Cell Binding and Tailored Intracellular Delivery of Macromolecular Therapeutics.

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Targeting a disease process inside a cell with a macromolecular therapeutic still represents a major challenge. Investment in this approach isjustified when one considers the number individual intracellular targets that are now availableto us as we continue to understand disease processes at the gene and protein level. This is true for many high burden diseases including cancer and inherited genetic defects such as cystic fibrosis.

The concept of targeting diseases throughbiopharmaceutical entities introduced the design and characterisation of a wide range of non-viral drug delivery vectors including those that are based on peptides, proteins, polymers and lipid. These are, most often, complexed with membrane impermeable therapeutics to deliver them, following administration, to disease sites such as tumours. The vector is then required to promote cell entry of the therapeutic and allow it to gain access to distinct intracellular locations such as the cytosol and nucleus.

Endocytosis is a process encompassing different mechanisms and pathwaysof cellular uptake and then endosomal traffic to different cell destinations. It is highly complex and for drug delivery these pathways offer significant opportunities for internalisation and cellular targeting of therapeutic macromolecules.

Our research is focused on studying endocytosis and specifically on designing methods to analyse individual endocytic pathways to characterise how drug delivery vectors and associated therapeutics gain access to cells. As vectors we have paid particular attention to cell penetrating peptides and have studied their capacity to not only interact with and enter cells, but also how they and their cargo reach the cytosol.

In this lecture I will describe work we have performed that focuses on design and characterization of methods to study endocytosis of drug delivery vectors such as cell penetrating peptides, various types of nanoparticles and more recently ligands and antibody conjugates targeting plasma membrane receptors. Our involvement in a recent €30M FP7 Innovative Medicine Initiative (IMI) consortium (COMPACT www.compact-research.org/) will also be discussed. This represents a public-private collaboration between 14 European academic institutes, 2 biotechnology companies and 7 large pharmaceutical companies with the goal to improve the cellular delivery of biopharmaceuticals across major biological barriers of the intestine, lung, blood brain barrier and skin.