CR-UK5

Amphiphilic hypercoiling polymer mediated delivery of novel cytotoxics

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We have shown a viral protein, Apoptin, to have enhanced cytoxicity against a variety of murine and human cancer cells, compared to their normal, untransformed counterparts. In an independent project we have developed strategies for inhibition of target molecules by thioaptamers. Currently we are examining the in vivo activity of liposome encapsulated thioaptamers that are able to target and inhibit EGFR and NF-κB. A major obstacle to the exploitation of the therapeutic potential of Apoptin and thioaptamers is the current inefficiency in both the delivery methods.

Our chemical engineering collaborators have developed synthetic polymers, referred to as "amphiphilic hypercoiling polymers – AHP" that mimic the molecular action of viral hemagglutinins and are suitable for the transport of various macro- and micro-molecules not only to the cytoplasm, but also the nucleus of eukaryotic cells. The efficient AHP mediated transport of several micro/macromolecular structures to eukaryotic tumour cell cytoplasm and nucleus has recently been demonstrated. Furthermore, doxorubicin-conjugated AHP can evade P-glycoprotein efflux in multi-drug resistant tumour cells.

The proposed collaboration will combine the chemical, structural biology, *in vivo* imaging, cancer biology and gene therapy, to develop ligand/antibody conjugated AHP for tumour targeted delivery of therapeutic agents. These studies will in the first instance focus on the conjugation of Apoptin and thioaptamers to AHP, using already developed methodologies. The labelled Apoptin and NF-κB thioaptamers will be tested for cell entry, subcellular localization and biological activity. These studies will use time lapse confocal microscopy, quantification of apoptosis and NF-κB responsive reporter assays.