Unravelling how Histone Deacetylases (HDACs) regulate progenitor cell differentiation

Supervisory team:
Main supervisor: Dr Michael Taylor (Cardiff University)
Second supervisor: Dr Walter Dewitte (Cardiff University)

Collaborators: Prof Paola Borri (Cardiff University), Dr Simon Scofield (Cardiff University)

Host institution: Cardiff University

Project description:

Background: Understanding cell differentiation programs is essential for many aspects of pure and applied Biology, including directing stem cells to make specific cell-types for biomedical applications. The family of histone deacetylases (HDACs) has crucial roles in cell differentiation, largely through effects on gene transcription. HDACs modify histones and hence modulate chromatin structure, but also target other proteins, including transcription factors. HDACs are also implicated in many diseases and attract much interest as drug targets. HDACs have been shown to be transcriptional repressors, but most such studies were in cell culture and there remains much to learn about these important regulators during cell differentiation programs in vivo. This project will fill this gap by focussing on the Class IIa HDACs, which have more restricted expression patterns and are associated with specific aspects of cell differentiation.

Project outline: You will analyse HDAC function in vivo using the full range of genetic techniques available in the classic model organism, Drosophila melanogaster, complemented by other molecular/cell techniques (Y2H, FLIM, cell culture). Drosophila has significant advantages in the sophistication and speed of available genetic techniques, and has an impressive history of informing human biology. An added advantage for rapid progress is having just one Class IIa HDAC (HDAC4) in contrast to the four in mammals. The project will focus on the muscle differentiation program. In mammalian cell culture Class IIa HDACs bind to and inhibit the Mef2 transcription factor, thus inhibiting muscle differentiation. During Drosophila development we have already found that HDAC4 inhibits muscle differentiation and genetically interacts with Mef2. Thus, this in vivo system is set up for a functional analysis of HDAC4.

Experimental Approach: You will have the opportunity to use diverse genetics and molecular cell biology techniques. Using available genetic tools, you will determine the phenotype of HDAC4 loss-of-function and over-expression of HDAC4. You will then use CRISPR/Cas9 gene editing to make an engineered HDAC4 null allele containing a “landing site” ready to accept any gene sequence. You will use this to fluorescently tag HDAC4: first to determine in which cells HDAC4 is expressed and to analyse nucleo-cytoplasmic shuttling; second, to apply the sophisticated, recently developed FLIM-FRET optical technique to explore for the first time in vivo interactions of HDAC4 with other proteins. You will also undertake an in vivo structure/function analysis of HDAC4, including using the same gene editing approach, to determine whether specific protein domains are required for specific functions.