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Targeted Nanoparticles for the Delivery of Novel Bioactive Molecules to Pancreatic Cancer Cells

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Pancreatic cancer (PaCa) is a multifaceted disorder with an extremely poor prognosis. There is an urgent need to identify new and safe drugs as well as to develop novel tumor-targeted controlled release systems for effective treatment of late stage and resistant PaCa. Active targeting via the inclusion of specific ligands on the nanoparticles (NPs) is envisioned to provide a powerful therapeutic strategy (1). In this context, identification of ligand/receptor systems that enable functionalized NPs efficiently target the pancreatic ductal adenocarcinoma (PDAC) holds great promise for the development of novel approaches for treatment of PaCa. Plectin-1 (Plec-1) was recently identified as specific biomarker to detect PDAC at an early stage (2). Moreover, multivalent attachment of small molecular entities can increase specific binding affinity and high specificity for PaCa cells (3). On the other hand, altered cellular bioenergetics and oxidative stress are emerging hallmarks of many types of cancer including pancreatic cancer. Cancer cells are more prone to reactive oxygen species (ROS)-mediated cell death due to their inherent elevated basal oxidative stress as compared to normal cells. In this scenario, we have recently discovered a novel class of potential PaCa therapeutics (i.e., DFCs compounds) that exert their cytotoxic effects by modulating ROS-mediated cell signaling (4).

Herein, we present a study on the design and the development of novel DFC-encapsulated biocompatible polymeric NPs, functionalized with peptides to selectively bind to Plec-1 (PTP), or densely decorated by low molecular weight organic molecules as alternative targeting ligands (2-ABA), and evaluated a) the impact on ligand binding and b) the *in vitro* antiproliferative efficacy against a panel of PaCa cells.

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