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The combination of pH-responsive peptide and cationic liposomes can improve siRNA transfection efficiency in cancer cells

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Statement of the Problem: The presence of small interfering RNA (siRNA) in a cell leads to silencing of protein expression, offering the potential of a powerful therapeutic option for treatment of many conventionally intractable diseases. Due to the negative charge and sensitivity against RNase, siRNA has a short half-life in the blood and struggles to penetrate within the target cells. Successful development of siRNA therapies depends on the ability for it to be efficiently delivered inside the target cells efficiently while avoiding enzymatic degradation and aggregation.

Methodology & Theoretical Orientation: We present the design and optimization of a cationic liposomal/pH responsive cationic peptide based nano-carrier for siRNA delivery. The major used components in the formulation are; DODAG (1 N',N'-dioctadecyl-N-4,8-diaza-10aminodecanoylglycine amide), a cationic lipid which was designed to be a structural chimera involving the N(1)-cholesteryloxycarbonyl-3-7-diazanonane-1,9-diamine (CDAN) polar head group and the dialkylglycine amide moiety of dioctadecylamido glycylspermine (DOGS) to improve positively charged lipid interaction with siRNA and LAH4-L1 is a 26-amino acid, histidine rich helical peptide. It is a membrane-active peptide that displays increased affinity towards anionic lipids and possesses DNA delivery capabilities. Liposomes (20% DODAG, DOPC/cholesterol/DSPE-PEG2000)/siRNA, LAH4-L1/siRNA and their combination with siRNA have been investigated as delivery systems. Their physicochemical characteristics such as size, zeta potential, siRNA retention, release behaviour and aggregation behaviour of formulations were tested. In vitro cell uptake and luciferase knock-down studies were also tested in MDA-MB231 and A549 cells. Complexes were tested in vivo for bio-distribution.

Findings: The hydrodynamic diameter and zeta potential of the particles was characterized. Size was adjusted to be around 130 nm and zeta potential was slightly positive. All complexes associated with siRNA have more than 80% complexation efficiency. Lipoplexes showed better encapsulation but were less stable as leakage was observed after co-incubation in serum. Improved cell uptake was seen with ternary complex in comparison with liposomal and Peptide siRNA complexes (siRNA cells uptake was increased from 1.4% to 32.9% in some cases). *In vitro* studies suggest improvement in gene silencing with ternary complex even when compared with generic positive control. *In vivo* studies are on-going to understand the pharmacokinetic behaviour of the particles.

Conclusion & Significance: A stable lipid/peptide ternary complex for siRNA delivery with defined physicochemical properties was designed and evaluated and shown to be a promising delivery system for siRNA for both *in vitro* and *in vivo* applications. Current and future work is focused, *in vitro*, on the improvement of cell targeting and *in vivo* on studying the PK/PD properties of the new system.

Biography

Shahd Abuhelal has obtained her BSc in Pharmacology with first class honor from Al-Quds University, Jerusalem in 2009. She has then worked as a rheumatology biopharmaceuticals Product Specialist at Roche Pharmaceuticals in Palestine and took part in various healthcare projects. She has completed her MSc in Biopharmaceuticals with a distinction at King's College London, United Kingdom, where she is currently pursuing her PhD research. She is investigating the use of nanotechnology to develop smart delivery systems to help overcoming cell barriers for siRNA to aid the treatment of cancer.

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