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CCK-B targeted PEG-poly (L-Lysine) polyplex micelle for the effective delivery of gastrin siRNA to the pancreatic cancer

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis, with late detection, rapid progression, high metastasis rate and poor treatment options culminating in the worst 5-year survival of all gastrointestinal malignancies. Two of the major obstacles in treating PDAC are the inefficient delivery of therapeutic agents to the tumor and profound drug resistance that necessitates development of novel delivery and treatment strategies. One such novel approach is the targeted delivery of gene therapies to PDAC. The cholecystokinin-B (CCK-B) receptor and its ligand gastrin are both overexpressed in PDAC, and contribute to PDAC development and proliferation through an autocrine mechanism. We have developed a novel gastrin targeted polyethylene glycol-*block*-poly (L-Lysine) (PEG-PLL) polyplex (Ga-polyplex), selective for the CCK-B receptor, in order to deliver gastrin siRNA (Figure 1) to PDAC and disrupt proliferation.

Methods: The targeted polyplex micelle (Ga-polyplex) was prepared by complexing gastrin-10 (Ga-10) conjugated PEG-poly (L-lysine) polymer, Ga-PEG-PLL, with gastrin siRNA (Figure1). Ga-polyplex was characterized for hydrodynamic size and stability in serum. The Ga-polyplex was then assessed for targeting ability, gastrin mRNA knockdown, and tumor growth inhibition, both *in vitro* and *in vivo*.

Results: The Ga-polyplex micelle formation was confirmed from its monodisperse hydrodynamic size (~44.3 nm). The Ga-polyplex demonstrated 7h serum stability, selective tumor uptake, superior mRNA knockdown and tumor growth inhibition compared to untargeted and scrambles siRNA polyplex both *in vitro* and in PDAC bearing mice. Furthermore, the targeted gastrin siRNA polyplex micelle prevented metastasis in pancreatic tumor bearing mice.

Conclusion: The CCK-B receptor targeted polyplex micelle was successfully developed, characterized and evaluated for selective delivery of gastrin siRNA to the PDAC. This targeted platform has tremendous potential for oligonucleotide therapeutic delivery to pancreatic cancer.

Biography

Abdullah Mahmud is a Scientist at the nanotechnology characterization laboratory (NCL) of U S Frederick National Laboratory for Cancer Research, Frederick, working on the development of nanotechnology based formulations for cancer therapeutics. He possess 8+ years of experience working in the chemistry-biology interface utilizing chemistry principles to address the formulation and delivery challenges of novel cancer therapeutics including nucleic acid therapeutics, chemotherapeutics and biologics. His areas of expertise include pharmaceutical sciences, formulation and drug delivery, and physicochemical characterization with extensive laboratory experience in functional modification of polymer, liposome and lipid chemistry and analytical method development. He possesses several patents and publications in the field of nanotechnology based drug delivery. Prior to Join NCL, he was a Post-doctoral Researcher with Prof. Dennis Discher at the University of Pennsylvania. He received his PhD in Pharmaceutical Sciences, specializing in polymer based drug delivery from the University of Alberta, Canada.

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