A Novel Nanoparticle that selectively delivers RNAi Oligonucelotides to Tumors, Preventing Side Effects to Tissues (Ramot)

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UNMET NEED

Pancreatic cancer numbers among the most aggressive cancers known today. The overwhelming majority of pancreatic cancer patients pass away within just a year of diagnosis. However, a small minority of patients may live several years with the disease. Our findings pinpoint the inverse correlation between a known oncogene (PLK1) and the expression of an oncosuppressor microRNA (miR-34a) as the reason for extended pancreatic cancer survival. In order to bring RNAi technology to the clinic many hurdles such as stability in serum, targeting the tumor tissue, ability to cross cellular membranes and ability to escape the endosome and reach the mRNA target, have to be overcome.

OUR SOLUTION

We devised a novel nanoparticle that selectively delivers RNAi oligonucleotides to the tumor and prevent side effects in healthy tissues.

OUR PRODUCT

We developed a large globular supramolecular structure based on a polyglutamic acid (PGA) nanocarrier for delivering a synergistic combination of miRNA and siRNA to tumors in vivo. Via the pendent free γ-carboxyl group in each repeating unit of L-glutamic acid of the PGA, we conjugated in parallel ethylenediamine and alkylamine moieties to form a positively-charged amphiphilic nanocarrier (APA). Utilizing electrostatic-based interaction, this cationic nanocarrier forms a polyplex with the negatively-charged oligonucleotide cargo. The nanocarrier facilitates oligonucleotides delivery by improving their stability in the bloodstream and enabling accumulation of the polyplex at the tumor site due to the enhanced permeability and retention (EPR) effect. Two negatively-charged small RNAs were used: miR-34a for miRNA replacement therapy and PLK1-siRNA for oncogene silencing in an orthotopic pancreatic cancer mouse model. We evaluated the formation of therapeutically active nano-scaled polyplexes in pancreatic cancer cells and measured the miRNA mimic-based activity and siRNA silencing achieved in vitro. We further examined the tumor accumulation profile of the nano-polyplexes carrying miRNA-siRNA combination, their safety profile ex vivo and anticancer efficacy in vivo.

Systemically-administered APA-miRNA-siRNA polyplexes to orthotopically-inoculated PDAC-bearing mice showed no toxicity, accumulated at the tumor and resulted in an enhanced antitumor effect compared to the monotherapies. These effects were due to inhibition of MYC oncogene, a common target of both miR-34a and PLK1. Taken together, our findings warrant this unique combined polyplex’s potential as a novel nano-therapeutic for PDAC.

DIFFERENTIATION

Despite the better understanding of pancreatic ductal adenocarcinoma (PDAC) molecular biology in the past decade, almost all targeted therapies have failed to demonstrate efficacy in late phase clinical trials. A promising strategy to treat cancer is knocking-down the expression of specific cancer-promoting genes by RNA interference (RNAi)-based therapeutics such as small interfering RNA (siRNA) and microRNA (miRNA). siRNAs are currently under investigation in several clinical trials for cancer treatment. As opposed to siRNAs, which target a specific gene, miRNAs regulate hundreds of mRNA targets at once, thus making them an even more attractive tool to treat cancer. miRNAs have been shown to be dysregulated in various human cancers including PDAC, and to be involved in cancer pathogenesis and progression. Reversion of tumor suppressor miRNAs expression to normal levels can restore perturbed cellular homeostasis and activate a therapeutic response. Although

miRNAs and siRNAs are usually administered separately when tested in cancer animal models and clinical trials, our approach proves that their combination, aiming at various targets, can significantly improve therapeutic efficacy. This is mainly due to the unique structure of our stable APA-siRNA-miRNA polyplex that allows for the synergistic activity shown selectively in the tumor tissue where both OLNs are released from the APA nanocarrier following cathepsin-enhanced cleavage.

PATENTS

Patent application WO2017056095 titled “Polyaminated polyglutamic acid-containing compounds and uses thereof for delivering oligonucleotides”

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