

**YI -P 382 Tuning a gene delivery vector: the role of peptide sequence and peptide branching in delivering of DNA and siRNA to the cytoplasm**

K.Welser<sup>1</sup>, F. Campbell<sup>1</sup>, A. Mohammadi<sup>1</sup>, L. Kudsiova<sup>2</sup>, N.L. Dawson<sup>1</sup>, M.J. Lawrence<sup>2</sup>, H.C. Hailes<sup>1</sup> and A.B. Tabor<sup>1</sup>

<sup>1</sup>*Department of Chemistry, University College London,* <sup>2</sup>*Institute of Pharmaceutical Science, King's College London*

The success of non-viral gene therapy is fundamentally driven by the design and architecture of the gene vector. Fine tuning of the delivery vector is essential to ensure efficient package, transport and controlled release of the genetic material. Our work is focused on the design of a three component delivery system comprising of lipid (L) and peptide (P) that self- assembly on mixing with either DNA (D) or siRNA (R). In this work, we investigated the role of the peptide component in nanocomplexes for both DNA and siRNA delivery. To maximize packaging capacity, improve targeting and to promote intracellular release, we have synthesized and tested a series of novel cleavable polycationic peptides differing in their composition and degree of branching. Furthermore, we have functionalized the peptides for magnetic resonance imaging, using the contrast agent gadolinium. To prepare the nanocomplexes, the peptide and the plasmid DNA/siRNA were co-formulated with a 1:1 mixture of a cationic lipid (DOTMA) and a neutral helper lipid (DOPE). Biophysical characterization of the nanocomplexes revealed the vectors are small in size (less than 100 nm in diameter), stable and capable of both efficiently condensing and protecting DNA and siRNA from enzymatic degradation. *In vitro* experiments showed that both toxicity and transfection/knock-down efficiencies are strongly influenced by the composition of the peptide and their degree of branching. Our results clearly show how important it is to fine tune the peptide component in a nanocomplex to achieve an optimal delivery vector for both DNA and siRNA.