Development of Dendritic Polymers as a Modular Drug Delivery Platform for Avascular Tissues

by
Brandon Michael Johnston

Submitted to the Department of Chemical Engineering on April 24th, 2023 in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Chemical Engineering

Abstract

Avascular tissues, such as articular cartilage, meniscus, intervertebral discs, and cornea stroma, pose a number of challenges for disease treatment. Systemic therapies will not reach the target tissue at efficacious levels. Local therapies are rapidly cleared from the tissue due to turnover of biological fluids, but repeated administration causes tissue damage and poor patient compliance. One method of improving the residence time of treatments is by utilizing drug delivery systems that target and bind to the extracellular matrix (ECM) with high affinity. The ECM is composed of a dense mesh of collagen and highly anionic proteoglycan chains. As such, small, cationic nanocarriers have been studied to electrostatically bind to avascular tissues and deliver therapeutics for extended periods.

Recently, cationic poly(amido amine) dendrimers partially modified with poly(ethylene glycol) chains (PEG-PAMAM conjugates) have shown promise in electrostatic based drug delivery to articular cartilage to treat osteoarthritis (OA), a debilitating disease of synovial joints affecting millions of people. Currently, there are no cures for OA. Though PEG-PAMAM conjugates have shown promise in delivering biologics to treat the disease, and have great potential for delivery to other avascular tissues, the impact of PEGylation on the surface charge presentation and drug delivery properties of these conjugates had not been well studied.

The first part of this thesis developed an experimental technique to probe how PEG chain length and chain density impact the charge presentation of PEG-PAMAM conjugates. This technique facilitated quantification of important characteristics like non-covalent interactions between PEG and PAMAM and the number of cationic amines on the dendrimer surface accessible to the physiological environment. A number of drug delivery properties to articular cartilage, such as binding kinetics, diffusion, biocompatibility, and pharmacokinetics, were probed using *ex vivo*, *in vitro*, and *in vivo* models, and a mechanistic understanding of how PEG influences these properties was achieved. Increasing accessible charged amines by reducing PEG chain density or chain length increased electrostatic binding strength while longer PEG chains improved binding reversibility. By controlling binding strength and reversibility, specific delivery profiles could be achieved and fine-tuned.

The second part of this thesis improved the bioconjugation of proteins to PEG-PAMAM conjugates and expanded the platform to other biologics and tissues. A robust synthetic scheme using click chemistry was introduced, improving loading efficiency while conserving protein bioactivity. Protein content influenced drug delivery properties to articular cartilage in a predictable manner, and improved joint residence times of proteins 20-fold. An anabolic protein, insulin-like growth factor 1 (IGF-1), and anti-catabolic protein, interleukin-1 receptor antagonist (IL-1RA), both with OA therapeutic potential, were loaded onto PEG-PAMAM conjugates and delivered to an *in vivo* OA model. Preliminary results show sustained delivery of IL-1RA relieved pain while both proteins showed signs of reduced OA severity (reduced osteophyte formation and cartilage degradation) compared to free proteins. Finally, proof-of-concept studies exemplify the utility of these cationic nanocarriers in similar tissues, including meniscus and cornea stroma. These findings inform optimization of PEG-PAMAM conjugates for future drug delivery applications to avascular tissue, and provide preclinical development crucial for translation.

Thesis Supervisor: Paula T. Hammond
Institute Professor, Department Head, David H. Koch (1962) Professor of Chemical Engineering