Exploring genotype-phenotype correlations in Sox10 mutations

Supervisory team:
Main supervisor: Prof Robert Kelsh (University of Bath)
Second supervisor: Dr Beck Richardson (University of Bristol)
Dr Keith Vance (University of Bath)

Collaborators: Prof Nadege Bondurand (Institut Imagine, France), Prof Veronique Pingault (Institut Imagine, France)

Host institution: University of Bath

Project description:
What genetic variants cause what phenotypic changes? The SOX proteins form a family of transcription factors with key functions in embryonic development and cellular homeostasis, with these functions highly conserved across the vertebrates. Due to their complex roles in multiple cell-types, SOX mutant phenotypes are often diverse, even for a single gene. Whilst much is known of their protein structure and DNA binding characteristics, we are still ignorant of the relationship between their structure and their cellular functions, with the genotype-phenotype correlation remaining obscure even in well-studied examples, such as SOX10 (Pingault et al., 2022, J. Med. Genet. 59, 105-114). SOX10 is expressed widely in the neural crest, an embryonic population of highly multipotent progenitors, and SOX10 mutations may result in pigment, hearing, olfactory and neural phenotypes, individually or in various combinations. The variation in phenotypes may reflect subtle impacts of the mutations (e.g. gain of function), or other factors (e.g. presence of modifier loci). We have shown the conserved role for Sox10 in zebrafish and mammals (e.g. Kelsh, 2006, Bioessays 28, 788-798). Furthermore, in the course of a current DTP studentship supervised by same team, we have established a method for generating CRISPR/Cas9-induced precise genomic modifications, using chemical modulation to enhance Homology-Directed Repair (Zhang et al., 2018, J. Biol. Chem. 293, 6611-6622; Aksoy et al., 2019, Communications Biology, 2, 198). This, combined with the ready accessibility and phenotypic characterisation of zebrafish embryos (e.g. Alhashem et al., 2022, eLife 11:e73550; Camargo-Sosa et al., 2019, PLoS Genetics 15, e1007941), makes the zebrafish an ideal system to explore the precise impacts of specific mutational changes in a relatively constrained genetic background.

To assess the genotype-phenotype discrepancy, the successful applicant will create an extensive series of zebrafish sox10 alleles, selected from amongst the human variants linked to disease phenotypes; mutations will be maintained as heterozygotes, since most are likely to be homozygous lethal. Dominant and recessive phenotypes will then be characterised quantitatively for all the pigment and neural cell-types. This will enable us to disentangle the currently obscure, but fundamental, structure-function relationships for this vital developmental regulatory factor.

This interdisciplinary project will give an opportunity to develop numerous specific skillsets, including in zebrafish genetics and husbandry, phenotypic analysis including by in situ hybridisation and immunofluorescence, confocal and light sheet microscopy, molecular biology, and bioinformatics. In addition, the student will benefit from collaborative interaction with mouse and human geneticists at the Institut Imagine (Paris).

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.