UNIVERSITY of York

CID CATS

2015 entry Rotation Projects

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1. **Translating viral DNA nanomotors into biotech and biomed applications**
   Supervisor: Prof Fred Antson
   Term: Spring/Summer

2. **Using Single-Molecule Approaches to Probe Bacterial Mechanisms for Infection**
   Supervisors: Dr Christoph Baumann/Prof Jennifer Potts
   Term: Spring/Summer

3. **Probing the role of outer membrane micro-domains in antibody-mediated bacterial cell killing**
   Supervisors: Dr Christoph Baumann/Dr Mark Coles
   Term: Spring/Summer

4. **Computational methods for predictive bacteriotherapy design**
   Supervisors: Prof. Michael Brockhurst/Dr Leo Caves
   Term: Spring/Summer

5. **Modelling Lymph Node Architecture In Silico**
   Supervisors: Dr Mark Coles /Prof Jon Timmis
   Term: Spring/Summer

6. **New methods for the analysis and validation of 3D sugar-protein structures**
   Supervisor: Prof Gideon Davies
   Term: Spring/Summer

7. **ChemGlycoSEPSIS: Chemical glycobiology for the study and exploitation of Pseudaminic acid sugars in infectious diseases**
   Supervisors: Dr Martin Fascione/Prof Gideon Davies
   Term: Spring/Summer

8. **Targeting the thrombopoietin receptor to mediate haematopoietic stem cell maintenance and platelet production**
   Supervisors: Dr Ian Hitchcock/Prof Marek Brzozowski
   Term: Spring/Summer

9. **Scanning the bacterial replisome for druggable sites.**
   Supervisors: Prof Rod Hubbard/Prof Peter McGlynn
   Term: Spring/Summer

10. **An eco-immunology approach to understanding the transmission of leishmaniaisis.**
    Supervisors: Prof Paul Kaye/Dr Jon Pitchford
    Term: Spring/Summer

11. **IL-22 in cecal versus colonic inflammation**
    Supervisor: Dr Marika Kullberg
    Term: Spring/Summer

12. **Memory and Silence**
    Supervisors: Dr Dimitris Lagos/Prof Jon Timmis
    Term: Spring/Summer

13. **Measuring reactive oxygen species in cold plasmas for new antimicrobial therapies**
    Supervisors: Prof Deborah O'Connell/Dr Marjan Van Der Woude
    Term: Spring/Summer

14. **Revealing the secrets of repetitive bacterial proteins**
    Supervisor: Prof Jennifer Potts
    Term: Spring/Summer

15. **Barriers to infection**
    Supervisors: Prof Jenny Southgate /Dr Steve Johnson
    Term: Spring/Summer

16. **Metabolic engineering of sialic acid super-consumers: an approach to reduce post-antibiotic expansion of enteric pathogens.**
    Supervisors: Dr Gavin Thomas/Dr Marika Kullberg
    Term: Summer

1. **Translating viral DNA nanomotors into biotech and biomed applications**
   Supervisor: Prof Fred Antson
   Term: Spring/Summer

   The majority of dsDNA viruses assemble by packaging their genome, inside the infected host cell, into an empty pre-formed capsid shell. DNA translocation is performed by a molecular motor, which translocates DNA with the speed of 100-2000 base pairs per second. Portal protein serves as a nucleation point for capsid assembly and as a docking site of the DNA motor.
   Project 1 will focus on engineering phage portal proteins for docking into molecular membranes, for subsequent translocation of DNA.
   Project 2 will investigate if segments of herpes virus portal proteins, that are essential for portal assembly and function, could serve as potent drug targets.

   Key References/Resources
   Casjens, S.R. (2011) The DNA-packaging nanomotor of tailed bacteriophages. Nat Rev Micro, 9, 647-657.

   Lebedev A, Krause MH, Isidro AL, Vagin A, Orlova EV, Turner J, Dodson EJ, Tavares P, Antson AA: Structural framework for DNA translocation via the viral portal protein. EMBO J, 2007, 26:1984-94.

   Skills Development
   Laboratory Skills and Methods, Data Analysis / Visualisation, Modelling / Simulation, Bioinformatics, X-ray structure determination using computational (crystallographic) approaches; Biophysics

2. Using Single-Molecule Approaches to Probe Bacterial Mechanisms for Infection
Supervisors: Dr Christoph Baumann/Prof Jennifer Potts
Term: Spring/Summer

Staphylococcal strains can form biofilms on inserted medical devices. Biofilm formation is promoted by bacterial surface proteins, e.g. S. aureus surface protein G (SasG). SasG contains a multidomain organisation of tandemly arrayed G5 domains interspersed with ~50 residue sequences (E regions). The Potts group has recently reported the structures and biophysical characterisation of single and multidomain fragments from SasG. In the Baumann lab, single-molecule high-resolution fluorescence imaging was used to characterise the end-to-end distance of a multidomain SasG fragment. By precise localisation of bright fluorophores covalently-coupled to cysteine residues engineered at the N- and C-terminae of SasG, its bending rigidity was inferred from the inter-fluorophore spacing measured for immobilised single protein molecules viewed by TIRF microscopy. This approach revealed SasG behaves like an extended, rigid nanorod. This project will build on this successful initial work by probing the effects of electrostatics and an intrinsically flexible hinge on the end-to-end distance distribution. The role of electrostatics will be probed by introducing charge neutralising/reversing mutations, while a hinge can be introduced by incorporating a glycine-rich linker sequence at a G5-E domain interface. Results obtained will improve our understanding of the chemical and physical basis of SasG rigidity.

Key References/Resources
Nature Commun. 6: 7271

Proc. Natl. Acad. Sci. USA 109: E1011-E1018.

Skills Development
Laboratory Skills and Methods, single-molecule fluorrescence microscopy

3. **Probing the role of outer membrane micro-domains in antibody-mediated bacterial cell killing**
Supervisors: Dr Christoph Baumann/Dr Mark Coles
Term: Spring / Summer

A major component of human immune responses to bacterial pathogens is complement mediated. Classical complement activation can occur through C1 binding to antibody-antigen complexes. The first stage involves C1 binding, which leads to auto-activation driving the classical complement pathway to macrophage engulfment, or membrane attack complex formation. It remains unknown why high-affinity IgGs do not activate C1 despite antigen presence in the pathogen's outer membrane. We discovered that Gram-negative bacteria possess outer membrane protein (OMP) islands with very restricted two-dimensional diffusion. Due to the very restricted OMP diffusion, the effectiveness of C1 association with the cell surface may be influenced by the relative antigen abundance in the OM, i.e. antibody spacing on surface relative to distance between C1-globular heads. The aims of this project are as follows: i) determine how the translational and rotational diffusion of bound IgG is influenced by abundance of OMP-associated antigens, and ii) understand whether antibody binding occurs preferentially at certain sites in the bacterial outer membrane. This project will use cutting-edge single-molecule fluorescence microscopy approaches, along with Monte Carlo simulations of 2D diffusion, to probe the dynamics of membrane-associated immunological processes on live bacterial cells.

Key References/Resources
Nature 523: 333-336

Trends Immunology 25: 368-373

Skills Development
Laboratory Skills and Methods, Modelling / Simulation, single-molecule fluorescence microscopy

4. **Computational methods for predictive bacteriotherapy design**
   Supervisors: Prof. Michael Brockhurst & Dr Leo Caves
   Term: Spring/Summer

   GOAL: Alternatives to small molecule drugs are urgently required due to high levels of resistance to antimicrobials in many pathogens and the lack of new antimicrobials in the development pipeline. A promising alternative to small molecules is to engineer the resident community of microbes inhabiting the body-site to outcompete, displace or resist invasion by the pathogen (bacteriotherapy). Trial and error empiric bacteriotherapies have been clinically successful (e.g. in C. difficile infection, see ref) but we lack a predictive framework for designing effective therapies. The project will develop and experimentally validate computational methods of predictive bacteriotherapy design.

   PROJECT: We will use an iterative loop of empirical data collection > model prediction from these data > empirical validation of model predictions. Experiments will focus on the common pathogen Pseudomonas aeruginosa that causes drug resistant chronic lung infections. Predictive modelling will use a range of approaches (e.g. network theory, Jacobians, permanence) to predict in silico the resistance to invasion by P. aeruginosa of all possible community structures, optimal assembly of higher-order (beyond pairwise) communities and therapeutic stability.

   OUTCOMES: Modelling approaches will reduce the reliance upon “trial and error” by clinicians, giving a modelling tool-kit to improve the efficiency of bacteriotherapy that could be applied to other chronic bacterial infections.

   Key References/Resources
   http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1002995
   http://www.esajournals.org/doi/abs/10.1890/14-1324.1

   Skills Development
   Laboratory Skills and Methods, Programming Skills, Data Analysis / Visualisation, Modelling / Simulation, Bioinformatics

5. **Modelling Lymph Node Architecture In Silico**
   Supervisor: Dr Mark Coles/Prof Jon Timmis
   Term: Spring / Summer

   Following immunization and infection, lymph nodes (LNs) undergo changes in architecture to facilitate robust adaptive immune responses. Specifically, we hypothesize that LN remodeling can perturb communication between B-cells and their environment. To address this research question we employ engineering, biophysical and immunology techniques.

   The aim of this project is to refine an existing computational model using established software engineering techniques. This project is suitable for a student with previous programming experience wishing to learn and apply object-oriented programming and software design principles in the development of simulations to explore biological systems, as well as gaining some exposure to mathematical and statistical techniques

   Learning outcomes: Object-oriented programming, multiscale modeling, model and test driven development of biological simulators, statistical analyses of simulators.

   Key References/Resources
   Cosgrove J, Butler J, Alden K, Read M, Kumar V, Cucurull-Sanchez L, Timmis J, Coles M, Agent-Based Modeling in Systems Pharmacology, CPT: Pharmacometrics & Systems Pharmacology, DOI: 10.1002/psp4.12018, 2015

   Alden k, Timmis j, Andrews PS, Veiga-Fernandes H, Coles M, Pairing experimentation and computational modelling to understand the role of tissue inducer cells in the development of lymphoid organs. Frontiers in Immunology. Vol 3. DOI:10.3389/fimmu.2012.00172, 2012.

   Skills Development
   Modelling / Simulation

6. **New methods for the analysis and validation of 3D sugar-protein structures**
   Supervisors: Prof Gideon Davies
   Term: Spring / Summer

   Privateer (http://www.ccp4.ac.uk/html/privateer.html) is a software package for the analysis, validation and correction of anomalies in protein-carbohydrate structures. It has been recently used to uncover a widespread issue involving ring conformation in N-glycosylated structures from the Protein Data Bank (PDB).

   A rotation project is available for a highly motivated student to work on how to detect (and fix) these and other anomalies present in publicly-available structures of glycoproteins and sugar-protein ligand complexes.

   The findings will have a direct impact on improving Privateer, which is currently used at many laboratories around the world, and may find their way into a scientific publication. The project will also offer the opportunity for a hands-on programming experience depending on the student's skills on C++ and/or Python.

   Key References/Resources
   Agirre, J., Davies, G.J., Wilson, K.S. and Cowtan, K.D. (2015). “Carbohydrate anomalies in the PDB”. Nature Chemical Biology 11 (5), 303.

   Agirre, J., Iglesias-Fernandez, J., Rovira, C., Davies, G.J., Wilson, K.S. and Cowtan, K.D. (2015). “Privateer: software for the conformational validation of carbohydrate structures”. Nature Structural & Molecular Biology, in press.

   Skills Development
   Programming Skills, Data Analysis / Visualisation, Modelling / Simulation, Bioinformatics

7. **ChemGlycoSEPSIS: Chemical glycobiology for the study and exploitation of Pseudaminic acid sugars in infectious diseases**
Supervisor: Dr Martin Fascione/Prof Gideon Davies
Term: Spring / Summer

Pseudaminic acid (Pse) is a rare non-mammalian sialic acid-like sugar present on the surface of a number of bacteria including Pseudomonas aeruginosa, Acinetobacter baumannii, Campylobacter jejuni and Helicobacter pylori, and has been postulated to play influential roles in the etiology of associated infectious diseases through modulating flagella assembly and the recognition of bacteria by the human immune system. To date, no enzymes that catalyse the transfer of Pse sugars onto bacterial surfaces have been unambiguously characterised. We propose to use chemical glycobiology tools and X-ray crystallography to develop probes for the study of Pse-processing enzymes in bacteria and exploit native Pse biosynthetic pathways to inhibit bacterial Pse glycosylation, with the overarching aim of developing novel antimicrobial therapies.

Key References/Resources
Full research proposal available from MAF on request

Zunk et al., RSC Advances, 2014, 4, 3413-3421

Skills Development
Laboratory Skills and Methods, Data Analysis / Visualisation, Analytical Science / Instrumentation

8. **Targeting the thrombopoietin receptor to mediate haematopoietic stem cell maintenance and platelet production**
   Supervisors: Dr Ian Hitchcock/Prof Marek Brzozowski
   Term: Spring / Summer

   Thrombopoietin (TPO) is one of the principal regulators of haematopoietic stem cell maintenance and myeloid differentiation. TPO, acting through its receptor MPL, not only drives platelet production, but also activates key downstream signalling cascades promoting the proliferation of myeloid progenitor cells. The recent development of agents modify TPO/MPL signalling is proving to be extremely successful for the treatment of a number of conditions, especially in the autoimmune disorder idiopathic thrombocytopenia purpura (ITP). Interestingly, we have recently shown that reducing the expression of MPL prevents the development of myeloid malignancies, highlighting a key role for TPO/MPL in blood cancer development. However, the development of new and/or more effective MPL modulators relies on the determination of the receptor structure which is currently unknown. In this project, we will determine the structure of the MPL transmembrane domain, with focus on preventing receptor dimerization and down-modulating receptor activity. The project will involve protein production, crystallography, in silico drug design, in vitro cell line assays and dissection of intracellular signalling pathways. The work will be based in laboratories of Dr Hitchcock (CII) and Professor Brzozowski (YSBL).

   Key References/Resources
   http://www.bloodjournal.org/content/124/26/3956?sso-checked=true

   http://www.jbc.org/content/288/15/10230.full

   Skills Development
   Laboratory Skills and Methods, Data Analysis / Visualisation, Analytical Science / Instrumentation

9. Scanning the bacterial replisome for druggable sites.
Supervisors: Prof Rod Hubbard/Prof Peter McGlynn
Term: Spring/Summer

The bacterial replisome is an essential machine that replicates DNA. The McGlynn laboratory can reconstitute a functional replisome from the 15 components and in collaboration with the Hubbard laboratory has demonstrated that small molecular fragments can selectively disrupt the function. This project will combine experimental and computational (modelling and bioinformatics) analyses alongside the work of others in the search for novel antibiotic binding sites in the replisome that could provide a new approach to combat antibacterial resistance. A series of projects are underway: (1) to screen the York fragment library against the complete replisome; established assays should be able to identify which protein or sub-complex is being affected; (2) use biophysical techniques (NMR and TSA) to screen for fragments that bind to specific protein(s) and (3) to analyse the known crystal structures of replisome components for suitable binding sites. The balance between computational and experimental work will depend on the progress in the project at the time of the placement, as well as the aptitude and interests of the student.

Key References/Resources

Gupta, M. K. et al. Proc Natl Acad Sci U S A 110, 7252-7257, (2013)

Murray, J.M., Hubbard, R.E. Methods in Enzymology 493, 509-532 (2011)

Skills Development

Laboratory Skills and Methods, Data Analysis / Visualisation, Modelling / Simulation, Bioinformatics

10. An eco-immunology approach to understanding the transmission of leishmaniaisis.
Supervisors: Prof Paul Kaye/Dr Jon Pitchford
Term: Spring/Summer

Most immunological research on leishmaniasis has focused on understanding the cellular and molecular basis of host protection, using quantitative measures of parasite load in target tissues where disease occurs, and / or measures of immune function ("correlates of protection"). In contrast, little is known about how prevailing immune status affects the transmission of this disease from one individual to another, which requires sandflies to acquire parasites from skin and/or blood. This rotation project, will combine a quantitative analysis of parasite distribution in the skin and blood, using mathematical approaches taken from classic ecology, with methods to assess local skin immunity (e.g. flow cytometry, confocal microscopy and transcriptomics). Our overall hypothesis is that there may be a trade off between systemic immunity, that serves to protect from severe disease, and local immunity, that regulates host infectiousness to the sandfly vector. If correct, this would have significant consequences for the implementation and effectiveness of leishmanasis control programs.

11. IL-22 in cecal versus colonic inflammation
Supervisors: Dr Marika Kullberg
Term: Spring / Summer

The Kullberg group uses experimental lab work and computational approaches (in collaboration with Prof Jon Timmis) to better understand the processes active in the gastrointestinal tract during intestinal inflammation. Using a model of Helicobacter hepaticus (Hh)-induced colitis, we have recently demonstrated that individual Th17-type cytokines can have pro- or anti-inflammatory effects in different regions of the intestine. Thus, while IL-17A was found to play a disease-protective role in the cecum, IL-22 was shown to be pathogenic in the colon. The reason for the difference in IL-22 dependence of the inflammation in the cecum versus colon is currently unknown. One potential contributing factor may be differences in IL-22 receptor expression seen between the two tissues. This CIDCATS rotation project offers the possibility to learn more immunology and getting some additional lab experience. Depending on your specific interests, you will have the opportunity to learn intracellular cytokine staining to identify the cells secreting IL-22 in the cecum versus colon following Hh inoculation. Alternatively, you will be able to explore the role of type I and/or type III interferons in Hh-induced inflammation, cytokines that have been shown to affect responses downstream of IL-22 signaling.

Key References/Resources
Morrison, PJ, SJ Ballantyne, SJ Macdonald, JWJ Moore, D Jenkins, JF Wright, LA Fouser, and MC Kullberg. (2015) Differential requirements for IL-17A and IL-22 in cecal versus colonic inflammation induced by Helicobacter hepaticus. Am J Path (in press).

Bachmann M, S Ulziibat, L Härdle, J Pfeilschifter, and H Mühl. (2013) IFNα converts IL-22 into a cytokine efficiently activating STAT1 and its downstream targets. Biochem Pharmacol. 85:396-403.

Skills Development
Laboratory Skills and Methods

12. Memory and Silence

Supervisors: Dr Drimitris Lagos/Prof Jon Timmis

Term: Spring / Summer

Exposure of mammalian cells to a microbial stimulus leads to formation of gene regulatory networks that readjust the basal state of the cell. Often these priming events result in profoundly different responses to secondary challenges with the same or different stimuli. Such cell-intrinsic memory events have been studied in neuronal function, cellular differentiation, and adaptive immunity. Intriguingly, in contrast to the current immunological dogma, it was recently proposed that cells of the innate immune system, such as macrophages, are capable of acquiring memory following primary stimulation with inflammatory or microbial factors. However, the mechanisms underpinning innate immune memory remain largely unexplored. Through wet-lab experimentation and computational simulation, we aim to investigate these mechanisms and explore the possibility of engineering innate cell memory to achieve optimal immune responses to infection or vaccination.

This project will begin to develop an integrated computational and molecular cell biology approach to investigate mechanisms underpinning innate immune cell-intrinsic memory. Specifically, the project will investigate the role of microRNA-mediated silencing in the formation of innate immune memory.

It is expected that the student will explore both wet-lab and computational approaches during the rotation. The relative weighting and emphasis will depend on the student's interests.

Key References/Resources

Netea MG, Latz E, Mills KHG, O'Neill LA. Innate immune memory: a paradigm shift in understanding host defense. 2015. Nature Immunology, 16, 675–679.
http://www.nature.com/ni/journal/v16/n7/full/ni.3178.html

https://www.york.ac.uk/computational-immunology/

Skills Development

Laboratory Skills and Methods, Programming Skills, Modelling / Simulation

13. Measuring reactive oxygen species in cold plasmas for new antimicrobial therapies
Supervisors: Prof Deborah O'Connell/Dr Marjan Van Der Woude
Term: Spring / Summer

This project will examine the potential of low-temperature plasmas as a new technology to tackle antimicrobial resistance. 'Cold' plasmas, operated at ambient temperature and pressure, have the ability to produce and deliver high concentrations of highly reactive oxygen and nitrogen species (RONS) that can have damaging effects on biomolecules. Plasmas offer a multi-modal approach therefore potentially decreasing the chance of developing resistance. In order to specifically develop this therapy we need to be able to tailor the plasma and to this end measuring and tuning the RONS in the plasma is critical.

This project will focus on plasma diagnostics for ROS. An advanced UV absorption spectroscopy diagnostic setup will be used to measure plasma generated ROS (specifically hydroxyl and ozone within this rotation). Results will be compared with an already existing 0-dimensional global chemical kinetics model. The skills you will learn within the project include alignment of an optical diagnostic setup, data collection and analysis, and benchmarking pre-existing computational models. The project will be carried out within an interdisciplinary team, with regular interactions and discussions with researchers across many departments at York.

Key References/Resources
J.S. Sousa et al., J Appl Phys., 12 109 (2011)

S. Reuter et al., Plasma Sources Sci Technol., 24 5 054001 (2015)

Skills Development
Laboratory Skills and Methods, Data Analysis / Visualisation, Modelling / Simulation

14. Revealing the secrets of repetitive bacterial proteins
Supervisors: Prof. Jennifer Potts
Term: Spring/Summer

Pathogenic protein aggregation is important in neurodegenerative disease and results in significant losses during the production of high value biotherapeutics. Thus finding new mechanisms of aggregation resistance would be of significant interest to scientists in a wide range of fields.
Aggregation increases with protein concentration and with sequence similarity thus it is perhaps not surprising that in multi domain proteins adjacent domains (which are in high local concentration due to covalent attachment) usually have less than 40% sequence identity (Wright et al., Nature 2005; Borgia et al., Nature 2011).
However, the Potts group works on repetitive bacterial surface proteins that appear to break these 'rules'; that is, they are multi-domain proteins with arrays of identical sequences. How do they avoid aggregation between adjacent sequences? This project is at an interesting stage. We have shown that these protein sequences fold into structures with interesting properties (Whelan et al. Nat. Commun. 2015). In the project we will test a key part of the hypothesis; that is, that domains in repetitive proteins are resistant aggregation. If correct, this will lead to the recognition that repetitive proteins hide previously unrecognised mechanisms to resist aggregation that could inform medical or biotechnology applications.

Key References/Resources
Han, J. H., Batey, S., Nickson, A. A., Teichmann, S. A. and Clarke, J. (2007) The folding and evolution of multidomain proteins. Nat. Rev. Mol. Cell. Biol. 8, 319-330

Gruszka, D.T., Whelan, F., Farrance, O.E., Fung, H.K.H., Paci, E., Jeffries, C.M., Svergun, D.I., Baldock, C., Baumann, C.G., Brockwell, D.J., Potts, J.R.*, Clarke, J.* (2015) Cooperative folding of unstable domains drives formation of a long, strong protein. Nat. Commun. 6, 7271

Skills Development
Laboratory Skills and Methods, Data Analysis / Visualisation, Analytical Science / Instrumentation

15. Barriers to infection

Supervisors: Prof Jenny Southgate/Dr Steve Johnson
Term: Spring / Summer

Urinary tract infections (UTI) are amongst the most common of human infections and a major cause of antibiotic use. Although most UTI are self-limiting, in some children and adults these infections can have serious sequelae, including kidney failure and death. Urothelium, the epithelial lining of the bladder and urinary tract provides the first line of defence to UTI. Urothelium is a self-repairing physical barrier which carries an arsenal of innate defence features able to sense, respond to and attack invading pathogens. Human urothelial cells grown in vitro can be differentiated to form a functional, self-repairing barrier tissue; this provides an experimentally-tractable system to investigate emergent and regenerative urothelial barrier and defence properties. Whereas trans-epithelial electrical resistance provides a useful overall measure of barrier function, it is comprised of a combination of passive and active transport properties as a result of active ion absorption and/or secretion across the barrier. The aims of this study are 1) to explore the electrophysiological properties of urothelium during barrier formation and repair and 2) to consider how such data may be used to parameterise computational models of barrier homeostasis and function, with the long term objective of boosting the urothelial "defendome" as a therapeutic strategy.

Key References/Resources

Baker SC, Shabir S, Southgate J. Biomimetic urothelial tissue models for the in vitro evaluation of barrier physiology and bladder drug efficacy. Mol Pharm. 2014 Jul 7;11(7):1964-70. doi: 10.1021/mp500065m. Epub 2014 Apr 17. PubMed PMID: 24697150.

Koutsoumpeli, E, Murray, J, Langford, D, Johnson, SD & Bon, R 2015, 'Probing molecular interactions with methylene blue derivatized self-assembled monolayers' Sensing and BioSensing Research., 10.1016/j.sbsr.2015.09.004

Skills Development

Laboratory Skills and Methods, Data Analysis / Visualisation, Analytical Science / Instrumentation

16. **Metabolic engineering of sialic acid super-consumers: an approach to reduce post-antibiotic expansion of enteric pathogens.**
Supervisor: Dr Gavin Thomas/Dr Marika Kullberg
Term: Summer

The metabolic interactions between bacteria in the gut and their host are essential for the maintenance of a healthy microbiota. Disruption of this by antibiotics or inflammation is known to lead to metabolic unbalancing and the accumulation of sialic acid, which can then be used as food by opportunistic pathogens to proliferate (Ng et al 2013; Huang et al 2015). In this project the student will use a combined metabolic modelling and genetic engineering approach to create probiotic strains of bacteria that can consume this sialic acid and prevent the expansion of dangerous enteric pathogens in this niche.
The project builds on work in the Thomas lab on the transport and catabolism of sialic acid by bacteria, combined with expertise in metabolic modelling of bacterial metabolic symbioses. The student will use these modelling methods combined with extensive genetic engineering to create and test resultant strains for their ability to consume sialic acid, also providing more fundamental insight into how bacteria use sialic acids. The expertise of the co-supervisor, Kullberg, will allow the student to test their strains in a mouse model of infection to measure colonisation and assess if they can reduce post-antibiotic or inflammation induced expansion of bacterial pathogens.

Key References/Resources
Ng et al (2013) Nature. 502(7469):96-9. PMID:23995682

Huang et al (2015) Nat Commun. 6:8141. PMID: 26303108

Skills Development
Laboratory Skills and Methods, Modelling / Simulation, Bioinformatics