

Investigating the role of the oncofetal splice factor MBNL3 in metastasis

Project ID: 3542

Supervisory team

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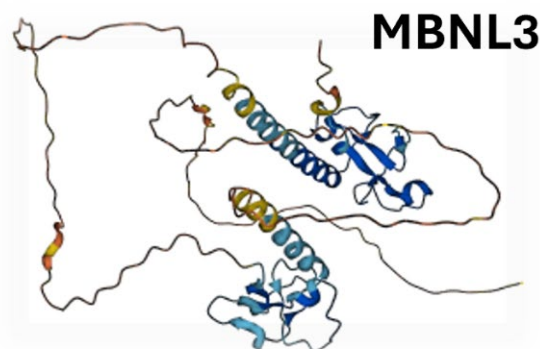
Registered institution: University of the West of England (UWE)

Host institutions: University of the West of England (UWE)/University of Exeter

Project description: Alternative splicing is a key mechanism of gene regulation, affecting over 94% of human protein-coding genes. It plays a crucial role in normal development and in disease including cancer. It is vital to understand how alternative splicing is regulated by proteins called 'splice factors', how regulation of splicing is critical in development and goes wrong in disease, and how it can be manipulated for therapeutic benefit. Our laboratories have focused on the splice factor MBNL3, a member of the so-called "muscleblind" family famously known for their involvement in myotonic dystrophy. There are three human MBNLs (1-3) each with unique functions. Among them, MBNL3 is described as an "oncofetal" splice factor, meaning that while it is highly expressed in development, it can be hijacked by cancer cells to promote their proliferation and migration. Building on a previously completed Industrial Partnership PhD project at UWE, we have obtained compelling evidence that MBNL3 promotes the migratory phenotype of cancer cells. To this end we have worked on a key RNA target of MBNL3, the long noncoding RNA lncRNA PXNAS1. We show that MBNL3 regulates the alternative splicing of PXNAS1 in multiple ways (intron retention and a cassette exon). The PXNAS1 splice isoforms in turn modulate the expression of Paxillin (PXN), a focal adhesion adaptor protein that plays an important role in cell migration, invasion, and metastasis. We wish to advance this research project by dissecting in detail the molecular mechanisms through which MBNL3 plays a role in migration/metastasis, providing the PhD student excellent training in cutting-edge techniques. The aims will include performing in-depth analyses to determine how MBNL3 regulates the alternative splicing of its targets (including PXNAS1). This will include bioinformatics, RNA binding assays, minigene splicing assays, and RIP (immunoprecipitation assays). Continued on next page.....

PhD SWBio DTP

ROLE OF THE SPLICE FACTOR MBNL3 IN METASTASIS



- ✓ Investigate the function of MBNL3 in cancer cell metastasis
- ✓ Identify downstream targets of MBNL3
- ✓ Characterise MBNL3 splicing targets
- ✓ Explore the therapeutic potential of MBNL3 modulation

In parallel in vivo experiments will be performed to study the role of MBNL3 in migration/metastasis, exploiting a chicken embryo model system (chorioallantoic membrane, CAM), a widely used, versatile in vivo model for studying multiple steps of tumour progression and metastasis. The project will be supervised by a highly experienced supervisory team with decades of experience in RNA biology, alternative splicing, developmental and cancer biology, combining complementary expertise with a world-wide network of contacts and collaborators in the field. The project fits with the BBSRC key challenge area “Lifelong health” in the context of understanding fundamental biological mechanisms of development and disease; including fundamental mechanisms of RNA regulation, cellular behaviour and development.

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.