selection. (2 weeks) • PEO coating synthesis with the chosen electrolyte under different electrical parameters, aiming to optimise the coating morphology. (1 – 1.5 weeks) • Coating characterisation using Scanning Electron Microscopy and X-Ray Diffraction analysis to evaluate surface morphology, chemical and phase composition. Corrosion tests of PEO-coated Mg alloys. Screening tests and extended corrosion evaluations of selected coatings will be performed in Simulated Body Fluids. (1.5-2 weeks)

Supervisor Details	**Dr. Alissa Ferry and Dr. Ross Dunne** **Enquiries:** Alissa.ferry@manchester.ac.uk and ross.dunne@gmmh.nhs.uk 0161 275 2577 (Ferry) Dr. Alissa Ferry https://www.research.manchester.ac.uk/portal/alissa.ferry.html Dr. Ross Dunne https://dementiaacademy.co/speakers/dr-ross-dunne/
Project Title	The investigation of pupil dilation responses as an early biomarker of Alzheimer's Disease

Project outline	The locus coeruleus (LC) is one of the earliest brain regions affected by AD, and an area highly affected by neuronal loss. The LC also plays a key role in modulating pupil size in response to changes in luminance. Deviations from the standard pupil responses are a potential diagnostic tool to measure LC functioning, and thus are a possible biomarker for AD. Some preliminary studies support this idea, but these studies generally focus on a single pupil effect (e.g., pupil constriction in response to a specific intensity of light). The current project will provide a comprehensive measure of pupil luminosity responses designed to elicit varying degrees of both constriction and dilation in AD patients, healthy controls, and patients with Mild Cognitive Impairment (MCI). Pupil size will be recorded as participants (20 per group) watch solid squares appear on a grey background on a computer screen. The squares will differ in their luminosity (white to elicit constriction; black to elicit dilation) and size (larger squares result in a greater luminosity change). This project will investigate whether there are marked differences in the responses in those with AD compared to healthy age-matched controls, and whether any differences can be found in patients with MCI to assess the possibility that pupil deviations can be used as a potential early AD biomarker. Pupil responses will also be correlated with cognitive assessment (e.g., ADAS-Cog12 scores) to identify if certain types of pupil responses are more sensitive as a potential biomarker. The student will be responsible for collecting data from participants in Greater Manchester Mental Health Foundation Trust Memory Clinics, as well as coding and analysing the data in collaboration with the supervisors.

Supervisor Details	**Dr Antje Heinrich** **Enquiries:** antje.heinrich@manchester.ac.uk 58679 https://www.research.manchester.ac.uk/portal/antje.heinrich.html
Project Title	Examining the suitability of the reading span task to measure cognitive ability associated with speech-in-noise perception
Project outline	Communicating in noisy environments is crucial for participation in everyday life and a prerequisite for a good quality of life. However, listening to speech in noise can be difficult. Hearing ability as a cause of this difficulty has long been a focus of research and indeed the provision of hearing aids is based on this work. However, there is growing consensus that differences in cognitive ability must also play an important role as many people have similar hearing ability, yet differ greatly in how well they understand speech in noise. The most commonly used test to assess cognitive ability in connection with speech-in-noise perception is the Reading Span Test (RST)1,2. This test is meant to measure a person's ability to simultaneously store and manipulate information, a skills that is deemed crucial for speech-in-noise listening. Participants read a series of sentence, decide on a semantic aspect of the sentence and recall designated words from the sentence at the end of a set. Clinical practitioners would like to use this or a similar test to increase sensitivity of assessment but, at this point, it is unclear precisely what the test measures and what the best, quickest, and most practical way would be to incorporate it into clinical practice. This student project aims to contribute to finding answers to these questions. With the supervisor's help the student will set up a short behavioural experiment in which different version of the RST are presented. The student will use a cognitive technique called Selective Reminding3 to probe and measure the contribution of different types of memory for each version of RST. Finally, after characterising each version of RST in such a way the student will look at the predictive ability of a particular version of RST for a speech-in-noise perception test

	1 Daneman, M., & Carpenter, P. A. (1980). Individual differences in working memory and reading. Journal of Verbal Learning and Verbal Behavior, 19(4), 450-466. 2 Rönnberg, J., Arlinger, S., Lyxell, B., & Kinnefors, C (1989). Visual evoked potentials: Relation to adult speechreading and cognitive function. Jounral of Speech and Hearig Research. 32, 725-735. 3 Rose, N. S., Myerson, J., Roediger III, H. L., & Hale, S. (2010). Similarities and differences between working memory and long-term memory: Evidence from the levels-of-processing span task. Journal of Experimental Psychology: Learning, Memory and Cognition, 36(2), 471–483. doi:10.1037/a0018405

Supervisor Details	**Dr Beatriz Mingo** **Enquiries:** Beatriz.mingo@manchester.ac.uk
Project Title	Halloysite Nanotubes with enlarged lumen for controlled release of biomedical agents on PEO coatings
Project outline	Plasma Electrolytic Oxidation (PEO) is an environmental-friendly surface treatment that results in ceramic-like coatings on light metals such as aluminium, titanium and magnesium. The coatings offer excellent wear and corrosion resistance for the materials, enhancing their longevity and reliability. With appropriate tailoring, PEO coatings can exhibit extraordinary barrier properties, offering a possibility of developing magnesium into bio-absorbable orthopaedic implants. Besides the enhanced corrosion resistance, the micro-roughness of the coating surface enables the incorporation of nano-containers. This is thanks to the porous surface morphology of the PEO coatings. The drug-loaded nano-containers, specifically, Halloysite Nanotubes (HNT), can be a local drug delivery system, to reduce the inflammation or infection caused by the implanting process. So, the objective of the work is: enlarge the inner lumen of halloysite nanotubes (HNT), and incorporate the drug-loaded HNT on biocompatible Plasma Electrolytic Oxidation (PEO) coatings. The work mainly consists of the following parts: • Synthesise biocompatible PEO coatings. (1 week) • Enlarge the inner lumen of the HNT. This will be achieved by alumina selective etching using sulphuric acid. Characterisation of the enlarged HNT will be done including Scanning Electron Microscope and Transmission Electron Microscope. (2 weeks) • Load the enlarged HNT with a choice of drug, such as penicillin, using vacuum induced capillary. Fourier-Transform Infrared Spectroscopy will be performed to justify the existence of the drug in the HNT. (1 weeks) • Evaluate the release kinetics of the drug with a UV-VIS spectroscopy. (1 week) • Incorporate the drug-loaded HNT on PEO coatings using immersion post-treatment. The morphology of before and after the incorporation will be examined by Scanning Electron Microscopy. (1 week)

Supervisor Details	**Dr Ceri Ellis** **Enquiries:** Ceri.ellis@manchester.ac.uk 67941 http://research.bmh.manchester.ac.uk/socialdevelopment/eden
Project Title	Infants temperament in Neurofibromatosis type 1
Project outline	Temperament is a well-known predictor of future psychopathology. Examining temperament in neurogenetic groups can help inform biological factors that may confer later risk for psychopathology in the general population. The aim of this study is to examine early infant temperament in a common single-gene genetic disorder Neurofibromatosis type 1 (NF1) as compared to a control group of infants. The student will code video recordings of the infant laboratory temperament assessment battery (Lab-TAB) of 30 infants with NF1 and 30 infants with typical development at three points -5, 10 and 14 months. The video recording will be correlated to parent rated measures of infant temperament and with behaviour at 24 and 36 months. Cognitive and behavioural problems including autism, ADHD, anxiety and depression are frequently occurring comorbidities in the NF1 paediatric population. This study will help us understand how emerging temperament relates to later psychopathology in the NF1 group. Data for this project has been collected as part of the EDEN (Early Development in Neurofibromatosis 1) study.

Supervisor Details	**Dr David Jenkins** Enquiries:David.jenkins-5@manchester.ac.uk/ Matthew.sperrin@manchester.ac.uk / Glen.martin@manchester.ac.uk https://www.research.manchester.ac.uk/portal/matthew.sperrin.html https://www.research.manchester.ac.uk/portal/glen.martin.html
Project Title	Identifying trends in publically available health data.
Project outline	Disease populations are constantly changing and the healthcare system is evolving daily. New treatments, policies and guidelines are introduced into healthcare regularly. There is a need to understand and identify changes over time to provide accurate up to date information to improve patient care. This project aims to use publically available data sets to investigate changes/trends over time. The aim will be achieved by completing the following objectives; 1. Identify available/open source datasets by conducting a brief literature search or a search of available online resources. (week 1) 2. Learn the basics of the R, a software used to analyse and visualise data. (week 2) 3. Analyse the data and identify any trends, including changes in prevalence or patient characteristics. (week 3-5) 4. Produce visualisations of results and write a brief report of findings. (week 6) The ideal candidate to undertake this project will have an analytical background and ideally some experience using statistical software, for example, R, SPSS, Matlab or STATA. Throughout the project the student will work at the Centre for Health

	Informatics and gain experience working in a research environment, as well as gain hands on experience programming and using real-world data.

Supervisor Details	**Dr Darren Plant** **Enquiries:** Darren.Plant@manchester.ac.uk and Megan.Sutcliffe@postgrad.manchester.ac.uk https://www.research.manchester.ac.uk/portal/en/researchers/darren-plant(d5b92cf0-62bb-4b87-8cf7-9740d6999dfd).html
Project Title	Quantifying interleukin-7 plasma concentrations in patients with rheumatoid arthritis who have been treated with a tumour necrosis factor inhibitor therapy.
Project outline	Background: Previous studies report that low plasma levels of interleukin-7 (IL-7,<10pg/mL) are associated with more severe disease in patients with rheumatoid arthritis (RA). Interestingly, RA patients in clinical remission, or following treatment with a disease modifying anti-rheumatic drug (DMARD) show a recovery of IL-7 to a level comparable to healthy subjects (>17pg/mL). (Churchman and Ponchel, 2008; Goëb *et al.*, 2013; Burska, Boissinot and Ponchel, 2014) We hypothesise that IL-7 is an important biomarker for predicting treatment success in RA. Aims: - Measure IL-7 levels in the plasma of patients with RA at 7 different time points (pre-treatment, 0h, 1h, 6 days, 2 weeks, 4 weeks, 12 weeks, post treatment with TNFi). - Validate literature findings which report that peripheral IL-7 levels are low in established disease and increase following treatment. - Quantify changes in IL-7 concentration between different time points. Objectives: - Plasma samples for the proposed project have already been collected. - IL-7 enzyme linked immunosorbent assays (ELISA) will be performed in order to quantify IL-7 concentration in patient samples. - Sample preparation will be optimised to ensure assay sensitivity is maximised. - Statistical analysis will be performed to test for significant changes between treatment time points. The results of the project will be a valuable contribution to the investigation of early treatment response in RA patients. The student will work with a group of scientific researchers within the Versus Arthritis Centre for Genetics and Genomics. They will be given the opportunity to develop a range of skills including practical laboratory experience, sample handling, data analysis and scientific writing.

Supervisor Details	**Dr Matthew Sperrin** **Enquiries:** Matthew.sperrin@manchester.ac.uk Glen.martin@manchester.ac.uk David.jenkins-5@manchester.ac.uk

	https://www.research.manchester.ac.uk/portal/matthew.sperrin.html https://www.research.manchester.ac.uk/portal/glen.martin.html
Project Title	Identifying trends in publically available health data.
Project outline	Disease populations are constantly changing and the healthcare system is evolving daily. New treatments, policies and guidelines are introduced into healthcare regularly. There is a need to understand and identify changes over time to provide accurate up to date information to improve patient care. This project aims to use publically available data sets to investigate changes/trends over time. The aim will be achieved by completing the following objectives; 1. Identify available/open source datasets by conducting a brief literature search or a search of available online resources. (week 1) 2. Learn the basics of the R, a software used to analyse and visualise data. (week 2) 3. Analyse the data and identify any trends, including changes in prevalence or patient characteristics. (week 3-5) 4. Produce visualisations of results and write a brief report of findings. (week 6) The ideal candidate to undertake this project will have an analytical background and ideally some experience using statistical software, for example, R, SPSS, Matlab or STATA. Throughout the project the student will work at the Centre for Health Informatics and gain experience working in a research environment, as well as gain hands on experience programming and using real-world data.

Supervisor Details	**Prof James O'Connor (main supervisor) and Dr. Denis Alferez (Co-supervisor)** **Enquiries:** James.O'Connor@manchester.ac.uk Denis.Alferez@manchester.ac.uk Grazyna.lipowska-bhalla@manchester.ac.uk 0161-306-0862
Project Title	Characterisation of Hypoxia levels in Patient Derived Xenograft models of Triple Negative Breast Cancer
Project outline	Characterisation of Hypoxia levels in TNBC PDX models and its effect on distant metastasis Background The rapid growth of solid tumours often results in the development of hypoxic regions. This occurs as incessant growth and vascular abnormalities lead to insufficient perfusion of the tumour mass [1, 2]. Areas of hypoxia can be found in as many as half of all breast cancers [3] and are directly linked to aggressive disease and poor response to chemo- and radiotherapy [4]. The transcription factor hypoxia inducible factor (HIF) -1 drives tumour growth and metastasis and is associated with poor prognosis in breast cancer. This is especially the case with Triple Negative Breast Cancer (TNBC) the most aggressive form of Breast cancer. HIF-1 activity in vitro and is associated with activation of hypoxia in a number of cancer types, but whether tissue HIF-1 levels or other hypoxic factors influence the propensity of metastasis in breast cancer is unknown. In this study we investigated the association between tumour HIF-1 levels and other markers linked hypoxic activation to the occurrence of metastasis in a panel of human triple breast cancer models.

	Aims: 1. Understand the contribution of hypoxic markers in the growth of Triple Negative Breast Cancer (TNBC) in patient derived xenograft (PDX) models and their metastasis. Objectives: • Characterise the expression levels of 3 hypoxic markers (HIF1a, CaIX, and BNIP3) in a series of TNBC preclinical models. • Quantify the hypoxia markers with models that display metastasis against models that are not pro metastatic. • Evaluate different strategies to block metastatic progression in preclinical models of TNBC. Methodology This will be a retrospective analysis of an in vivo panel of 5 TNBC PDX primary tumours and the organs most associated with metastasis. We aim to measured levels of HIF-1α, CAIX and BNIP-3 along with other relevant markers of vascular perfusion (CD321, PIMO and VEGF). Tissue will be analysed by Halo image analysis software to devise and characterise the pattern of these markers across the tissue cohort.

Supervisor Details	**Professor Garth J S Cooper** **Enquiries:** garth.cooper@manchester.ac.uk 0161 275 1206 https://www.research.manchester.ac.uk/portal/garth.cooper.html
Project Title	Role of localized vitamin B5 deficiency in cerebral demyelination and neurodegeneration
Project outline	**Title: Co-localization study of vitamin B5 with myelinated cerebral structures in Huntington's disease (HD)** Background: Vitamin B5 (pantothenate) is an essential trace nutrient/obligate precursor of coenzyme A (CoA), through which it plays key roles in myriad biological processes. In brain, acetyl-CoA is necessary for synthesis of the fatty-acyl chains of myelin. Cerebral pantothenate deficiency is a newly-discovered metabolic defect in HD including presymptomatic disease (Patassini 2019). We are currently extending these studies to Alzheimer's disease (AD). By immunohistochemistry of normal rat brain, we found that pantothenate localizes in myelinated/white-matter structures, where acetyl-CoA is required for synthesis of the myelin sheath. We hypothesize that pantothenate deficiency is a probable cause of demyelination in HD, and other causes of age-related neurodegeneration/dementia such as AD. Aims: (i) We aim to perform a case-control study of two human brain regions in HD and controls using our established methods (Patassini, 2019; Ismail, 2019), and expect that these studies will discover defective vitamin B5 distribution coupled to defective myelination. Objectives: Perform the following: (i) undertake/complete literature review of white matter disease/demyelination in HD (2 weeks); (ii) in parallel, perform an immunohistological study of pantothenate/myelin co-localization using already-prepared/slide-mounted brain sections, thereby determining the disposition of myelin and pantothenate; (iii) write-up methods/results sections and complete first manuscript draft. References: Patassini, S., Begley, P., Xu, J., Church, S. J., … , Cooper, G. J. S. Cerebral vitamin B5 (D-pantothenic acid) deficiency as a potential cause of metabolic perturbation and neurodegeneration in Huntington's disease (2019) Metabolites 9, 113. Ismail, N., Kureishy, N., Church, S. J., Scholefield, M., … , Cooper, G. J. S. Vitamin B5 (D-

	pantothenic acid) localizes in myelinated structures of the rat brain: potential role for cerebral vitamin B5 stores in local myelin homeostasis (2019) Biochem Biophys Res Commun doi: 10.1016/j.bbrc.2019.11.052

Supervisor Details	**Dr Grazyna Lipowska-Bhalla** **Enquiries:** Grazyna.Lipowska-Bhalla@manchester.ac.uk Denis.Alferez@manchester.ac.uk James.O'Connor@manchester.ac.uk 0161-306-0862 https://www.research.manchester.ac.uk/portal/grazyna.lipowska-bhalla.html https://www.research.manchester.ac.uk/portal/en/researchers/james-oconnor(df5a4eb1-80f9-4113-b1d4-028439e9291a).html
Project Title	Characterisation of immune environment in murine solid tumours following radiotherapy and immunotherapy treatments
Project outline	The role of T cell immunity in cancer eradication is becoming increasingly well-recognised. Infiltration of tumours by T cells correlates with tumour regression and patient survival. Latest immunotherapies designed to enhance T cell function, such as checkpoint inhibitors, have produced spectacular clinical outcomes and revolutionised the way in which many solid tumours are treated. Combination with conventional treatments including radiotherapy can further improve the outcome. Understanding changes in tumour immune contexture following radiotherapy/immune therapy treatments is critical for the development of more effective anti-cancer therapies. This project will focus on characterization of tumour immune environment following radiotherapy and immunotherapy treatments in murine colorectal (CT26) and triple negative breast (4T1) cancers. In particular, we aim to evaluate infiltration of immune cells such as CD4 T cells, CD8 T cells, macrophages and natural killer (Nk) cells. We will also assess an activation status of the tumour resident T cells. The project will be based on retrospective analysis of murine tumours excised from BALB/c mice at defined time points following radiotherapy/immunotherapy treatment. Infiltration of immune cells will be measured using flow cytometry and immunohistochemistry (IHC) methods. Activation status of tumour resident T cells will be determined using flow cytometry. Flow cytometry data will be analysed using FlowJo software and IHC data will be analysed using Halo image analysis software.

Supervisor Details	**Dr Hervé Boutin** **Enquiries:** Herve.boutin@manchester.ac.uk x50078 https://www.research.manchester.ac.uk/portal/herve.boutin.html
Project Title	Are the protein synthesis regulatory pathways altered in the transgenic rat model of Alzheimer's disease TgF344-AD?
Project outline	Alzheimer's disease (AD) is a devastating disease, which incidence increases in developed countries due to ageing populations. **AD affects memory and other cognitive functions**, ultimately leading to a complete loss of independence for the patients. **So far there is no cure or even preventive treatment for AD**, only symptomatic treatments. **AD is a complex multifactorial disease** of which, for the non-familial (i.e. sporadic) form, the causes remain unknown. **Protein synthesis** is an integral part of cell homeostasis and function and in neurons it **is essential for synaptic function and memory formation**

	and retention and hence advanced cognitive functions. It has been shown that **pathways regulating protein synthesis are sensitive to protein misfolding, such as β-amyloid plaques and Tau aggregation that characterise AD. These pathways have been showed to be altered in animal models and in AD post-mortem tissue**. However, being able to measure **p**rotein **s**ynthesis **r**ate (**PSR**) *in vivo* in AD would allow monitoring the efficacy of drugs targeting PSR. Therefore, in collaboration with GSK, **we have been investigating PSR using [^{11}C]leucine positron emission tomography (PET) imaging** in the transgenic rat model TgF344-AD at 6, 12 and 18m of age. **We have shown a modest decrease in PSR in the striatum and *globus pallidus* of TgF344-AD rats** when compared to WT control littermates at 18 months of age. **This project aims at measuring *ex vivo* in brain sections** of the same animals that were scanned **the level of proteins regulating protein synthesis** such ATF4 or eI2Fα **in order to confirm our *in vivo* findings and try to establish which regulatory pathways and mechanisms are affected in TG rats**. We are hypothesizing that PET imaging may have lacked the sensitivity and resolution to measure more subtle changes and/or changes limited to small volumes of tissue in the vicinity of β-amyloid plaques.

Supervisor Details	**Dr Jason Taylor** **Enquiries:** jason.taylor@manchester.ac.uk x60454 https://www.research.manchester.ac.uk/portal/jason.taylor.html https://sites.manchester.ac.uk/mcrneuroim/eeg-lab/
Project Title	Towards Early Detection of Dementia with Functional Neuroimaging: Automatic Classification of Patients and Controls using Machine Learning
Project outline	Currently, the diagnosis of Alzheimer's disease (AD) depends on the observation of a decline in cognition as demonstrated by performance on neuropsychological tasks. However, the neuropathology of AD is believed to begin a decade or more before diagnosis can be made. As new potential treatments are developed, early detection and differential diagnosis are becoming crucially important. Studies investigating task-related brain activity using EEG and functional MRI have shown that neural responses related to word repetition (episodic memory) and category-exemplar relatedness (semantic memory) are effectively absent in individuals with mild AD, and critically, are abnormal in individuals with Mild Cognitive Impairment that later receive a diagnosis of AD (Olichney, Taylor, et al. (2008), *Neurology*; Olichney, Taylor, et al. (2010), *Neuropsychologia*; Mazaheri et al. (2018), *NeuroImage Cinical*). Therefore, these functional neuroimaging effects may serve as biomarkers that are sensitive to AD-related neuropathology that accumulates prior to diagnosis. Along with an MRC-DTP funded PhD student, we are currently planning a study to be run from January to July 2020. We will acquire EEG and fMRI data from patients with mild AD and healthy controls whilst they perform a simple semantic judgement task. We will analyse these data to extract features related to semantic memory (relatedness) and episodic memory (repetition). The Research Experience Placement student will then apply machine learning (ML) algorithms (e.g., support vector machines, artificial neural networks) to classify individual participants as being patients or controls using these EEG and fMRI features. The aims will be to (i) optimise the performance of the ML algorithims, (ii) compare performance across different algorithms, and (iii) compare classification performance

	when using features from EEG alone, fMRI alone, or EEG and fMRI combined. Training will be provided. The student may also have the opportunity to assist with data collection on a follow-up study.

Supervisor Details	**Dr Lucy Higgins** **Enquiries:** Lucy.Higgins@manchester.ac.uk 0161 701 6957 https://www.research.manchester.ac.uk/portal/en/facultiesandschools/division-of-developmental-biology--medicine(cbb929a8-5dfb-4bf1-aadf-77ae97d6cabe).html https://www.tommys.org/our-organisation/research-by-location/manchester-research-centre https://www.research.manchester.ac.uk/portal/en/researchers/lucy-higgins(0abcbc69-f2cf-4a50-876d-9d8c26daabce).html https://www.research.manchester.ac.uk/portal/michelle.desforges.html https://www.research.manchester.ac.uk/portal/jenny.myers.html
Project Title	Defining placental dysfunction by angiogenic marker status: what is the relationship between angiogenic markers and underlying placental pathophysiology?
Project outline	**Background:** Placental dysfunction often underlies the pregnancy complications fetal growth restriction, preeclampsia and stillbirth. In some cases there are abnormal maternal plasma concentrations of hormones produced by the placenta, including low placental growth factor (PlGF) and high soluble fms-like tyrosine kinase-1 (sFlt-1). This hormone imbalance is evident prior to the clinical onset of disease but the underlying regulatory mechanisms are largely unknown. Our preliminary data suggests there may not be a direct relationship between placental tissue PlGF production and maternal plasma PlGF concentration. We hypothesise that PlGF secretion, rather than production, is altered in placental dysfunction and that excessive unfolded protein response (UPR) activation is involved. **This project aims to** interrogate further the relationship between placental PlGF content and maternal plasma PlGF concentration, and explore the role of the UPR in determining plasma PlGF concentrations. **The main objectives** are to describe the relationship between: 1) Placental PlGF and maternal plasma PlGF and sFlt-1 concentrations 2) Placental UPR activation and maternal plasma PlGF and sFlt-1 concentrations 3) Placental PlGF content and UPR activation. **Methods:** • Immunohistochemistry to detect PlGF and markers of the UPR in placental villous tissue (including image analysis) • Enzyme linked immunosorbent assay (PlGF and sFlt-1) • Statistical analysis **Supervision:** The student will be supervised in the laboratory until competent to work independently. Weekly progress meetings will be scheduled. In addition the supervisors operate an open-door policy.

	Expected outputs: This summer project contributes to a wider study, funded by Rosetrees Trust and Tommy's, aiming to understand the regulatory mechanisms underlying abnormal PlGF concentrations in maternal plasma, and how this relates to aspects of placental dysfunction. The work arising from this summer project is expected to be presented in manuscript format as one part of the wider study, with the student as a co-author, appropriate to the level of their contribution.

Supervisor Details	**Dr Matthew Sperrin** **Enquiries:** Matthew.sperrin@manchester.ac.uk 67629
Project Title	Handling uncertainty correctly in risk prediction
Project outline	Clinical prediction models (CPMs) take what we know about a person and predict the probability of subsequent outcomes using a regression model or machine learning algorithm. They are widely used in early detection of disease (e.g. planning screening for cancer), as well as prevention (e.g. prescribing statins for people at risk of cardiovascular disease). CPMs are often based on regression models, but the probability of outcome is usually calculated based on the point estimate of the coefficients in the regression model, and ignores the uncertainty around these point estimates. This may lead to probabilities reflecting over-confidence in our knowledge of whether or not a person is likely to develop a disease. The aim of this project is to explore, mathematically and statistically, 1) how the variance in coefficient estimates should be propagated through to the predicted probability, 2) the implications of this in terms of the final probability quoted. Practically, the project will involve 1) learning new statistical methods such as generalised linear models and Bayesian statistics; 2) some mathematical work in deriving estimates of variance, 3) computational work: simulating by sampling from the sampling distributions of parameters, using a statistical package such as R; and 3) presentation work: writing up the results and providing effective visualisations to ensure they are understood. There is potential for the work to be written up as a paper for publication. The project would suit an undergraduate undertaking a mathematics degree (or closely related subject).

Supervisor Details	**Dr Michael Harte** **Enquiries:** Michael.harte@manchester.ac.uk 52328 https://pure.manchester.ac.uk/admin/workspace/personal/overview/
Project Title	Investigating markers of inflammation in Alzheimer's disease post-mortem tissue.
Project outline	**Background:** Current treatments for Alzheimer's disease (AD) are symptomatic and do little to slow down the progression of the disease. This has led to an array of research investigating hallmark pathologies in the search for novel therapeutic strategies. One such process is

	neuroinflammation – a chronic form of which is seen in AD. Microglia, the resident brain immune cell, fulfils a number of key roles in the brain including maintaining homeostasis, phagocytosis, synaptic pruning and they are key players in the immune response. Evidence is emerging from in vitro and in vivo preclinical animal models for a role of inflammation in the progression of the disease. **Aim:** In the current project we will investigate this further in human post-mortem brain tissue from controls and individuals with mild and severe Alzheimer pathology. **Techniques:** Tissue (both frozen blocks and sections) will be prepared for protein analysis. Tissue blocks will be used to analyse proteins of interest using state of the art Wes Protein Simple technology. Tissue will be homogenised, total protein determined and different antibodies optimised for protein analysis using Wes. Complimentary studies will be carried out using immunohistochemistry and cellular imaging on sections to assess the changing role of microglia in disease progression.

Supervisor Details	**Prof Paul Popelier (MIB)** **Enquiries:** pla@manchester.ac.uk 64511 http://www.qct.manchester.ac.uk/
Project Title	Rigorous atomistic modelling of peptide structure
Project outline	**Background:** Understanding the detailed behaviour of 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 :** 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 we are working on. Our 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) altogether. 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. The student will help testing the in-house software called ICHOR (written in Python) on peptide-capped amino acids. Small molecules need to be properly understood first, before one can aim for the ambitious goal of handling a polypeptide with FFLUX. The project straddles machine learning (which is very much in demand currently) and

	quantum chemistry, which ultimately governs the behaviour of all biomaterials. ter.

Supervisor Details	**Dr Stephen Fowler** **Enquiries:** Stephen.Fowler@manchester.ac.uk clare.mills@manchester.ac.uk waqar.ahmed@manchester.ac.uk timothy.felton@manchester.ac.uk 0161 291 5864 http://mancbreathgroup.net/
Project Title	Development of a screening method to differentiate Carbapenemase-producing Enterobacteriaceae cultures using volatile metabolites
Project outline	Nosocomial infections caused by Enterobacteriaceae are a major concern to healthcare workers. Clinically important species include Escherichia coli, Klebsiella pneumoniae, and Enterobacter cloacae, all of which are prevalent in nosocomial respiratory infections such as ventilator-associated pneumonia (VAP). The spread of drug resistant species (e.g. for Extended Spectrum Beta Lactamase-producing Enterobacteriaceae) is usually circumvented with combination therapy consisting of a beta-lactam antibiotic and a beta-lactamase inhibitor. However, Enterobacteriaceae are becoming resistant to carbapenems, often said to be the 'last resort' class of antibiotics. Volatile organic compounds (VOCs) are small molecules, extensively studied in the environmental sciences. However VOCs are also a product of by bacterial metabolism, and therefore can potentially be used for molecular phenotyping. There are currently three classes of carbapenem-resistance enzymes known (Class A carbapenemases, Class B Metallo-β-lactamases, and Class D OXA carbapenemases), which are further divided into several subgroups dependant on the microorganism. The aim of this project will be to describe a core set of VOCs emitted by drug-resistant and drug-sensitive Enterobacteriaceae. VOCs emitted from pure cultures will be sampled and analysed using thermal desorption-gas chromatography-mass spectrometry to produce volatile metabolite profiles. These profiles will used to classify Enterobacteriaceae species and type of carbapenemase produced using untargeted multivariate analysis. Information gained from this project may potentially be used in the development of exhaled breath sensors integrated into mechanical ventilators for rapid screening of drug resistant infection to guide personalised dosing and selection of antimicrobials.