Lipid-Based Codelivery of Doxorubicin and siRNA PD-L1, as a Multi-function Chemo-Immunotherapy, Selective to Pancreatic Cancer via Its MUC1 Overexpression

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Pancreatic cancer is the second leading cause of death, with 90% of occurrences as Pancreatic ductal adenocarcinoma (PDAC). Currently, Doxorubicin (DOX) is the leading treatment for cancers. However, chemotherapy penetration in PDAC is limited due to its dense stromal barrier and destructive tumor-microenvironment (TME). Herein, a pancreas-specific chemoimmunotherapy utilizing DOX, siRNA PD-L1, and MUC1 antibodies was designed for PDAC treatment. To begin, mPEG-b-PHEP were fabricated as the nanoparticle (NP) interior, exhibiting flow-core capability. These were loaded with DOX, which were later coated with an SiO2 layer for stability. Chitosan was then added as a binder for the inclusion of siRNA-PD-L1, to inhibit the PD-L1 pathway, restoring immune activity. Finally, DOPE-Anti-MUC1 was conjugated to the NP-surface, to provide friendly delivery through the TME, with selectivity to the overexpression of PDAC cell-surface MUC1. DOX-siRNA-DOPE dissolution studies in normal extracellular fluid (pH 7.4) versus that of the PDAC-TME (pH 6.8) demonstrate 100% degradation of the DOPE outer layer within five minutes. HPLC analysis was used to subsequently demonstrate DOX-siRNA release, where 95% of a 20ug DOX-load was released within the same 5-minute period following introduction to a simulated PDAC-TME. To simulate DOX-siRNA-DOPE selectivity and function, an MUC1 ELISA-kit was modified using ATR-FTIR analysis, which highlighted adhesion of the NP's DOPE-Anti-MUC1 functionality to PDAC-MUC-1 overexpression. Finally, Giant Unilamellar Vesicles (GUVs) were created with fluorescently-labeled lipid-bilayers that mimic both normal and PDAC cells (with MUC1). DOX-siRNA-DOPE again targeted PDAC GUVs due to Anti-MUC1 selectivity.

Awards Won: