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A novel miR-198-based mimic as a potential therapeutic against pancreatic ductal adenocarcinoma (PDAC).

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Background: Pancreatic ductal adenocarcinoma (PDAC) remains an extremely aggressive disease for which no effective therapeutic modality has been found. Our group and others have previously found that miR-198 acts as a tumor suppressor in PDAC and several other cancers, through the regulation of a tumorigenic network of factors through a central vantage point. In this study, we investigate the efficacy and safety profile of NM198, (NoPass Mimic-miR-198) a novel therapeutic based on a specially engineered miR-198 mimic condensed with LGA-PEI-based nanoparticles-for systemic delivery. **Methods:** NM198 formulation consists of two technologies: (i) a novel lactic-co-glycolic acid-modified polyethyleneimine (LGA-PEI) polymer that spontaneously forms nanoparticles when it condenses with nucleic acids through electrostatic interaction and (ii) a non-canonical miRNA processing engineered flexible single-stranded RNA scaffolding system that enables administration of RNA interference (RNAi) molecules while minimizing off-target effects. MIA-PaCa2 cell lines were modified to overexpress mesothelin, an important factor involved in PDAC pathogenesis, and a target of miR-198. Nude (CrI: NU-Foxn1nu) CDX and PDX mouse models were used for NM198 efficacy studies, while Wistar Han rats, CD-1 mice, and *ex vivo* human blood were used for NM198 safety studies. **Results:** Orthotopic CDX mice were treated with 2.4 mg/kg of NM198 in a q.o.d dosing regimen for 4 weeks, resulting in a significant > 40% reduction of tumor growth when compared to controls in several different CDX animal models. To address the potential of the observed effect in the context of the heterogenic nature of PDAC, we confirmed our findings in a PDX mouse model, where a marked reduction of 44% in tumor growth was observed when treating with 2.4 mg/kg of NM198 in a q.o.d. dosing regimen for 8 weeks. Finally, to complete NM198 profiling, safety studies were carried out in two rodent models (mice and rats) where no MTD was reached in a dosing range of up to 10 times the effective dose in a q.o.d dosing regimen for 12 weeks, as observed per clinical signs, hematology, blood chemistry, and histopathology analysis. In addition, no hematotoxicity or significant immune responses were observed when exposing human blood from healthy volunteers to NM198. **Conclusions:** Our results indicate that therapeutic administration of a miR-198 mimic formulated for processing through a non-canonical RNAi administration pathway delivered through the use of a non-toxic polymeric nanoparticle formulation prevents off-target effects and unwanted immune responses while successfully delivering therapeutic doses to tumors through intravenous injection. These findings establish the novel therapeutic LGA-PEI polymer as an effective delivery mechanism for RNAi and nucleic acids *in vivo and* NM198 as a potential clinical cancer treatment. Research Sponsor: U.S. National Institutes of Health.