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FUNCTIONAL PHOSPHORYLCHOLINE POLYMERS: PRODRUGS AND BIOMATERIALS

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Abstract
This thesis describes the synthesis and applications of multifunctional, hydrophilic polymers consisting of a methacrylate backbone and zwitterionic phosphorylcholine (PC) pendent groups, prepared by free radical polymerization of the zwitterionic monomer, 2-methacryloyloxyethyl phosphorylcholine (MPC). Advances in polymer chemistry, applied to PC polymers, allowed for the preparation of well-defined structures with controlled molecular weight, narrow polydispersity, and facile incorporation of functional comonomers, giving breadth to the range of materials accessible for different applications. Built-in functionality included fluorophores and reactive groups for post-polymerization transformations,

such as drug conjugation or cross-linking. The ability to form well-defined structures based on the polyMPC backbone is attractive to the fields of polymer therapeutics and biomaterials, due to the high level of biocompatibility associated with PC polymers. The work presented here examines methacrylate-based PC polymers as (1) polymer-protein conjugates, (2) polymer prodrugs, and (3) polymeric hydrogels.

In Chapter 2, synthetic advances center on tailoring chain-end functionality and utilizing such structures as polymer-protein conjugates. The design of new ATRP initiators containing specific functionality allowed for polymer conjugation to lysozyme as a model protein. PolyMPC-lysozyme conjugates retained their native enzymatic activity, and pharmacokinetic profiles of the conjugates in mice revealed increased circulation half-life compared to lysozyme alone.

Chapter 3 describes PC-polymers that enhance intravenous drug delivery of potent chemotherapeutic agents. Functionalized methacrylates for copolymerization with MPC were designed, such that multiple copies of a drug can be loaded onto the polymer backbone, affording highly water soluble polymer prodrugs with unprecedented drug loading (>30 wt %). PolyMPC prodrugs of camptothecin (CPT) and doxorubicin (DOX) demonstrated cytotoxicity against several human cancer cell lines *in vitro*. PolyMPC-DOX prodrugs displayed prolonged circulation half-lives, and reduced uptake in healthy tissue, enhanced accumulation in tumors, and superior treatment efficacy in 4T1-tumor bearing mice.

Chapter 4 highlights multifunctional polyMPC as a precursor to new phosphorylcholine hydrogels. Two cell lines, live mouse skeletal muscle myoblasts (C_2C_{12}) and human ovarian cancer (SKOV3) cells, were observed to specifically attach, spread, and proliferate on PC-hydrogels containing the GRGDS peptide sequence, with a notable dependence on peptide concentration. The remarkable hydrophilicity and biocompatibility attributed to polyMPC combined with facile gelation conditions affords a platform of new bio-cooperative materials suitable for cell studies.