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Hypoxia-activated pro-drug for the treatment of pancreatic cancer: Liposomal formulation approach to improve the PK profile of the drug

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Pancreatic tumors pose a unique challenge for drug delivery due to the presence of hypoxic regions. Vinblastine-N-Oxide (CPD100) is a hypoxia-activated prodrug (HAP) that selectively transforms into its parent compound, vinblastine, a potent cytotoxic agent, under hypoxic conditions. The FDA has not approved any HAP agents, which may be attributable to unfavorable patient inclusion criteria in clinical trials. This study evaluates the efficacy of microfluidics-formulated liposomal CPD100 (CPD100Li) in pancreatic adenocarcinoma cells (PDAC). The liposomes possess an approximate size of 100 nm and a polydispersity index of 0.2, exhibiting stability for 18 months when freeze-dried at a concentration of 3.65 mg/mL. CPD100 and CPD100Li are selectively activated in two-dimensional cancer cell lines under low oxygen levels. Notably, CPD100Li demonstrated superior penetration and disruption of the three-dimensional spheroid model compared to CPD100. In patient-derived three-dimensional organoids, CPD100Li revealed more significant cell inhibition in organoids that expressed elevated levels of hypoxia-inducible factor 1 alpha (HIF1A) relative to CPD100. In an orthotopic animal model, the combination of CPD100Li with gemcitabine (the standard of care for PDAC) exhibited significantly enhanced efficacy compared to CPD100Li alone over 90 days, thereby demonstrating the potential of this treatment. In conclusion, the assessment of CPD100Li across multiple cellular models, including two-dimensional and three-dimensional cancer cell lines, patient-derived three-dimensional organoids, and an orthotopic animal model, provides a robust and reliable foundation for its clinical application. The selective activity related to HIF1A levels presents a promising avenue for exploration in personalized treatment of PDAC.

Biography

Adam WG. Alani is an Associate Professor of Pharmaceutics at the College of Pharmacy, Oregon State University. His research interests are primarily centered on designing biocompatible and biodegradable therapeutic polymers tailored for specific disease states. In particular, my investigations have concentrated on nanotherapeutics and hydrogels as advanced drug delivery systems, providing novel and innovative methodologies for addressing disease conditions that are not easily treated with conventional therapeutics. At present, the focus of my laboratory's efforts is directed toward cancer treatment and imaging, enhancing drug delivery to the lymphatic systems, developing long-acting drug delivery systems for the administration of immunosuppressant medications to transplant patients, and exploring the use of natural products in the treatment of cancer as well as the mitigation of cardiac toxicity associated with chemotherapy.

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