CRUK Cambridge Centre MRes rotation project

Rotation Project Title	**Global epigenetic reprogramming and cancer**
Head of Laboratory (PI) Name	Wolf Reik
Second supervisor if applicable	Richard Gilbertson
Programme	Early Detection
Supervisor's Email	wolf.reik@babraham.ac.uk
Laboratory Location	Babraham Institute

Project Outline	**Aims and objectives** Global epigenetic reprogramming occurs in the mammalian germline and is linked with naïve pluripotency of stem cells and mitigates against large scale transgenerational epigenetic inheritance. Global reprogramming erases key repressive epigenetic marks such as DNA methylation and H3K9 methylation. Global loss of DNA methylation is also a hallmark of pretty much all cancer types, but neither how it arises nor its functional impact on cancer cells is known. We have recently discovered a unified mechanism of global demethylation which operates in early embryos, primordial germ cells, naïve pluripotent stem cells, and iPS cells. This is based on downregulation of UHRF1, a multifunctional epigenetic integrator which is critical for the inheritance of DNA methylation patterns at mitosis. Downregulation of UHRF1 by transcriptional silencing, diminished protein stability, or exclusion from the nucleus (depending on the biological system) orchestrates global demethylation. Hence a molecular understanding of the mechanisms by which UHRF1 is downregulated will provide an opportunity to experimentally manipulate global reprogramming.
Experimental plan	This student project will investigate the molecular mechanisms of UHRF1 regulation at the transcriptional and posttranslational level. Having identified critical mechanisms by which UHRF1 is downregulated, you will design mutant alleles of UHRF1 in cell systems and *in vivo* in mice with the aim of abolishing its silencing. You will then study the effects of these UHRF1 variants on global demethylation, potency of embryonic stem cells, and transgenerational epigenetic inheritance. In somatic cells, UHRF1 downregulation may induce global demethylation together with senescence or apoptosis, thereby acting as an early cancer sensor system. You will also be designing new alleles of UHRF1 in mice to test the idea that UHRF1 destabilisation is an early cancer detection and protection system. Altered epigenetic states will be monitored by single cell epigenome sequencing and potentially *in vivo* with novel live imaging probes we are developing. The rotation project (the above plan describes the full PhD project) specifically deals with introducing UHRF1 mutations that abolish its silencing into ES cells and from these you will derive *in vitro* primordial germ cell-like cells in which global reprogramming (or its absence) can be assessed.

Main Techniques	• protein biochemistry • ES cell culture • CRISPR/Cas mutagenesis • gene targeting in mice • single cell epigenomics • bioinformatics • *in vivo* imaging.
Key References	**Branco et al** *2016 Dev Cell* **Angermueller et al** *2016 Nature Methods* **von Meyenn et al** *2016 Mol Cell* **von Meyenn et al** *2016 Dev Cell*