**BBSRC White Rose DTP in Mechanistic Biology - Studentships available commencing in October 2019**

**Deadline for applications: Monday 7th January 2019**

**We offer a 4-year programme of integrated research and skills training, with cross-disciplinary supervision and opportunities for professional internships with external partners.**

**Our vision is to train researchers of the future equipped to address and solve fundamental and strategic biological questions of national and global importance in the following areas:**

**• Food Security**  
**• Industrial Biotechnology and Bioenergy**  
**• World Class Bioscience**

**The programme builds on the excellent track records of the Universities of Leeds (The Faculties of Biological Sciences and Maths and Physical Science), Sheffield (Faculty of Science) and York (Departments of Biology and Chemistry) as leading centres of research and training in molecular and cellular biosciences.**

These Projects are competitive studentships based at the University of Sheffield funded by BBSRC covering:

(i) a tax-free stipend at the standard Research Council rate (~£14-£15K, to be confirmed for 2019) for 4 years

(ii) research costs, and

(iii) tuition fees at the UK/EU rate for 4 years.

**What are the requirements for applicants?**

At least a 2:1 honours degree in a relevant subject, or equivalent. The interdisciplinary nature of this programme means that we welcome applications from students with backgrounds in any biological, chemical, and/or physical science, or students with mathematical backgrounds who are interested in using their skills in addressing biological questions.

Studentships are available to UK and EU students who meet the UK residency requirements. Students from EU countries who do not meet the residency requirements may still be eligible for a fees-only award. Further information on eligibility: http://www.whiterose-mechanisticbiology-dtp.ac.uk/wp-content/uploads/2018/06/studentshipeligibility.pdf. There are language requirements for international students.

**Application process**: When you have found a project you want to apply for, you can apply using the University of Sheffield's online application form http://www.shef.ac.uk/postgraduate/research/apply/applying

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| **Applicants** | **Department** | **Project title** | **Details of project** |
| Prof Julie Gray with Prof Andy Fleming | Department of Molecular Biology and Biotechnology | Speeding towards efficient stomata | We all understand that plants have stomata that can open and shut. This lets plants control their water loss, and led to them ‘greening the Earth’ half a billion years ago, thus paving the way for animals. Since then some plants have evolved stomatal features that allow them to close their stomata faster when they encounter drying environments. For example, ferns have ‘slow stomata’ and the later evolving grasses have ‘speedy stomata’. These speedy stomata have equipped grasses to conquer dry savannah and desert environments, and have led to our selection of cereals as major food crops. Surprisingly, despite our reliance on ‘speedy stomata’ for food security, we know little about the molecular underpinnings of stomatal efficiency. In this project, for the first time, the student will use infrared gas exchange to quantify stomatal efficiency and compare this between plant groups, and between crops and their wild relatives. These will be compared with cell wall immunocytochemical and RNAseq transcriptome studies to pinpoint the key genetic, developmental, and structural traits that underpin improved stomatal efficiency. The knowledge gained will be invaluable in designing crops better suited to more frequent drought periods.  For further information contact Prof Julie Gray (j.e.gray@sheffield.ac.uk) |
| Prof David Strutt with Dr Alexander Fletcher | Department of Biomedical Science | Epithelial morphogenesis: coordinating planar polarity and tissue mechanics | As an organism develops, tissues are shaped and patterned in a coordinated way. The long-standing dogma of developmental biology is that secreted proteins diffuse to form expression gradients throughout tissues thereby providing spatial cues to direct growth, fate and pattern, drawing responses from cells even at some distance from the source. More recently, studies have revealed critical roles for mechanical forces in regulating tissue development, however, the interplay between these two systems is poorly understood.  The model organism *Drosophila* provides an ideal system for dissecting mechanisms of development in cell sheets, as it is highly amenable to genetic manipulation and has easily accessible simple tissues suitable for live imaging. Experimental approaches will be coupled with computational modelling of cell sheets. This project will be suitable for a biology student with knowledge of cell or developmental biology and genetics, who is keen to develop quantitative skills. Alternatively, a physical scientist seeking to increase their biological knowledge may be suitable. Moreover, the student will be provided with an interdisciplinary training in laboratory skills, quantitative analysis and computational modelling.  For further information contact Prof David Strutt (d.strutt@sheffield.ac.uk) |
| Prof Michael Brockhurst with Dr Ellie Harrison, Prof Duncan Cameron and Dr Jamie Wood | Department of Animal and Plant Science | The evolution of multidrug resistant bacterial pathogens | The evolution of antibiotic resistance poses a serious global threat to human and animal health. The emergence of multidrug resistant pathogens is often driven by the spread of plasmids that encode genes giving resistance to multiple antibiotics. However, gaining a plasmid is not always beneficial for the bacterium because plasmids disrupt a wide range of cellular processes to cause large fitness costs. An exciting possibility is that if we understood how these fitness costs are caused we could exploit this weakness to select against resistance plasmids, reducing the burden of antibiotic resistance. This project seeks to understand the general rules governing how diverse resistance plasmids impact cellular processes to create fitness costs in an important bacterial pathogen of humans and animals. To do this we will use multiple cutting-edge omics techniques (genomics, transcriptomics, proteomics and metabolomics) and systems biology approaches in combination with experimental evolution and molecular biology. The supervisory team combines expertise in microbiology, evolutionary biology, biochemistry and mathematics. The project will provide a broad interdisciplinary training with both wet-lab and dry-lab experience, bioinformatics and computing skills.  Bottery M, Wood AJ, Brockhurst MA. Adaptive modulation of antibiotic resistance via intragenomic coevolution. Nature Ecology and Evolution. 2017. 1:1364-1369.  For further information contact Prof Michael Brockhurst (m.brockhurst@sheffield.ac.uk) |
| Dr Julien Bergeron with Dr William Durham | Department of Molecular Biology and Biotechnology | Structural and functional characterization of the TAD pilus of the multi-antibiotic-resistant bacterium *P. aeruginosa* | Surface attached biofilms bacteria are major cause of recurrent infections because they allow cells to withstand much higher concentrations of antibiotics. *Pseudomonas aeruginosa* is a notorious biofilm-forming pathogen that uses filamentous Tight Adherence (Tad) pili to stick to surfaces during the initial stages of biofilm formation, yet there is currently very little understanding of the Tad pilus at either the molecular or behavioural level.  We propose to use cryo-EM, a revolutionary technique to investigate protein complexes at the atomic level, combined with cutting-edge microfluidic experiments, to characterize the Tad pilus. This hybrid approach, combining structural biology, bacteriology, and biophysics, will provide new insights on how *P. aeruginosa* utilizes the Tad pilus to initiate biofilm formation. Ultimately this could but used to develop new antimicrobial treatments in the fight against the deadly *P. aeruginosa* infections that routinely occur in cystic fibrosis patients and burn victims.  For further information contact Dr Julien Bergeron (j.bergeron@sheffield.ac.uk) |
| Dr Natalia Bulgakova with Prof Elizabeth Smythe | Department of Biomedical Science | Plasticity of clathrin-mediated endocytosis in development | Levels of cell surface proteins are key for tissue integrity and cell-cell communication and, during development, proteins levels are rapidly adjusted to the needs of the developing tissue. For example, rapid removal of cell-cell adhesion molecules from the cell surface is vital for cell rearrangement during tissue elongation, while adhesion molecules need to be present after rearrangements are completed to permit correct patterning. This means that there must be sophisticated systems to fine-tune levels of proteins at the cell surface.  Clathrin-mediated endocytosis (CME) is the principal pathway for the removal of cell surface proteins and many of the molecular players in CME have been elucidated from work in cultured cells. However, cells in culture are not subjected to developmental cues such as signaling and mechanical forces, which shape an organism, and are therefore unsuitable for understanding of how these cues regulate CME.  In this project we aim to understand the plasticity of CME in vivo. A combination of state-of-the-art genetic, imaging and computational techniques will be applied in Drosophila, as a model organism, and mammalian cells. The successful candidate will be trained in quantitative developmental and cell biology and acquire skills in optogenetics, super-resolution microscopy and automated image analysis.  For further information contact Dr Natalia Bulgakova (N.Bulgakova@sheffield.ac.uk) |
| Dr Freek Van Eeden with Prof Sherif El-Khamisy and Dr L Matthews (Leeds) | Department of Biomedical Science | Characterisation of the mechanism of HIF mediated genoprotection in zebrafish | Failing DNA-repair and the resulting genome instability is now recognized to be a major factor in two important diseases that are becoming more and more prevalent due to our aging population: cancer and neurodegeneration.  While studying the hypoxic signaling pathway in zebrafish we identified a surprisingly strong effect of HIF activation on the protection of cells against DNA damaging treatments. We found that embryos with a strongly activated HIF pathway survived otherwise lethal doses of irradiation and it could even protect embryos that have a mutation in certain DNA repair genes like BRCA2. These data suggest that HIF can activate as yet unknown genoprotective mechanisms  This project aims to understand and exploit this genoprotective effect of HIF, using zebrafish genetics, fluorescent protein transgenics and technologies including CRISPR and CRISPRi, to identify and characterize the pathways involved in HIF based protection against genotoxins.  For further information contact Dr Freek Van Eeden (f.j.vaneeden@sheffield.ac.uk) |
| Dr Matt Johnson with Dr Ash Cadby | Department of Molecular Biology and Biotechnology | Super-resolution video rate imaging of photosynthetic membrane dynamics in plants and algae | Remarkable images of the internal workings of plant chloroplasts and algae provided by structured illumination microscopy suggest a major role for photosynthetic membrane morphological changes in the adaptation to changing light intensity. Our study of this largely unexplored phenomenon has revealed rapid dynamics that help the plant match the conversion of light to chemical energy with its consumption for CO2 fixation into biomass. Now we have the ability to image these dynamics in real time at super-resolution for the first time using a breakthrough microscopy technology. The super-resolution programmable array microscope (SR-PAM), can adapt during imaging to optimise signal to noise and resolution. The adaptability of the system means that we can push super-resolution further in to deep samples. Utilising this exciting new microscopy technique we will investigate how the thylakoid membrane dynamics regulate photosynthesis. The results of this study have the potential to provide an unexpected route to improving photosynthesis for enhanced crop and biofuel production.  For further information contact Dr Matt Johnson (matt.johnson@sheffield.ac.uk) |
| Prof Jamie Hobbs with Dr Christian Voigt | Department of Physics and Astronomy | The relationship between molecular organization and mechanical properties in the leaf cell wall with a focus on infection | The plant cell wall plays a critical role in mechanically resisting turgor, defining morphology and as a barrier against microbial attack. However, the precise molecular architecture of the cell wall is still poorly understood. We have recently shown that there is considerable variation in mechanical properties within the walls of individual cells, between different cell types, and after microbial attack, linked to local variations in chemical composition; but the details of how chemistry and molecular organisation leads to function remain elusive. This project aims to use and develop cutting edge biophysical imaging techniques, in particular atomic force microscopy (AFM) and super-resolution (SR) optical microscopy, to elucidate the molecular organization of the cell wall in unprecedented detail. Once this basis of new information has been obtained, we will use it to explore the role played by the glucan-polymer callose in reshaping and reinforcing the cell wall following fungal attack, which in future may inform the development of novel anti-fungal agents. The project will build on internationally leading developments in the application of AFM to cell wall systems, and in the use of SR optical microscopy to follow cell wall growth in plants.  For further information contact Prof Jamie Hobbs (Jamie.hobbs@sheffield.ac.uk) |
| Dr Bin Hu with Dr John Rafferty | Department of Molecular Biology and Biotechnology | Mechanistic dissection of cohesin DNA loading process | The DNA, our genetic information carrier, is accurately duplicated into ‘sisters’ and equally transmitted to the two new-born daughter cells during cell proliferation. To ensure the precise sharing out of the duplicated genetic information, sister DNAs produced after DNA replication are held together until they are ready to move to opposites poles of the cell, just before the cell divides. This phenomenon is called sister chromatid cohesion. Sister chromatid cohesion is mediated by a special machine called cohesin. Precise regulation of cohesin’s association with DNA is fundamental for its actions. Defects in this regulation compromise cohesin’s function, which in humans would lead to cancer and inherited developmental disorders (such as Cornelia de Lange CdLS and Roberts syndromes). Although cohesin has been studied over twenty years, our knowledge of molecular details in its DNA association has progressed very little. In this study, we will investigate the molecular mechanism by which cohesin is recruited to DNA using comprehensive genetic, biochemical, and cell biology approaches. Insight into this fundamental process will help us understand how DNA segregation sometimes fails in cell division, as in cancer cells, or how our developmental programme goes wrong, which gives rise to cohesin-related diseases.  For further information contact Dr Bin Hu (b.hu@sheffield.ac.uk) |
| Dr Stephane Mesnage with Prof Mike Williamson | Department of Molecular Biology and Biotechnology | Structural characterization of the enterococcal polysaccharide antigen and analysis of its contribution to cell growth, division and antibiotic resistance | The proposed project is focused on the functional analysis of a surface rhamnopolysaccharide produced by all enterococci, required for normal cell growth, division, resistance to antibiotics and pathogenesis. This enterococcal polysaccharide antigen (EPA) is encoded by two gene clusters: (i) 18 genes extremely conserved (epaA-epaR) encoding a core synthetic machinery and (ii) 10-20 genes variable from one strain to another, responsible for the decoration of the polysaccharide backbone. We have built a mutant with a complete deletion of the epa variable region and shown that the decoration of EPA (but not its core structure) is essential for the biological activity of this polymer. We propose investigate the structural properties of Epa and dissect the specific contribution of this polymer and its decoration to bacterial physiology and antibiotic resistance.  We will take a multidisciplinary approach to explore EPA structure and to understand how EPA controls the distribution and activity of surface proteins involved in cell wall assembly and resistance to antibiotics. The project will involve state-of-the-art methodologies including super-resolution microscopy (fluorescence and electron microscopy), structural glycobiology (NMR, mass spectrometry) and conventional approaches to study bacterial physiology and antimicrobial resistance. The candidate will work with members of the supervisors’ laboratories studying bacterial cell surface assembly and host-pathogen interactions.  For further information contact Dr Stephane Mesnage (s.mesnage@sheffield.ac.uk) |
| Dr Dan Bose with Prof Stuart Wilson and Dr Timothy Craggs | Department of Molecular Biology and Biotechnology | Investigating the role of phase separation in enhancer-dependent gene regulation | Enhancers are regulatory DNA sequences that control when, and in what tissue, particular genes are turned on and off. The process of gene activation from enhancers requires a number of factors, including epigenetic enzymes that bind to enhancer regions in the genome, and non-coding RNAs (eRNAs) transcribed from enhancers.  Phase separation has recently emerged as one of the most exciting and fast-moving areas of biology. Phase separated condensates are membraneless organelles containing high densities of proteins and nucleic acids. They exist in a separate phase to the surrounding cellular environment, providing a method to compartmentalize and concentrate biochemical reactions in the nucleus.  Recent evidence has pointed to a role for phase separated condensates as regulators of highly active enhancers. In this project, we will develop new methodologies to understand how phase separation affects the activity of enzymes responsible for enhancer function. You will join a highly collaborative and dynamic research environment within the Sheffield Institute for Nucleic Acids, where you will learn cutting edge approaches including next generation sequencing, RNA biology, real time imaging (single molecule FRET) and biochemical approaches to study chromatin modifications. The work will provide a new understanding of one of the most relevant questions in biology and will have broad ranging outcomes, from understanding human diseases to improving biotechnology.  For further information contact Dr Dan Bose (d.bose@sheffield.ac.uk) |
| Dr Ewald Hettema with Dr Stuart Warriner (Leeds) | Department of Molecular Biology and Biotechnology | Development of Debaryomyces hansenii as a robust host for production of high value fatty acid-based biochemicals | Petro-chemically derived biochemicals are used globally, however, there is a worldwide drive to replace them with sustainable, biological counterparts. Nature provides many tools to synthesise a huge variety of biochemicals but there are problems which arise when industrially harvesting these compounds such as low yields, pathogenicity and difficulty in culturing the organisms. The challenge frequently faced by the industrial biotechnology community is how to manipulate cellular synthesis machinery in order to yield products which can be used optimally.  In this synthetic biology project you will be part of an interdisciplinary team that is interested in the production of a class of bio-emulsifiers using the non-pathogenic yeast Debaryomyces hansenii as production host. You will address how the marine stress resistant cells adapt to the production of compounds that potentially emulsify their membranes. You will introduce the genes to produce the emulsifiers into D. hansenii and then address the question using a variety of techniques including transcriptome analysis, lipidomics and metabolic pathway analyses. Your findings will then be used to re-engineer the cellular biosynthesis pathway to improve bio-emulsifier production. This project is based around principles of industrial biotechnology but creates opportunities to work together with molecular biologists, bioinformaticians, chemists and physiologists.  For further information contact Dr Ewald Hettema (e.hettema@sheffield.ac.uk) |