Drug Delivery Systems in Oncology: From Polymeric Implants to Nanomedicine Approaches

A Dissertation Presented

By

Shicheng Yang

To

The Department of Chemical Engineering

in partial fulfillment of the requirements
for the degree of

Doctor of Philosophy

in the field of

Chemical Engineering

Northeastern University
Boston, Massachusetts

Nov 2023

ABSTRACT

Molecular inhibitors, including PARP inhibitor talazoparib, CDK inhibitor dinaciclib, and docetaxel, are critical in precision cancer therapy, offering novel therapeutic options for a range of cancers. While demonstrating potent activity as monotherapy or in combination in both preclinical and clinical settings, challenges such as drug resistance and off-target toxicity persist with these small molecule drugs. To mitigate these issues, innovative formulation strategies using implants or nanoparticles have been explored. These formulations are designed to alter drug uptake pathways, resist the emergence of drug resistance, and minimize direct contact with healthy tissues, thereby reducing toxicity. This thesis encompasses several nanotechnology approaches in formulating chemotherapy agents and their application across various cancers, including breast, ovarian, pancreatic, lung, and prostate.

In the context of ovarian cancer, known for its high mortality rate within the realm of female reproductive system cancers, more than 15% of cases involve defective BRCA-mediated homologous recombination repair pathways. Talazoparib, a PARP inhibitor, has been hindered in its clinical application due to severe systemic side effects. The development of a novel TLZ-loaded PLGA implant (InCeT-TLZ) is reported, designed for sustained release over 25 days directly into the peritoneal cavity, targeting BRCA-mutated metastatic ovarian cancer. Results from in vivo experiments indicated a doubling of survival in the InCeT-TLZ treated group compared to controls, with no significant toxicity observed in surrounding peritoneal organs. This suggests that localized and sustained delivery of Talazoparib can enhance therapeutic efficacy without significant toxicity. Additionally, the potential of combining CKD inhibitor and PI3K inhibitor with InCeT-TLZ to counteract acquired PARPi resistance was demonstrated in vitro, indicating a promising approach for enhanced ovarian cancer treatment.

While the biodegradable PLGA implants showed potency, the conventional solvent-based fabrication methods used to synthesize these implants, however, the use of toxic organic solvent and its safety issue pose difficulties for translation to clinical use. To address these challenges, a scalable, solvent-free hot-melt extrusion process was introduced for producing PLGA implants

with docetaxel. This process ensures uniform dispersion of clinically relevant concentrations of the drug without requiring organic solvents. Results showed the bioactivity of incapsulated docetaxel was maintained during fabrication and controlled degradation, enhancing tumor growth inhibition capabilities both in vitro and in vivo. The implants, when used intratumorally, act as both radiosensitizers and continuous chemotherapy sources, suitable for scale-up in compliance with Good Manufacturing Practices (GMP).

Furthermore, the combination of talazoparib and dinaciclib has been studied to overcome PARPi resistance in tumors. The short blood circulation time of dinaciclib and the high toxicity of combination therapies pose significant challenges. Nanomedicine formulations have been developed to address these issues, creating a nano-cocktail of talazoparib (nTLZ) and dinaciclib (nDCB) to enhance therapeutic efficacy at lower doses. The study showed that these nanoformulations effectively infiltrate tumor cells, with synergistic effects observed in both BRCA-mutant and BRCA wild-type cancer strains, particularly sensitizing BRCA wild-type cells to PARPi therapy. This approach demonstrates the potential of nanoformulations in broadening the applicability and enhancing the efficacy of combination cancer therapies.