Some Biological Applications of a Synthetic Cell Transduction Agent

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The presentation will address the application of a synthetic membrane lytic biopolymer for the delivery of functional agents across the cell membrane into mammalian cells. The delivery of two chemically different agents are considered.

The first application involves the use of small interfering RNAs (siRNAs) to down-regulate the expression of a disease-associated protein. One of the main barriers to the clinical use of siRNAs is the inability to efficiently deliver siRNAs to the cytoplasm of target cells. The entrapment and degradation of siRNAs within the endolysosomal pathway has been especially problematic. We report here the use of a lipid membrane disruptive anionic polymer, phenylalanine derivatized poly(L-lysine iso-phthalamide) (PP-75), that facilitates the release of endocytosed products into the cytoplasm. Endosomal imaging reveals that PP-75 safely permeabilizes the endosomes of live cells by causing pore formation. The covalent attachment of PP-75 to siRNAs using disulfide linkages generates conjugates that effectively traffic siRNAs to the cytoplasm of target cells. As proof of principle, a PP-75-siRNA conjugate directed against the chemoresistance protein stathmin silences its expression both *in vitro* and *in vivo*.

In the second application the amphipathic biopolymer PP-50 is shown to facilitate efficient delivery of trehalose, a bioprotectant normally impermeable to the phospholipid bilayer, into ovine and human erythrocytes (red blood cells). Biopolymer-mediated trehalose uptake was shown to yield improvements in erythrocyte cryosurvival: ovine erythrocyte cryosurvival increased by up to 20 ± 6 % and human erythrocyte cryosurvival increased by up to 15 ± 5 %. This was the first time intracellular trehalose had been harnessed to improve cryoprotection in erythrocytes.