Intra/Extracellular Multi-Drug Delivery for Osteoarthritis

by

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Osteoarthritis (OA), the most common form of arthritis, affects hundreds of millions of people worldwide and tens of millions of people within the United States. This disease is typically diagnosed only after extensive and irreparable damage to the joints. There are currently no clinically effective disease modifying drugs that can slow or stop disease progression. While cartilage degeneration is the hallmark of OA, there is increasing recognition that OA is a disease of the whole joint, and multiple joint tissues contribute to disease progression. Due to the complex pathogenic processes that involve interactions between different joint tissues, a successful disease modifying therapy will likely require treatment with multiple drugs, each having a different target.

While several disease modifying drug candidates have shown promise in disease models both *in vitro* and *in vivo*, delivering these drugs effectively and with minimal side effects remains challenging. Cartilage does not have a blood supply, which decreases the efficacy of systemic drug administration methods. In intra-articular injections, drugs are directly injected into the affected joints. But any drugs injected into the joint are rapidly cleared out by the joint capsule over the span of a few hours to a day. As a result, there is limited drug penetration into cartilage. Frequent injections with high drug doses can overcome this challenge, but such a treatment would lead to undesirable systemic side effects and increase the risk of infections within the joint. Recent prior work in our lab has demonstrated that positively charged drug delivery carriers can bind to negatively charged extracellular matrix components in cartilage and thereby improve drug uptake and retention.

In this thesis, we characterized the effect of varying the charge of drug delivery carriers on their uptake and penetration into human and bovine cartilage tissues and cells. We identified optimally charged carriers that can be used to deliver drugs to extracellular or intracellular targets. We successfully used these carriers to provide sustained and targeted delivery of growth factors to full-thickness human cartilage explants *in vitro*, and developed a mathematical model that predicts *in vivo* transport behavior in human knee joints. We further established an *in vitro* cartilage-synovium co-culture model that captures physiologically relevant tissue interactions that contribute to OA progression. We also tested drugs targeting inflammatory pathways in this co-culture model, and the results provide a starting point for developing a combination therapy of growth factors and anti-inflammatory drugs conjugated to optimally charged carriers.

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