Histidylated Poly(lysine) dendrimers for siRNA delivery

Nour Allahham, Asma Buanz, Steve Brocchini, Gareth R. Williams

Department of Pharmaceutics, UCL School of Pharmacy, WC1N 1AX, UK

Background: siRNA has gained increasing interest in recent years because of its great promise in the field of gene silencing. siRNA works via the RNA interference (RNAi) mechanism, where it can potentially target and silence any gene. Extrahepatic delivery, toxicity and endosomal escape remain major challenges for the wider clinical utility of siRNA, however. Highly branched lysine polymers have been widely investigated as biocompatible carriers for nucleic acid delivery including siRNA, but they raise concerns of toxicity and low transfection efficiency. The addition of histidine could reduce toxicity, enhance endosomal escape, and improve transfection. In this work, we investigate the synthesis of lysine and histidine-functionalised lysine dendrimers as biodegradable and biocompatible carriers for the safe and efficient delivery of siRNA.

Methods: Lysine dendrimers up to generation 3 (G3) and histidine-capped G3 lysine dendrimers were synthesised following divergent approach coupling reactions in solution. Dendrimer structure was confirmed with ^{1}H NMR. Polyplex formation was confirmed with gel electrophoresis and particle size and z-potential were measured by dynamic light scattering.

Results: NMR analysis confirmed the formation of lysine and histidine-capped lysine dendrimers. Both formulations could fully complex siRNA at different amine to phosphate (N:P) ratios. Histidylated lysine dendrimers could form much smaller particles compared to lysine dendrimers but show higher polydispersity. Polyplexes formed with lysine dendrimers, tend to aggregate forming larger nanoplexes.

Conclusions: This preliminary study shows that histidine-capped lysine dendrimers can efficiently condense siRNA into cationic nanoparticles and form smaller polyplexes than lysine dendrimers alone. Future work will investigate the impact of different histidine ratios on the complexation efficiency of these dendrimers and assess their cytotoxicity and transfection efficiency.