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Activating endocytosis for enhancing cellular delivery and modifying intracellular targeting of cancer therapeutics

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Targeting disease processes inside cells with biopharmaceuticals represents a major challenge, not least in overcoming biological barriers posed by the plasma membrane and endolysosomal organelles. Investment in this approach is justified when one considers the number individual intracellular targets now available to us as we continue to understand disease processes at the gene, protein and signaling level. This is true for many high-burden diseases such as cancer, infectious diseases and inherited genetic defects such as cystic fibrosis. Our research at Cardiff University is focused on studying endocytosis and specifically on designing methods to analyze individual endocytic pathways to characterize how drug delivery vectors (DDVs) and associated cargo interact with cells, endocytose and traffic on different endocytic pathways. In this lecture, I will summarise our collaborative work focusing on technologies and in vitro models, we have developed and exploited to study cell binding and endocytosis of DDVs including cell penetrating peptides, exosomes, ligand decorated polymer nanoparticles, lipid nanoparticles (LNPs) and antibodies targeting plasma membrane receptors on cancer cells. I will highlight how we recently demonstrated that internalization of receptors and associated ligands, can be significantly enhanced through manipulating ligand-receptor association and how normal endocytic routes can be modified to reach a desired intracellular location. This could act to decrease the overall delivery performance of ligand targeting nanoparticles or could be exploited to strategically deliver DDVs and cargo to defined endocytic organelles, resulting in higher therapeutic performance. Our work on endolysosomal profiling of different cancer cell lines and its influence on LNPs-mRNA transfection efficiency will also be discussed.

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