Development of peptide-based delivery systems to improve biotherapeutic efficacy within tumour models

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Project description:
The last three decades has witnessed the spending of billions of pounds on attempts to develop peptides and oligonucleotides into clinically effective therapeutics. Despite showing huge potential as the next generation of 'smart therapeutics', very few of these "biopharmaceuticals" (BPs) have developed into effective formulations available to clinicians to treat diseases. In part this is due to our inability to effectively deliver them into cells to their intracellular targets; this remains one of the greatest challenges associated with their translation to the clinic. Due to their high molecular weight and size, and most often high hydrophilicity, BPs are unable to traverse biological barriers posed by the plasma membrane and internal membranes. Thus the fraction reaching the target in the cytosol or nucleus is too low to mediate a biological effect. There is therefore a huge unmet need for further development and characterisation of tailored drug delivery systems with improved specificity, ensuring BPs are delivered to mediate biological effects.

Analysing effective intracellular delivery, however, has its own limitations. In order to develop suitable drug delivery systems there is a need for highly specific and sensitive reporter assays to detect functional delivery. As BPs structures are intrinsically coupled with their binding to targets, simply delivering them to cells is not enough; functional delivery to their intracellular site of action must be ensured for the system to remain viable. The use of light-emitting fluorescent and bioluminescent reporter assays for analysis of BP delivery, in vitro and in vivo is a particular powerful technology, using microscopy for the detection of both functional delivery and analysis of intracellular trafficking associated with the delivery systems of interest. Furthermore, development of these reporter assays allows visualization and tracking of delivery in real time, improving our understanding of the mechanisms by which delivery systems are internalised and processed by cells.

Utilising molecular biology, and state of the art confocal and lightsheet microscopy, this PhD project will build upon previous research in our laboratory to develop a reporter system that is capable of detecting the successful delivery of biotherapeutics in 2D and 3D model systems, producing a much needed tool to develop and test the next generation of BP delivery systems so urgently required to deliver therapeutics to their site of action.