Precision Imaging of Hypoxia-Induced Cellular mRNAs with an Advanced Cellular Penetrating and Near Infrared Emitting Molecular Probes Toolkit

Supervisory team:
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Host institution: University of Bath

Project description:
Hypoxia impacts tissue regeneration by activating wound healing, inflammation and angiogenesis pathways and is a poor prognostic factor in cancer, as well as other non-communicative diseases, due to resistance mechanisms initiated by cells in a low oxygen environment. Improved imaging of hypoxic tissues will enhance tumour detection and diagnosis, enabling early intervention against recurrence and metastasis, and aid in developing therapeutic strategies that promote healthy healing, such as in diabetic or fibrotic wounds that have compromised vascular function.

The aim of this highly interdisciplinary project is to create multimodal fluorescent biosensor probes that target hypoxia-specific mRNAs in living cells for use in research and diagnostic applications. The student will gain training in cutting-edge chemistry, tissue culture, microscopy and data science methods. The novel probes will be based on Peptide Nucleic Acid (PNA) constructs conjugated to cell entry peptides and fluorescent tags. PNAs are synthetic DNA/RNA mimics with nucleobases connected via a peptide backbone that bind extremely tightly to DNA/RNA and are not degraded by proteases or nucleases, allowing high-sensitivity detection of mRNA in cells. These biosensors will therefore provide multimodal readouts of hypoxia-induced gene expression, giving enhanced diagnostic and prognostic information. The multi-component probes will be assembled from peptide, nucleic acid, and fluorophore building blocks with established chemistries.

The major challenges for this type of probe are delivery into the cytoplasm, as opposed to endosomes, and specificity of binding to targets. To optimise biosensor efficacy, the student will use automated confocal and super-resolution microscopy to systematically screen nucleotide and peptide sequences for cellular uptake, subcellular localisation, and target specificity under normoxic and hypoxic conditions. Advanced computer vision and machine learning methods will be used to perform automated image analysis and determine the best combinations of probe properties. Optimisation and probe refinement will be carried out by advanced assays and testing in 2D and 3D cell culture models.

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.