Research Experience Placements 2021/22

Supervisor	Project Title (further details below)
Professor Jamie Kirkham	Understanding core outcome set development methods for rare diseases
Dr Riina Richardson	Aspergillus fumigatus immunoglobulin levels in Covid-19 patients with putative covid-associated pulmonary aspergillosis
Dr Lisa Miles	The role of online virtual support groups in the NHS Diabetes Prevention Programme
Professor Michael Brockhurst	Understanding the role for hypermutators in the emergence of antimicrobial resistance in Pseudomonas aeruginosa human airway infection
Dr Laoise Renwick	Co-developing a manualised adapted family intervention for people with schizophrenia in Indonesia; adapting and refining an existing evidence-based intervention
Dr Samuel Couth	Potential benefits of previous noise exposure for preventing noise-induced hearing damage
Professor Holly Shiels	Using imaging to probe the heart of the Greenland Shark
Dr Karen Lander	Understanding the facial 'mask' of Parkinson's
Dr Andrew Gilmore	Understanding early events in breast cancer initiation using ex vivo models

Supervisor Details	Professor Jamie Kirkham Enquiries: jamie.kirkham@manchester.ac.uk 0161 275 1135 **https://www.research.manchester.ac.uk/portal/jamie.kirkham.html**
Project Title	Understanding core outcome set development methods for rare diseases
Project outline	The aim of this project is to understand the methodological challenges and best practice for developing core outcome sets (COS) for rare diseases according to the minimum set of standards for COS development. The output of this project will feed into a dedicated theme on Rare Conditions focused on diagnostics, outcome measures and treatments which forms part of Manchester's Biomedical Research Centre programme. This will be a systematic review supported by supervisors with both a methodological background in outcomes based research and a clinician with experience in rare diseases.

	COS of rare diseases will be identified from the COMET (Core Outcome Measures in Effectiveness Trials) database against the inventory of rare diseases listed on 'Orphanet', a portal for rare diseases and orphan drugs. For each eligible COS identified the student will seek to gain an understanding of the study methodologies by focusing data extraction from the included studies around a published set of minimum standards for COS development [1]. Where it is documented by the COS development authors, the student will extract the challenges and limitations associated with the approaches that they used and any implications on the generalisability of the final COS. The student will also extract the outcomes from the COS studies and classify each of them according to the core areas of health identified by an outcomes taxonomy for classifying medical outcomes [2]. **References:** 1) Kirkham JJ, Davis K, Altman DG, Blazeby JM, Clarke M, Tunis et al. Core Outcome Set STAnDards for Development: The COS-STAD Recommendations. PLoS Medicine 2017; 14(11): e1002447 2) Dodd S, Clarke M, Becker L, Mavergames C, Fish R et al. A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. Journal of Clinical Epidemiology 2018; 96:84-92

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Project Title	Aspergillus fumigatus immunoglobulin levels in Covid-19 patients with putative covid-associated pulmonary aspergillosis
Project outline	Severe acute respiratory syndrome caused SARS-CoV-2 (coronavirus disease, COVID-19) results in damage to the respiratory tract epithelium, facilitating invasion by environmental fungi (moulds). COVID-19 has revealed a group of patients who are vulnerable to severe invasive fungal infection. These include patients who have had an organ transplant, those having chemotherapy or antibody treatment for cancer, those with a severe lung condition, such as cystic fibrosis, severe asthma or severe COPD. Reports of COVID-19-associated pulmonary aspergillosis (CAPA) from around the world but principally in Europe have raised concerns about it worsening the disease course of COVID-19 and increasing mortality. Numerous reports, critiques and international guidelines have proposed that CAPA should be defined as possible, probable, or proven on the basis of conventional and enhanced diagnostic certainty. When reviewing cases of putative CAPA and its pathophysiology it is important to understand the distinction between *Aspergillus* colonization and infection. Fungal colonization is the presence of non-invasive, actively growing fungi in the respiratory airways. Fungal colonization does not necessarily involve direct host damage or disease. There is increasing understanding of the host-pathogen in the context of allergic bronchopulmonary aspergillosis, chronic pulmonary aspergillosis and aspergillus bronchitis). The challenges in classifying patients with CAPA include distinguishing between airway colonization and invasive infection, a

	reluctance to do diagnostic procedures that generate aerosols, restricted validation studies of Aspergillus biomarkers in clinical specimens, and few data on aspergillus test performance in patients with COVID-19. The kinetics of *Aspergillus* IgG and IgM in these patients may be able to distinguish between colonization and infection in these patients and contribute towards a definitive diagnosis. The Mycology Reference Centre has a large number of residual serum samples from patients with suspected Convid-19. Enzyme-linked immunosorbent assays and lateral flow devices designed to detect Specific IgG and IgM will be applied to these samples.

Supervisor Details	Dr Lisa Miles Enquiries: lisa.miles-2@manchester.ac.uk, 0161 3065435 https://www.research.manchester.ac.uk/portal/lisa.miles-2.html **https://www.arc-gm.nihr.ac.uk/projects/diploma-evaluation-national-nhs-diabetes-prevention-programme/** david.french@manchester.ac.uk
Project Title	The role of online virtual support groups in the NHS Diabetes Prevention Programme
Project outline	The NHS Diabetes Prevention Programme (NHS-DPP) is a behavioural intervention for adults in England at risk of developing Type 2 diabetes. The programme is designed to support participants change their dietary and physical activity behaviours across nine months, so they can avoid progressing to Type 2 diabetes. The NHS-DPP is the largest diabetes prevention programme globally to achieve universal national coverage. The University of Manchester is conducting an evaluation of the NHS-DPP, to provide ongoing, independent feedback to NHS England on the success of the roll-out, and to explore the variability in delivery across different formats and how this might impact on effectiveness. This project focuses on the digital version of the NHS-DPP, which involves delivery of the programme across a range of routes including an app, support from a Health Coach, moderated online virtual support groups (group chat function) and e-learning material. Four providers deliver the digital version of the programme. Forty-five participants in the digital programme have been interviewed to understand their experiences of and engagement with the programme. Each participant was interviewed twice and interviews lasted 30-60 minutes. This project aims to analyse this interview data to explore the role of virtual support groups as a route to support participants change their behaviours. The student will analyse the content of this data to answer the following questions and write a report of the key findings: 1. How do participants engage with the virtual support groups available within the NHS-DPP? 2. How do Health Coaches offer support to participants through virtual support groups? 3. How do participants offer each other support through virtual support groups? The student will be provided with further detail of the NHS-DPP and its digital delivery including relevant features of the apps. Training will be provided in how to analyse interview data using Nvivo software.

Supervisor Details	Professor Michael Brockhurst Enquiries: michael.brockhurst@manchester.ac.uk https://www.research.manchester.ac.uk/portal/michael.brockhurst.html beth.grimsey@manchester.ac.uk
Project Title	Understanding the role for hypermutators in the emergence of antimicrobial resistance in Pseudomonas aeruginosa human airway infection
Project outline	Hypermutators (bacteria with elevated mutation rates) are common in chronic bacterial infections where they can accelerate the emergence of multidrug resistance (MDR). For example, ~20% of *Pseudomonas aeruginosa* isolates recovered from cystic fibrosis patients have elevated mutation rates. The hypermutable phenotype is often caused by deficiencies in MutS that increase the mutation rate by ~1,000 fold thus increasing the supply of resistance mutations. Reduced efficiency of MutS can be caused by mutations in the *mutS* gene itself, or by decreased expression of *mutS* resulting from overexpression of efflux pump genes, which is a common adaptation to antibiotic exposure. This studentship builds upon an on-going Wellcome Trust-funded project: ORBIT-3 was a phase 3 clinical trial in which patients with bronchiectasis, who were chronically infected with *P. aeruginosa*, were treated with inhaled ciprofloxacin. However, in ~40% of patients resistance to ciprofloxacin emerged. This project aims to answer the following question: does hypermutability influence the ability of *P. aeruginosa* to evolve high-level MDR? To answer this, you will test the following hypotheses: 1. Infecting *P. aeruginosa* populations that possess an intrinsic hypermutator phenotype are genetically predisposed to evolve MDR. 2. *P. aeruginosa* can acquire a hypermutable phenotype through the mutation of efflux pump regulator genes To do this you will: 1. Perform evolutionary assays to select for ciprofloxacin resistance 2. Calculate the mutation rates/frequencies of *P. aeruginosa* isolates that evolved ciprofloxacin resistance and compare them to that of isolates which remained susceptible. 3. Determine whether different mechanisms of ciprofloxacin resistance influence mutation rate. 4. Analyse whole genome sequencing data to find a link between the mechanism of ciprofloxacin resistance, hypermutability and the acquisition of compensatory mutations. The skills you will learn include bacteriology and culturing techniques, evolution assays, calculations of mutation rate, interpretation of whole genome sequences and molecular biology techniques including PCR.

Supervisor Details	Dr Laoise Renwick Enquiries: Laoise.renwick@manchester.ac.uk 0161 3067833 https://www.research.manchester.ac.uk/portal/en/researchers/laoise-renwick(d48add69-bc0f-48bc-b09d-82fc782e4b17).html
Project Title	Co-developing a manualised adapted family intervention for people with schizophrenia in Indonesia; adapting and refining an existing evidence-based intervention
Project outline	A discrete project within an existing MRC Joint Global Health Trials Initiative funded project that aims to culturally adapt and refine an evidence- based, family intervention for relatives and carers of people with schizophrenia in Indonesia using the Medical Research Council framework for complex interventions. This is a three phase study combining stakeholder consultation and consensus workshops to produce a manual to guide intervention implementation in the first two phases. Phase 3 comprises assessing the feasibility and acceptability of conducting a randomised, single-blind trial comparing the intervention to standard care for its effect on relapse rates. Project Details Phase 1 (0-6 months) comprises a series of up to 4 stakeholder consultation groups to explore attitudes and beliefs about the support needs of families, experiences of accessing services, priorities for treatment delivery, preferences for content and their views on what training should provide. Phase 2 comprises consensus workshops with structured synthesis of findings from phase 1 and 2 to co-produce a manual to support intervention delivery and resources to support sustainable training methods. Recruitment is being conducted primarily by researchers in Indonesia with support from the team based at Universitas Indonesia and University of Manchester. Objectives of Student Project The student will assist with synthesis of findings from the first two phases to develop the manual comprising the intervention protocol and training resources to support training healthcare professionals. The student will assist with data synthesis using an existing heuristic model for intervention adaptation (will involve liaising with Indonesian researchers and wider study team to collate information in English, record and guide synthesis decisions by the study team, compile synthesized data in a manual and coordinate translation and back-translation). Student will also collate data on training requirements and resources identified in stakeholder workshops, incorporate in the manual and facilitate pilot testing.

Supervisor Details	Dr Samuel Couth Enquiries: Samuel.couth@manchester.ac.uk 0161 275 6924 https://www.research.manchester.ac.uk/portal/samuel.couth.html https://sites.manchester.ac.uk/mancad/ https://www.research.manchester.ac.uk/portal/en/projects/understanding-the-consequences-of-recreational-noise-exposure(9e4a107d-c79d-4d06-b62f-921c5e1875ba).html
Project Title	Potential benefits of previous noise exposure for preventing noise-induced hearing damage
Project outline	Regular exposure to high levels of noise can lead to hearing loss and tinnitus (i.e. a ringing or buzzing in the ears). However, there is also some evidence from animal studies to suggest that low-to-medium levels of noise exposure may help to "toughen-up" the ears so that they are less susceptible to damage from subsequent high levels of noise exposure. This could explain some of the variability in individuals' susceptibility to noise-induced hearing problems, where previous noise exposure may serve to have a protective effect. Across a range of different experiments in our lab, we have used the Noise Exposure Structured Interview (NESI) to gain estimates of lifetime noise exposure for 100s of participants. These studies consistently show large between-subject variability in terms of levels of noise exposure and effects on hearing. However, these studies have only considered noise exposure in terms of total lifetime "dose", but have never considered how the type or pattern of noisy activities, such as regular use of personal listening devices, could account for individual differences in hearing. In this project, we will reanalyse the NESI data from our previous experiments to better understand how the level, frequency, and duration of noisy activities may account for hearing function (including sensitive behavioural and electrophysiological measures). **The project will test the hypothesis that frequent exposure to moderate level sounds is protective to the human ear, reducing the risk of noise damage.** If confirmed, this will radically change the basis for all noise exposure regulations, which currently depend on the "equal energy" rule (essentially, all exposure is damaging). Under the guidance of the supervisor and working alongside the extended research team, the student will acquire substantial knowledge of the literature, gain valuable statistical analysis skills, and will make a significant contribution to an unexplored area of research.

Supervisor Details	Professor Holly Shiels Enquiries: Holly.shiels@manchester.ac.uk 0161-275-5092 https://www.research.manchester.ac.uk/portal/holly.shiels.html
Project Title	Using imaging to probe the heart of the Greenland Shark
Project outline	The life span of the Greenland shark is at least 272 years and may be as long as 500 years making this animal the longest living vertebrate on the planet[1]. It was one of the lesser-known species of sharks up until 2016 when its extreme longevity was revealed. The finding that they live in the deep, dark Arctic waters for hundreds of years has captured the imagination of the world and the attention of scientists. How does an animal born in Shakespeare's time still patrol the deep sea today? This extreme longevity is particularly interesting with respect to the heart, because heart disease is synonymous with aging in humans[2]. This project will use serial scanning 3D scanning electron micrograph image analysis to explore nuclear morphology in the heart of the Greenland shark and compare it with those from mammalian models of age. The student will learn about electron microscopy and machine learning image analyses. **References:** 1. Nielsen J, Hedeholm RB, Heinemeier J, Bushnell PG, Christiansen JS, Olsen J, Ramsey CB, Brill RW, Simon M, Steffensen KF, Steffensen JF. Eye lens radiocarbon reveals centuries of longevity in the Greenland shark (Somniosus microcephalus). Science. 2016 Aug 12;353(6300):702-4. 2. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013 Jun 6;153(6):1194-217.

Supervisor Details	Dr Karen Lander Enquiries: Karen.lander@manchester.ac.uk https://www.research.manchester.ac.uk/portal/en/researchers/karen-lander(30ccc015-81c4-42ba-9406-7eb76f8aa923).html
Project Title	Understanding the facial 'mask' of Parkinson's
Project outline	Parkinson's Disease (PD) is a neurology disease causing loss of control of muscles. The facial 'mask' of Parkinson's can lead to miscommunication. The healthy person sees an unresponsive face and concludes the patient is perhaps uncomprehending or not engaging in the conversation. Facial movements on PD are normally assessed based on static evaluation and self – or clinician evaluation of their expressed facial emotion. The aim of this project is to learn more about how widespread these problems with facial expression are amongst people with Parkinson's and how they affect their social relationships with others. In the proposed project we will create a questionnaire for people with Parkinson's to report their difficulties with facial expression. Specifically, we will ask them to record if and how they feel their facial expressions have changed with their disease progression. We will also ask them to report communication difficulties and miscommunication with those around them because of any expression difficulties. We will recruit Parkinson's patients by advertising via local Parkinson's UK groups and via Parkinson's UK research support network. The following background information will be obtained from the Parkinson's patients: motor function using the Revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz, et al., 2008), quality of life using

	the PDQ-39 (Jenkinson et al., 1997), current medication and disease history. We will exclude all participants with neurological problems (aside from PD), dementia (using Addenbrookes; Mioshi et al., 2006), perceptual problems and severe depression (using the Geriatric Depression Scale; Sheikh & Yesavage, 1986). They will also complete the Toronto Alexithymia Scale (TAS-20), which is a measure of deficiency in understanding, processing or describing emotions (Bagby, Parker & Taylor, 1994) and a measure of empathy (Davis, 1983). We will look at the relationship between reported facial expression difficulties and other measures of motor function, alexithymia and empathy.

Supervisor Details	Dr Andrew Gilmore Enquiries: Andrew.gilmore@manchester.ac.uk **https://www.wellcome-matrix.org/** **http://www.breastcentre.manchester.ac.uk/**
Project Title	Understanding early events in breast cancer initiation using ex vivo models
Project outline	Breast cancer (BC) is the second biggest cause of female cancer-related death in the UK, with around 55,000 cases and 11,500 deaths annually. Although 90% of BC cases are sporadic, we still know very little about how it is initiated, which limits the development of preventative treatments and biomarkers for early detection. There are key questions about the cellular changes associated with BC initiation, and how they promote oncogenic mutations. Understanding this will help to identify novel biomarkers for early detection of cancers and new targets for preventative treatments. One of the largest risk factors for BC is high mammographic density (MD). Regions of breast tissue with high MD occur where the extracellular matrix (ECM) is mechanically stiffer, in part due to changes in collagen organisation. All tissues have a distinct composition of ECM which defines its mechanical and chemical characteristics. The mechanical properties not only provide physical support to the tissue, but also coordinate cell function through mechanosignalling, where cells sense the stiffness of the ECM through adhesion receptors such as integrins. Changes in the properties of the ECM can drive alterations to cell phenotype and are associated with many diseases, including cancer. Several recent studies have shown that mechanosignalling remodels cell metabolism. As by-products of normal mitochondrial metabolism are an important source of genomic damage, any changes in mitochondrial function could lead to acquisition of oncogenic mutations. For this placement you will work in part or a larger project looking at how mechanosignalling in breast epithelial cells drives genomic damage. The aim is to determine if ECM stiffness alters mitochondrial function. You will grow epithelial cells on substrates of different stiffnesses and use markers of mitochondria to determine how this alters their function and morphology. The data will be analysed by fluorescent microscopy. Methods to be used: Cell culture, fluorescence microscopy, image analysis.