Enhancing MITF transcription factor activity using protein engineering to investigate melanocyte development and improve melanoma treatment

Supervisory team:
Main supervisor: Dr Keith Vance (University of Bath)
Second supervisor: Prof Jody Mason (University of Bath)
Prof Robert Kelsh (University of Bath), Prof Karim Malik (University of Bristol)

Collaborators: Prof Colin Goding (University of Oxford)

Host institution: University of Bath

Project description:
MITF is a central regulator of melanocyte development and melanoma biology. MITF is a transcription factor that binds to specific DNA sequences to control the expression of genes involved in a wide range of biological processes such as cell survival, growth, differentiation, migration and invasion. Whilst MITF is an important therapeutic target in melanoma it was originally thought to be undruggable as it did not appear to contain a binding pocket that could interact with small molecules. Recent studies however have demonstrated that the region of MITF that drives dimerization and DNA binding can be modulated to regulate its function and have revealed the potential of new approaches for the development of MITF targeting drugs.

We have thus developed a multi-disciplinary project using a novel peptide library screening platform in combination with human cell culture and zebrafish models of melanocyte development and melanoma to develop peptide based regulators of MITF function. We will identify MITF-activating peptides that specifically increase MITF DNA-binding activity and function. The gene regulatory activity and mode of action of peptide hits will be defined in human melanoma cells that have acquired resistance to the anti-melanoma drug vemurafenib. These cells feature down-regulated MITF expression, a key driver of the disease, are de-differentiated and have stem-cell like properties. We will measure cell growth, migration, and differentiation upon peptide expression and determine changes in MITF DNA binding and regulation of targets gene involved in these processes. We will then determine the mode of action of activating peptides in vivo in the control of MITF-dependent development of neural crest derived melanocytes in zebrafish. Neural crest cells are a population of multipotent stem cells that give rise to a number of different cell types including pigment producing melanocytes and mutations within these cells can give rise to melanoma.

This work will generate important insights into the mode of action of MITF in the regulation of genes controlling melanocyte development and melanoma. It is also an essential first step in the design of MITF-targeting strategies needed to overcome the massive problem of drug resistance in melanoma treatment.

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.