

## MRC Research Experience Placements Summer 2023

Supervisor	Project Title (further details below)
Professor Katherine Berry	Assessing adherence to the fidelity of the TULIPS intervention.
Professor Michael Brockhurst	How does antibiotic therapy impact the evolution of within-host adaptation and virulence in <i>Pseudomonas aeruginosa</i> bronchiectasis lung infections?
Dr Antje Heinrich	Measuring cognitive contributions to different speech-in-noise tests
Dr Andrew Higham	Detecting early chronic obstructive pulmonary disease: a histopathology study to identify small airway remodelling as a prelude to lung function decline
Professor Sue Kimber, Steven Woods, Nicola Bates	Hormone induced cell signalling through cAMP in chondroprogenitors
Professor Holly Shiels	Using imaging to probe the heart of the greenland shark.
Dr Michael A Stone	Extending the clinical usability of a set of acoustic signals developed for paediatric audiology
Dr Talveen Purba, Dr Matthew Harries	Testing novel agents to mitigate aberrant epithelial mesenchymal transition in a human model of scarring alopecia
Dr Fong Kuan Wong	Conversations with friends: Unravelling the role of intercellular cortical cell communication in interneuron maturation

<b>Supervisor Details</b>	Professor Katherine Berry Enquiries: <a href="mailto:Katherine.berry@manchester.ac.uk">Katherine.berry@manchester.ac.uk</a> <a href="#">Prof Katherine Berry BSc, MSc, Clin.Psy.D, PhD - Publications   The University of Manchester</a>
<b>Project Title</b>	Assessing adherence to the fidelity of the TULIPS intervention.
<b>Project outline</b>	The placement student will work alongside Professor Katherine Berry and colleagues at the University of Manchester on a research project to explore the benefits of a newly developed inpatient psychology service on acute mental health wards. The project is part of a programme of research funded by the National Institute for Health Research. Further details of the project can be found at <a href="https://sites.manchester.ac.uk/tulips/">https://sites.manchester.ac.uk/tulips/</a> <i>Specific Project Information: The project will use data from an RCT across 34 wards in England comparing psychological input on acute wards to treatment as usual. The trainee will have access to a large dataset from the trial and will be involved in assessing</i>

*fidelity to the intervention. This will involve assessing adherence to aspects of the psychological service model using diaries/questionnaires/audio recorded therapy session completed by trial psychologists.*

<b>Supervisor Details</b>	Professor Michael Brockhurst Enquiries: michael.brockhurst@manchester.ac.uk 0161 275 5755 <a href="https://sites.manchester.ac.uk/merman/">https://sites.manchester.ac.uk/merman/</a> <a href="https://www.research.manchester.ac.uk/portal/michael.brockhurst.html">https://www.research.manchester.ac.uk/portal/michael.brockhurst.html</a>
<b>Project Title</b>	How does antibiotic therapy impact the evolution of within-host adaptation and virulence in <i>Pseudomonas aeruginosa</i> bronchiectasis lung infections?
<b>Project outline</b>	<p>Non-CF bronchiectasis (NCFB) is a chronic lung disease similar to, yet distinct from, cystic fibrosis (CF). Prevalence is rising globally, amid concerns of a future NCFB epidemic fuelled by widespread lung damage from COVID-19 infection. NCFB features recurrent bacterial lung infections - particularly by <i>Pseudomonas aeruginosa</i> - associated with poorer prognosis necessitating prolonged antibiotic treatment. <i>P. aeruginosa</i> infections display characteristic adaptations to the CF lung promoting persistence and driving chronicity. Whether similar evolutionary processes underlie chronic infection in NCFB, and what impact prolonged antimicrobial therapy has on within-host adaptation is unclear. We hypothesise that by reducing bacterial genetic variation, antibiotic treatment may impede or delay emergence of host-adapted genotypes for virulence and persistence.</p> <p>This studentship enhances an on-going Wellcome Trust Collaborative Award project studying within-patient evolution of antimicrobial resistance in chronic <i>P. aeruginosa</i> NCFB infections during a clinical trial of inhaled ciprofloxacin therapy. High-throughput phenotyping of our isolate collection will test how the evolution of virulence and persistence traits is affected by antibiotic treatment.</p> <p>The project aims to answer the question: <b>How does antimicrobial therapy impact the evolutionary processes driving within-host adaptation in <i>P. aeruginosa</i> infections of NCFB patients?</b></p> <p>The objectives are:</p> <ol style="list-style-type: none"> <li>1. To test how the evolution of key bacterial traits (biofilm/motility/secreted molecules) varies between treatment and placebo patient infections.</li> <li>2. Whether evolved changes in these traits lead to altered virulence in an in-vivo infection model.</li> </ol> <p>You will run high-throughput screening of clinical isolates from treatment and placebo patients using a range of microbiological assays, identifying isolates with virulence-related changes from these assays to test in a <i>Galleria mellonella</i> larvae infection model.</p>

	You will gain skills in microbial culturing, high-throughput assaying of bacterial virulence traits, data interpretation and statistical analysis, and investigation of pre-existing DNA sequencing data to identify mutations associated with reduced virulence.
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<b>Supervisor Details</b>	Dr Antje Heinrich Enquiries: <a href="mailto:antje.heinrich@manchester.ac.uk">antje.heinrich@manchester.ac.uk</a> 0161-275 7986 <a href="https://www.research.manchester.ac.uk/portal/antje.heinrich.html">https://www.research.manchester.ac.uk/portal/antje.heinrich.html</a>
<b>Project Title</b>	Measuring cognitive contributions to different speech-in-noise tests
<b>Project outline</b>	<p>Effective communication is crucial for participation in everyday life, and a good quality of life. Listening to speech is difficult, particularly in a noisy environment. While hearing loss can play a role, many listeners have difficulties even when their hearing is normal or after their hearing loss has been treated. This suggests that processes other than hearing must be important. One such process is cognition. The most commonly used test to assess cognitive ability in connection with speech-in-noise perception is the Reading Span Test (RST)<sup>1,2</sup>. This test measures a person's ability to simultaneously store and manipulate information, a skill considered crucial in the context of listening. The RST exists in many variations. Normally, these variants are treated as equivalent and interchangeable. However, in previous instalments of this summer placements, we have shown that this assumption is false. The next step now is to test whether different versions of the RST are particularly appropriate to predict speech-in-noise perception in different listening situations. For instance, should one version of the RST be used to predict perception of single words in white noise and another version to predict perception of continuous speech in a restaurant setting? You will run an experiment with several versions of the RST and different speech-in-noise tests, and examine the question whether a particular RST is particularly suited to predict performance on a particular speech-in-noise test. In the future we hope to advice clinical practitioners on which RST they should employ when diagnosing and counselling patients with speech-in-noise listening difficulties in specific listening situations.</p> <p>Key aims and objectives:</p> <ol style="list-style-type: none"> <li>(1) Learn about the role of cognition for speech-in-noise perception</li> <li>(2) Develop skills in recruitment and experimental testing</li> <li>(3) Learn about the appropriate statistical tests to appraise the research question</li> <li>(4) Interpret results</li> </ol> <p><sup>1</sup> Daneman, M., &amp; Carpenter, P. A. (1980). Individual differences in working memory and reading. <i>Journal of Verbal Learning and Verbal Behavior</i>, 19(4), 450-466.</p>

	<sup>2</sup> Rönnberg, J., Arlinger, S., Lyxell, B., & Kinnefors, C (1989). Visual evoked potentials: Relation to adult speechreading and cognitive function. Journal of Speech and Hearing Research. 32, 725-735.
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<b>Supervisor Details</b>	Dr Andrew Higham Enquiries: <a href="mailto:Andrew.Higham@manchester.ac.uk">Andrew.Higham@manchester.ac.uk</a> 0161 291 5964
<b>Project Title</b>	Detecting early chronic obstructive pulmonary disease: a histopathology study to identify small airway remodelling as a prelude to lung function decline
<b>Project outline</b>	<p>Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide and is characterised by progressive and irreversible airflow limitation. The biggest risk factor for COPD is cigarette smoking which causes airway inflammation and tissue destruction. This leads to small airway disease and emphysema (parenchymal destruction).</p> <p>The small airways (&lt; 2mm in diameter) have been identified as the primary site of airflow obstruction in COPD. However, small airway remodelling can occur in the absence of spirometrically confirmed disease and this makes the small airways an area of interest when attempting to identify individuals with early or 'pre' disease. Capturing this information may help identify the cellular and molecular processes driving pathobiology during the early stages of disease and enable target identification for early intervention to slow disease progression. So far, a histopathology study has not been conducted to investigate early COPD.</p> <p>The aim of this study is to quantify early changes to the small airways and lung parenchyma in young smokers (&lt;50 years) with non-obstructed lung function (forced expiratory volume in 1 second (FEV<sub>1</sub>) / forced vital capacity (FVC) ratio &gt;0.7), who may be susceptible to COPD (&lt;80% FEV<sub>1</sub> % predicted). We will use archived resected lung tissue and measure small airway remodelling; airway wall thickness, luminal narrowing and luminal mucous plugging. We will also measure parenchymal destruction, (alveolar space size and supporting alveolar attachments per small airway).</p> <p>The candidate will learn key laboratory skills in the discipline of lung histopathology, including haematoxylin and eosin staining of human lung tissue, light microscopy, identification of microscopic lung architecture, image acquisition and analysis, and data handling with statistical analysis.</p>

	The objectives of the study are achievable in the time given. However, as a contingency, the student will have access to archived images of lung tissue to ensure they maximise their opportunity for data collection and analysis.
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<b>Supervisor Details</b>	Prof Sue Kimber, Steven Woods, Nicola Bates Enquiries: sue.kimber@manchester.ac.uk 0161 275 6773 <a href="https://www.research.manchester.ac.uk/portal/en/researchers/susan-kimber(3f720ebe-4a24-4eb8-926c-30402b47bc92).html">https://www.research.manchester.ac.uk/portal/en/researchers/susan-kimber(3f720ebe-4a24-4eb8-926c-30402b47bc92).html</a>
<b>Project Title</b>	Hormone induced cell signalling through cAMP in chondroprogenitors
<b>Project outline</b>	<p>This project will complement work in our MRC grant to understand the molecular pathology behind the skeletal disease Acrodysostosis. Acrodysostosis is a heterozygous gain of function genetic condition which causes short stature due to deficit in cAMP signalling and hormone insensitivity.</p> <p><b>Aim</b> To evaluate the time course of hormonal signalling in chondrogenic cell lines and induced pluripotent stem cell -derived induced mesenchymal stromal cells( iMSCs) which can differentiate to chondrocytes. This will contribute to our understanding of these signaling pathways and how they effect chondrogenesis in Acrodysostosis involving hormone insensitivity and deficit in cAMP signalling.</p> <p><b>Obj 1:</b> learn how to grow TC28a2 and iMSCs and learn immunofluorescence staining, design time course experiments and carry out immunofluorescence for chosen hormone receptors ( see obj 2) ( wks1-2).</p> <p><b>Obj2</b> Learn how to use plate reader. Carryout time course assay with one of several hormones (epinephrine, TSH or PTHrP). [The precise hormone will depend on lab data by July] (wks 3-5). This will be carried out in triplicate on the most suitable cell type determine by lab data and confirmed by the receptor immuno in Obj1 (and fitting the students level of competence). Evaluation of end point cells by RT-QPCR.</p> <p><b>Obj 3</b> Analyse data and generate graphs and ppt slides for presentation.(wk6)</p>

<b>Supervisor Details</b>	Professor Holly Shiels Enquiries: Holly.shiels@manchester.ac.uk 0161 275 5092 <a href="https://www.research.manchester.ac.uk/portal/holly.shiels.html">https://www.research.manchester.ac.uk/portal/holly.shiels.html</a>
<b>Project Title</b>	Using imaging to probe the heart of the greenland shark..
<b>Project outline</b>	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 <sup>1</sup> . 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

	<p>longevity is particularly interesting with respect to the heart, because heart disease is synonymous with aging in humans<sup>2</sup>. 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.</p> <p>[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 (<i>Somniosus microcephalus</i>). <i>Science</i>. 2016 Aug 12;353(6300):702-4.</p> <p>[2] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. <i>Cell</i>. 2013 Jun 6;153(6):1194-217.</p>
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<p><b>Supervisor Details</b></p>	<p>Dr Michael A Stone  Enquiries: Michael.stone@manchester.ac.uk  0161 275 8563  <b>Group site</b> :<a href="https://www.research.manchester.ac.uk/portal/en/projects/manchester-centre-for-audiology-and-deafness-mancad(90f5d28b-08c9-4c76-891b-9340c290529f).html">https://www.research.manchester.ac.uk/portal/en/projects/manchester-centre-for-audiology-and-deafness-mancad(90f5d28b-08c9-4c76-891b-9340c290529f).html</a></p> <p><b>Supervisors' personal pages : Michael Stone :</b>  <a href="https://www.research.manchester.ac.uk/portal/michael.stone.html">https://www.research.manchester.ac.uk/portal/michael.stone.html</a></p> <p><b>Anisa Visram :</b> <a href="https://www.research.manchester.ac.uk/portal/anisa.visram.html">https://www.research.manchester.ac.uk/portal/anisa.visram.html</a></p>
<p><b>Project Title</b></p>	<p>Extending the clinical usability of a set of acoustic signals developed for paediatric audiology</p>
<p><b>Project outline</b></p>	<p>The Manchester Centre for Audiology and Deafness (ManCAD) has developed a set of four acoustic test signals for assessing hearing status in difficult-to-test populations [1]. They were originally developed to test that hearing aids had been successfully fitted to very young deaf babies.</p> <p>These signals are now available on clinical audiology equipment for use in the original and very specific test conditions. In order to widen their usability, we need to determine the sensitivity of human hearing to these signals when measured using headphones routinely found on audiology equipment.</p> <p>The sensitivity measure, the Reference Equivalent Threshold Sound Pressure Level (RETSPL), is obtained by following an international standard, ISO 389-9 (2009). It requires recruiting and testing of 25 young adults with no known previous hearing problems. For each of the four signals, presented over different headphones, and with varying durations, we record the sound level of the quietest sound that can just be heard, the individual's RETSPL. We need to find the population-average RETSPL for each condition. The testing of each participant takes place over about 2 hours, with frequent opportunity for rests.</p>

	<p>The project requires attention to detail, numeracy, consistency and accuracy in experimental method, polite interactions during participant recruitment and testing, appreciation of acoustics, and use of simple statistics. Apart from the degree requirements listed below, the likely candidate should have good people skills. If the project output is of sufficient quality, it will be submitted for publication for international reference.</p> <p>[1] Stone M.A., Visram A., Harte J.M., Munro K.J. (2019) <i>A set of time-and-frequency-localised short-duration speech-like stimuli for assessing hearing-aid performance via Cortical Auditory-Evoked Potentials. Trends Hear. 23.</i>  <a href="https://doi.org/10.1177/2331216519885568">https://doi.org/10.1177/2331216519885568</a></p>
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<b>Supervisor Details</b>	<p>Dr Talveen Purba, Dr Matthew Harries          Enquiries: talveen.purba@manchester.ac.uk          0161 275 5641</p>
<b>Project Title</b>	<p>Testing novel agents to mitigate aberrant epithelial mesenchymal transition in a human model of scarring alopecia</p>
<b>Project outline</b>	<p>Lichen planopilaris (LPP) is a scarring alopecia with limited treatment options that results from the permanent destruction of hair follicles and hair follicle epithelial stem cells (HFSCs). Furthermore, it has been shown that HFSCs undergo epithelial-mesenchymal transition in scarring alopecia. Modelling the pathogenesis of this condition, a human tissue model of scarring alopecia was developed here in Manchester whereby epithelial stem cells were induced to undergo EMT using a drug “cocktail” (Imanishi et al. 2018; J Invest Dermatol).</p> <p>As there are a lack of new treatments in the pipeline for this condition, there is an urgent need to test new novel candidate agents that could prevent EMT and mitigate the progression of LPP. Several candidate drugs that could be used to treat LPP have been recently identified. This includes the COX-2 inhibitors Apricoxib and Etodolac which have been shown to influence EMT and modulate the expression of EMT markers E-cadherin, Vimentin, Snail and Slug (Sanz, Lin &amp; Miteva, 2022; Clin Exp Derm).</p> <p>In this project, the student will test the effectiveness of COX-2 inhibitors within our human hair follicle <i>ex vivo</i> EMT model to determine whether EMT in HFSCs can be prevented. The student will achieve this by analysing the <i>in situ</i> protein expression of Vimentin and E-cadherin within Keratin 15+ HFSCs (Purba et al. 2019. EMBO Mol Med) using established immunofluorescence protocols routinely employed within our lab. Time permitting, the student will expand this analysis to examine other markers such as Snail and Slug in the hair follicle. This work will support our research aims to identify new candidate treatments that could be used to prevent scarring alopecia.</p>

<b>Supervisor Details</b>	Dr Fong Kuan Wong Enquiries: <a href="mailto:fongkuan.wong@manchester.ac.uk">fongkuan.wong@manchester.ac.uk</a> 0161-306-4105 <a href="https://www.fongkuanwonglab.com">https://www.fongkuanwonglab.com</a>
<b>Project Title</b>	Conversations with friends: Unravelling the role of intercellular cortical cell communication in interneuron maturation
<b>Project outline</b>	<p>Nature versus nurture – this has been a long-standing debate in determining how fate is determined during development. Extrapolating this debate to the cellular level, cortical cell fate has also been linked to its genetic (nature) and environmental (nurture) components. In the brain, there are two main types of neuronal subtypes – excitatory and inhibitory neurons. For the inhibitory neurons or interneurons, recent works have shown that genetics through the regulation of gene expression plays an important role during early neuronal development in specifying interneuron subclasses. The fine tuning of cell fate and the acquisition of their final mature properties, however requires cells to interact with its environment. It is through these interactions, that cells are able to learn the appropriate response to different stimulus. These intercellular interactions are not limited to the neuronal population but also include other glial cell types such as microglia, astrocytes and oligodendrocytes. It is currently unknown to what extent does interactions with these glial cells shape the maturation of interneuron during development. Therefore, <b>the main aim of this project is to understand how intercellular glial interactions modulate interneuron maturation in the developing mouse cerebral cortex.</b> To study this, we will examine the maturation of a specific interneuron subclass – the parvalbumin (PV) interneurons. PV interneurons are the most commonly found cortical interneurons and play an important role in controlling information flow in cortical circuits. PV interneuron dysfunctions have been linked to multiple neurodevelopmental disorders ranging from autism spectrum disorder to epilepsy. Consequently, understanding how these cells develop during normotypic development will provide us insights into how their dysregulation can contribute to neurodevelopmental disorders. To achieve this, we will use techniques such as immunofluorescence, viral transduction, pharmacological perturbations, transgenesis, neuroanatomy and confocal microscopy to investigate the role of intercellular glial communication in shaping interneuron development.</p>