Elucidation of epigenomic and transcriptional mechanisms controlling stress-induced Fkbp5 gene expression in the hippocampus

Supervisory team:
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Collaborators: Dr Colin Campbell (University of Bristol)

Host institution: University of Bristol

Project description:

This PhD studentship is an exciting project to obtain insight into how stress impacts on the brain at the molecular level. Stress is part of everybody's life. It can become a health problem when a stressful situation is extremely traumatic, when exposure to stress becomes chronic, and in cases where there is an underlying genetic vulnerability. Recently, a genetic vulnerability (a so-called single nucleotide polymorphism (SNP)) for developing major depression and posttraumatic stress disorder was described for the gene Fkbp5 (Klengel et al. Nature Neurosci. 2013). The protein product of this gene, Fkbp51, reduces the sensitivity of the glucocorticoid receptor for binding the stress hormones cortisol or corticosterone, glucocorticoid hormones in man and rodents, respectively. Excessive stimulation of the glucocorticoid receptor is thought to have detrimental effects on the brain; therefore, Fkbp51 plays an important role in keeping glucocorticoid receptor activity within healthy limits. Accordingly, to maintain health and wellbeing appropriate expression of the Fkbp5 gene is of major importance. Presently, however there is only limited information available about how the gene is regulated. Glucocorticoid receptors are known to stimulate expression of the Fkbp5 gene and raise cellular levels of Fkbp51 protein, thus resulting in reduction of receptor sensitivity to respond to stress hormone. Recently, we discovered that glucocorticoid receptors bind to so-called glucocorticoid-response elements within the Fkbp5 gene in the hippocampus after stress *in vivo* (Mifsud & Reul, Proc. Natl. Acad. Sci. USA 2016).

The aim of this project is to elucidate how the activity of the Fkbp5 gene is regulated by glucocorticoid receptors and epigenetic factors like histone modifications and DNA methylation status *in vivo*. You will apply a range of state-of-the-art molecular techniques including chromatin immuno-precipitation (ChIP), quantitative PCR, hnRNA and mRNA analysis and DNA methylation analysis, bioinformatics analysis, radioimmunoassays as well as animal experimentation including surgeries. To obtain deeper insight into the functional properties of particular segments of the Fkbp5 gene *in vitro* you will use the front-line gene editing Crispr/Cas9 technology.

This project will be supervised by Professor Johannes Reul and Dr Oscar Cordero Llana at the University of Bristol and Professor Jonathan Mill at the University of Exeter.