RADIOLUMINESCENT NANOPARTICLES FOR MULTIMODAL CANCER TREATMENT

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ABSTRACT

Conventional clinical therapies for head and neck squamous cell carcinoma (HNSCC) include surgery, chemotherapy (CT), and radiotherapy (RT). For locally advanced HNSCC, the CT-RT combination ("chemoradiation") has been shown to be more effective than CT or RT alone, and it is currently the standard of care. Unfortunately, CT-RT involves severe side effects which negatively impact the quality of life of patients. Intratumoral (IT) CT-based CT-RT has the potential to overcome this limitation of the conventional, systemic CT-based CT-RT. A novel radiation-controlled drug release (RCDR) formulation (that is, paclitaxel (PTX) and $CaWO_4$ (CWO) nanoparticles (NPs) co-loaded within a capsule formed by poly(ethylene glycol)-poly (lactic acid) (PEG-PLA), called hereafter as "PEG-PLA/CWO/PTX" NPs) has been developed that can help realize the benefits of IT CT-RT. In response to low-dose X-ray irradiation, PEG-PLA/CWO/PTX NPs release PTX. This radiation-controlled PTX release mechanism provides a way of maximizing the bioavailability of the drug within the tumor, while minimizing the exposure of normal tissues to the drug, and therefore enables to significantly improve the therapeutic margin of the PTX-based CT-RT.

A focus of this research was to investigate the effect of the stereochemical structure of PTX on the X-ray-triggered PTX release kinetics and eventually the efficacy of the PEG-PLA/CWO/PTX NP formulation in the clinical CT-RT setting. Stereochemical differences between PTX products from two different pharmaceutical manufacturers were characterized by multiple spectroscopic techniques, and their effects on PTX release kinetics were investigated. We found that the stereochemistry of PTX significantly impacts both the *in vitro* and *in vivo* pharmacological (drug

release/pharmacokinetics, biodistribution, efficacy) properties of the PEG-PLA/CWO/PTX NP formulation. We also found that the effect of PTX stereochemistry on its release kinetics is manifested through its influence on the water solubility of the PTX. This study represents a first-ever demonstration of the effect of PTX stereochemistry on its controlled release properties.

Attempts have also been made to optimize the PEG-PLA/CWO/PTX NP formulation processes and radiation-triggered release characteristics of the NPs by systematic investigations. Several different pharmaceutical manufacturing processes (including solvent exchange, emulsion evaporation, etc.) have been explored toward formulation scale-up and improvements of drug encapsulation efficiency/yield and reproducibility. The effects of polymer molecular weight and fractionated X-ray radiation dose on drug release kinetics were investigated to demonstrate the feasibility of tailoring the kinetics of the radiation-triggered drug release process. The mechanisms by which these factors affect the drug release kinetics were also elucidated. An initial effort was also made to explore whether the same radiation-controlled release platform can be used for other relatively less hydrophobic drugs (such as β-lapachone). Finally, a suggestion is made regarding how the efficacy of IT CT-RT could be improved by mechanically enhancing homogeneity of PEG-PLA/CWO/PTX NP distribution within the tumor tissue.

Overall, the research in this thesis demonstrates the potential for clinical translation of the RCDR technology developed in our laboratory. On the other hand, studies have also identified issues that need to be addressed in order to achieve the goal of translating this technology into clinical trials.