Peterhouse Biology Symposium 2020 Abstracts

Saturday 7th March 2020, Peterhouse Theatre

Justin Gerlach (Bye-Fellow) – **Resurrecting species and projects**

Giant tortoises used to live on almost every island in the Indian Ocean but were almost all extinct by the 19th century due to consumption by human settlers. In 1996 an odd-looking captive individual was brought to my attention as a suggested survivor of one of the supposedly extinct Seychelles species. Examination of morphology and some preliminary genetic work seemed to support this. Genetic studies were relatively primitive at the time and the results were rapidly called into question as the techniques changed. By that time a conservation breeding programme had been set up for handful of putative Seychelles giant tortoises, resulting in 120 baby giant tortoises being released back into the wild by 2012. Whereas 20 years ago genetic analysis relied on partial sequences of a single gene, by last year techniques had moved on to such an extent that complete mitochondrial genomes were obtained from tortoise subfossils several thousand years old. Now this is being extended to sequence the old remains from the Seychelles islands and there is interest in reviving the old study of the living tortoises that led to our attempts to resurrect these 'species'.

Chris Chan Jin Jie (II Physiology, Development & Neuroscience student) – **How useful are synthetic embryos in the study of early mouse development?**

Mouse embryonic, trophoblast and extra-embryonic stem cells can self-assemble and organize in vitro, generating structures that acquire the embryo's architecture with all distinct embryonic and extra-embryonic compartments. Such structures are known to undertake epithelial mesenchymal transition, but how accurately these structures recapitulate key morphogenic events of murine embryogenesis remains to be determined.

Sam Woodman (PhD student) – **Chewing through biogeochemical cycles: insect outbreaks boost nitrogen and offset rising carbon concentrations in northern lake waters**

Terrestrial and aquatic ecosystems are connected by the movement of organic matter across their boundaries. Disturbance events, such as outbreaks of insects, reduce terrestrial carbon storage and disrupt the typical transfer of organic matter to lakes by converting leaves into a highly labile, nitrogen-rich waste product called frass. The addition of frass and reduction of leaf material entering into lake ecosystem results in a pulse of nitrogen and decrease in carbon that may shift base of the food web towards heterotrophic production. Our results suggest that the effects of insect outbreaks on biogeochemical cycling extend beyond forests into lakes and may increase rates of carbon release from lakes during outbreaks.

Talia Smithers (II Psychology, Neuroscience & Behaviour student) – **The neural, cellular and molecular basis of interoception in the rat**

Interoception can be defined as the sensation of internal bodily signals. Establishing the basis of this in animal models, such as the rat, requires evidence of behaviour based on interoceptive information utilised by the animal. I have aimed to characterise brain regions involved in the behavioural manifestation of interoception, as well as looking into the type of plasticity underlying the contribution of these regions to behaviour.

Wes Robertson (Research Associate) – **Total synthesis of a recoded *E. coli* genome**

Nature uses 64 codons to encode the synthesis of proteins from the genome, and chooses 1 sense codon — out of up to 6 synonyms — to encode each amino acid. Synonymous codon choice has diverse and important roles, and many synonymous substitutions are detrimental. Here we demonstrate that the number of codons used to encode the canonical amino acids can be reduced, through the genome-wide substitution of target codons by defined synonyms. We create a variant of *Escherichia coli* with a four-megabase synthetic genome through a high-fidelity convergent total synthesis. Our synthetic genome implements a defined recoding and refactoring scheme — with simple corrections at just seven positions — to replace every known occurrence of two sense codons and a stop codon in the genome. Thus, we recode 18,214 codons to create an organism with a 61-codon genome; this organism uses 59 codons to encode the 20 amino acids, and enables the deletion of a previously essential transfer RNA.

Rhea Mittal (II Psychology, Neuroscience & Behaviour student) – **The effect of stress on sensory associative learning and its interplay with anxiety and autistic traits**

To negotiate a complex and uncertain world, humans must make inferences and learn efficiently. Differences in learning in various neuropsychiatric conditions, such as autism spectrum disorder and anxiety, are increasingly coming under the spotlight. Stress and arousal - co-morbidities of many neuropsychiatric conditions - are also thought to impact learning. We investigated the effect of arousal on learning in easy (stable) and difficult (volatile) learning conditions, and its interplay with anxiety and autistic traits. Participants were tested using a sensory learning paradigm in which they had to complete probabilistic associative learning tasks, whilst listening to broadband noise (to increase arousal). Preliminary data suggests that learning is better in stable conditions compared to volatile, and this effect is more pronounced in arousal conditions. We expect that participants with higher autistic and/or anxiety traits will exhibit compromised learning as well as more dramatically impaired performance in volatile conditions with arousal.

Johanna Winder (II Plant Sciences student) – **Understanding drivers and consequences of microbial community change during permafrost thaw**

The release of greenhouse gases as a result of permafrost thaw in subarctic peatlands is a major potential consequence of global warming. These systems store vast amounts of frozen organic matter which becomes available for digestion by microbes upon thaw. Microbes can either feed directly on this organic matter, releasing methane as a metabolic byproduct (methanogenesis) or use methane as a carbon source, and release CO_2 (methanotrophy). Permafrost thaw also has far-reaching consequences for the geochemical characteristics of areas draining thawing peatlands. Microbial community structure and functional characteristics can be impacted by chemical characteristics of lakes, but can also be directly impacted by thaw, thereby altering other chemical characteristics e.g methane. This study looks at 20 boreal ponds in 4 permafrost zones in northwestern Canada, using a space for time model to predict the effects of permafrost thaw on their geochemistry and microbial communities, and the interaction between the two.

Fani Memi (Research Associate) – **MYC versus ASCL1 in Neuroblastoma: a battle for control**

Neuroblastoma is the most common solid childhood cancer, and is thought to arise from sympathetic neuroblast precursors that fail to engage the neuronal differentiation programme, and instead are locked epigenetically into a pro-proliferative developmental state. Recent evidence implicate ASCL1, a master transcriptional regulator of neuronal progenitor proliferation and differentiation in the embryonic and adult CNS, in the pathogenesis of

neuroblastoma. While during development ASCL1 is expressed transiently in the sympathetic precursors and is downregulated during differentiation, in high risk neuroblastomas the levels of ASCL1 remain high, maintaining the cells in a proliferative mode. Work from our lab suggests that the phosphorylation status of ASCL1 is the key determinant of its activity: a heavily phosphorylated form directs a pro-proliferative programme, while a less phosphorylated form directs cell cycle exit and a pro-differentiation programme. Genome-wide analysis of ASCL1 phosphorylation-dependent targets revealed a number of genes that are known targets of MYC(N), another bHLH transcription factor invloved in many cancers, including high risk neuroblastomas. Furthermore, we see that MYCN overexpression inhibits ASCL1-mediated differentiation in vivo, while the two transcription factors have been previously reported to directly compete for the same gene promoter (CCND1) in cerebellar granule cells. Our working hypothesis is that MYCN is preventing phosphorylated ASCL1 from driving neuroblast differentiation and that dephosphorylated (phosphomutant) ASCL1 is resistant to MYCN-mediated inhibition. We show that phosphomutant ASCL1 binds common (with MYCN) gene targets and regulates them in an opposite way (downregulates proliferation and upregulates differentiation genes). Future experiments will test whether MYCN and ASCL1 compete for the same regulatory elements and try to gain a mechanistic insight of the antagonism between ASCL1-driven neuroblast differentiation and MYCN-driven proliferation in neuroblastoma.

Tjasa Zaletel (II Pathology student) – **An investigation into putative host factors required for BK Polyomavirus infection**

BK polyomavirus (BKPyV) is a small, non-enveloped DNA virus that establishes persistent asymptomatic infections in the urinary tract of most people. Severe pathologies ensue following BKPyV reactivation in immunosuppressed transplant recipients, often leading to graft rejection. The lack of appropriate antiviral treatment necessitates a better understanding of BKPyV lifecycle. Given the limited coding capacity of its 5.3kb genome, BKPyV heavily relies on multiple host factors for its replication. Yet, the virus-host interplay remains poorly characterised. As a result, preliminary whole genome CRISPR screen was performed focusing on host proteins involved in early BKPyV lifecycle. In this report, we set out to validate the three most confident gene candidates – CTCF, MAT2A, PRP19. Using siRNA mediated gene knockdown, immunofluorescence microscopy and quantitative polymerase chain reaction (qPCR), we identified MAT2A and PRP19 to be essential for BKPyV infection, while CTCF failed validation. Intriguingly, although our data demonstrated direct involvement of MAT2A in nuclear replication, discordant effects of gene knockdown suggested PRP19 acts antagonistically at two spatiotemporally distinct, intricately balanced stages. Furthermore, BKPyV infection also induced nuclear enlargement. We therefore propose a model, which provides mechanistic insight into novel virus-host interactions and supports implications for the development of antiviral agents to treat BKPyV infections.

Zhu Xuan Zhong (II Pathology student) – **Role of BMPR2 in the maintenance of human Cytomegalovirus latency**

Human cytomegalovirus (HCMV) latently infects a large proportion of the population at any point in time. Bone morphogenic protein receptor (BMPR) 2 has been implicated in enabling the maintenance of latency, where inhibiting it or knocking it out results in the cells expressing the immediate early (IE) gene - a marker of the lytic life cycle. While not definitively proven, data supports the hypothesis that BMPR2 signalling ensures maintenance of latency by inhibiting TGFβ signalling. TGFβ is upregulated in latency and inhibiting TGFβ in cells lacking BMPR2 signalling results in cells being able to support latency once again.

Charlotte Wright (MPhil student) – **Uncovering the genetic basis of wing colour patterning in *Heliconius* butterflies**

Heliconius butterflies represent an iconic example of an adaptive radiation which is characterised by a wide variety in wing colour patterning and striking mimicry between closely related species. Colour patterning is known to be dictated by a few genes of large effect. While most of these genes have a clear mechanism by which they influence development, the role of one of these genes, cortex, remains elusive. I will discuss how long-read RNA sequencing is providing insight into the function of cortex and the potential role of alternative splicing in generating morphological diversity.

Leo Kiss (PhD student) – **Molecular matchmaking**

Post-translational modification of proteins ensures rapid adaptation to complex cellular happenings. Among these, ubiquitination enables to connect sophisticated signals with a plethora of cellular outcomes, resulting in the regulation of proteostasis, development and immunity. Although there is a wealth of knowledge about the basic machinery behind this, the interplay between its different partners is not. I will give insight into how the correct type of ubiquitin-modification is generated by specific interaction between two types of ubiquitination enzymes.

Ivan Phanada (II Zoology student) – **Chromatin remodelling during human DNA replication - the role of PRMT1 methyltransferase**

The initiation of DNA replication at the G1 to S phase transition is a key regulatory step of the cell division cycle in eukaryotic cells. A class of highly conserved small non-coding cytoplasmic RNAs (Y RNAs) regulate this process in all vertebrates, without which chromosomal DNA replication is abrogated. The molecular mechanisms by which Y RNAs exert their functional role during replication initiation remains elusive but suggestive of chromatin remodeling through interaction with other proteins. The arginine methyltransferase PRMT1 is a candidate human Y RNA interacting factor. Here, I showed that PRMT1 is required for both the initiation and elongation step of human DNA replication and appears to be recruited into replication origins in human.

Xianglin Huang (II Pharmacology student) – **Protein modulators of GABA receptors**

GABAA receptors are the principal mediators of inhibitory neurotransmission in the central nervous system (CNS). Traditional modulators, including important clinical ligands are small molecules, for example the benzodiazepines (e.g. Valium) and non-benzodiazepines (e.g. Zolpidem) used to treat generalized anxiety disorder, epilepsy, muscle spasm and insomnia. An alternative is to develop protein (antibody-type) modulators of GABAA receptors, which have the potential for higher selectivity between the many receptor subtypes. This project is to examine the pharmacological effects of different protein modulators in targeting various subtypes selectively and in inducing internalisation of the receptors.

Will Orchard (MPhil student) – **What's different in the 3D genome? (differential analysis of Capture Hi-C data)**

In recent years, there has been a growing appreciation for the importance of the 3D arrangement of the genome in space for understanding the logic of gene regulation, development and disease. Although many techniques have been developed to study the 3D genome, Capture Hi-C has emerged as a powerful approach for studying the role and logic of enhancer-facilitated regulation. Capture Hi-C allows genome-wide identification of physical promoter-enhancer interactions, but has not yet been widely adopted. In part this is because statistical challenges associated with the data has hampered the development of tools for performing powerful statistical analyses, such as differential analysis, which have become the norm for other genomics data. I will present the case for the importance of the 3D genome, differential analysis, and my work developing Chicdiff: the first and only tool for performing differential analysis of Capture Hi-C data.

Eleanor Sheekey (PhD student) – **Playing with p53; the most mutated protein in cancer**

p53 is commonly referred to as the “guardian of the genome”; it activates cellular processes to prevent proliferation and growth when a cell is damaged and induces cell death when a cell is beyond repair. This prevents a damaged cell from uncontrolled growth which can lead to tumorigenesis. Perhaps unsurprisingly then, mutations in the gene for p53 are the most frequent in cancer. Instead of completely deleting the gene, most of these mutations are missense – just one of the amino acids in the p53 protein is changed. Not only do these mutants cause loss of normal p53 function, it now seems these mutants are up to no good, performing novel functions in a cell as well. However, despite >90,000 publications on p53, these functions and their cellular

impact are incomplete. What is needed is a biochemical tool that can dissect these functions of mutant p53. What is needed then is a way to “play” with the levels of mutant p53.

Alice Bittleston (PhD student) – **Symmetry breaking of the cytoskeleton during asymmetric cell division**

Asymmetric cell division is the process by which one cell divides into two daughter cells that have different fates. Asymmetric cell fate assignation during asymmetric division relies on the biased dispatch of fate determinants between the two daughter cells. In particular, our lab recently discovered a novel mechanism of asymmetric dispatch of cell fate determinants in *Drosophila* Sensory Organ Precursors (SOPs). In these cells, the central spindle, the antiparallel array of microtubules characteristic of late mitosis, is asymmetric. This spindle asymmetry is in turn "read" by a molecular motor to carry endosomes containing cell fate determinants into only one of the two daughter cells. While our lab has made significant progress in understanding some of the key players in this pathway, how symmetry breaking of the central spindle is achieved *in vivo* remains an open and challenging question.