

Layer-by-Layer Nanoparticles for Targeted Delivery and Treatment of Ovarian Cancer

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Abstract

Ovarian cancer remains the most lethal gynecologic malignancy in the United States. Lack of early detection methods often leads to a late diagnosis and reduced survival outcomes for patients. The overwhelming majority of ovarian cancer patients are diagnosed with late stage high grade serous ovarian cancer (HGSOC), which is highly metastatic. While many patients initially respond to treatment with debulking surgery and adjuvant chemotherapy, most will have residual disease and relapse. Depending on the extent of metastatic spread and the size of nodal lesions, complete surgical removal of solid tumor may be impossible. Adjuvant chemotherapy is often associated with significant dose-limiting systemic toxicities, and can lead to platinum-resistant disease. To date, there are no FDA-approved therapies that significantly prolong the overall survival of HGSOC patients that relapse with platinum-resistant disease. Although therapies for downregulating mechanistic resistance are currently under investigation, efficacy is hampered by nonspecific interactions with healthy tissue and poor pharmacokinetics.

Targeted drug delivery carriers can reduce systemic toxicity caused by off-target interactions, increase drug solubility and stability in physiological fluids, and improve efficacy through enhanced targeting and intracellular delivery to cancer cells. Layer-by-layer nanoparticles (LbL NPs) are multifunctional drug delivery vehicles whose modular architecture allows for the incorporation of a broad spectrum of therapeutics with diverse chemistries, and functionalization with targeting moieties that increase delivery to solid tumors. This thesis explores LbL NP materials design for optimizing delivery and targeted treatment of HGSOC.

The first part of this thesis develops a synergistic combination LbL NP therapy for downregulating resistance pathways in metastatic HGSOC. Combination treatment with BH3 mimetics targeting the mitochondrial apoptotic pathway induced significant synergistic toxicity in a panel of patient-derived HGSOC cells. Formulation of LbL NPs was optimized for high drug loading and designed with tumor-targeting outer layer chemistry. Co-encapsulation of the combination therapy within an LbL NP significantly enhanced efficacy over free drug treatments. Combination LbL NP therapy was well tolerated in animal models of HGSOC, and resulted in a dramatic regression solid tumor. This suggests the use of LbL NP drug delivery carriers to improve the therapeutic profile of combination treatments.

The second part of this thesis explores the role of nanoparticle stiffness in overcoming physiological barriers to drug delivery. LbL NP architecture uniquely allows for the decoupling of targeting chemistry and particle stiffness effects. Soft-LbL NPs were found to preferentially accumulate in solid tumors and have higher tumor penetration over Rigid-LbL NPs. Decreased nanoparticle stiffness extends in vivo elimination half-life—leading to greater exposure of solid tumor to circulating nanoparticles. Thus, Soft-LbL NPs are preferred for systemically delivered (ie. intravenous) therapies. Increasing rigidity enhances intracellular uptake of LbL NPs by cancer cells. Uptake of Rigid-LbL NPs is most significant when NPs are functionalized with tumor-targeting chemistry, and appears to be receptor-mediated. These results highlight the importance of combined targeting and stiffness modulation in nanoparticle design, and suggest the use of Rigid-LbL NPs for localized (intraperitoneal) delivery where intracellular uptake is the dominant delivery barrier.

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