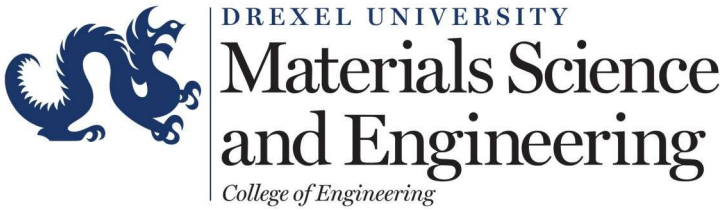

Department of Materials Science and Engineering,

M.S. Defense

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The Loading of Tolerogenic Drugs into Drug Vehicle Systems

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Abstract

Autoimmune disease is the third most common cause of chronic illness in the United States, affecting as many as 50 million Americans. The current standard of care relies on broadly immunosuppressive drugs, which compromise the immune system and increase susceptibility to infection and cancer. Developing an autoimmune therapy that is antigen-specific and directly targets the root cause of autoimmune disease, autoreactive T and B-cells, has been a central goal of the immune engineering community.

Dendritic cells (DCs), a subset of antigen presenting cells (APCs), regulate the T-cell response to foreign material and self-antigens, driving differentiation into either pro-inflammatory effector T-cells or tolerogenic T regulatory cells (Tregs). Tregs induce long-lasting tolerance by suppressing the function of autoreactive T and B-cells, offering a potential strategy to mitigate autoimmunity.

Tolerogenic dendritic cells (tolDCs) are a unique subset of DCs which overexpress tolerogenic markers, such as PD-L1, and lack co-stimulatory markers, such as CD86. These cell types have emerged as an APC of interest since they influence naïve T cells towards a Treg phenotype, re-establishing antigen-specific tolerance and preventing autoimmunity. Current strategies generate tolDCs by harvesting immature DCs from patients and differentiating them into a tolerogenic phenotype ex vivo. Unfortunately, this process is difficult, and induced tolDCs are short-lived. In vivo therapies, on the other hand, rely on immunosuppressive agents that are challenging to manufacture and lack antigen specificity.

Push and pull immunomodulation (PPI) describes a promising approach which overcomes these challenges, generating robust tolDCs that produce antigen specific Tregs. PPI elicits tolDCs

through a unique combination of agonist and inhibitor drugs paired with an antigen of interest. Currently, free drug PPI formulations fail to induce tolDCs in vivo or enable simultaneous delivery of an autoantigen. By synergistically loading these tolerogenic drugs with an antigen of interest into Poly(lactic-co-glycolic acid) (PLGA) microparticles, in vivo co-delivery is achieved. Size-selective uptake of microparticles by DCs allows for direct delivery of drugs and antigen proteins to intracellular targets. Once phagocytosed, encapsulation protects therapeutic cargo from premature degradation, enabling sustained release and modulation of cell phenotype.

The present study evaluates the loading of two PPI combinations—PPI-7 and PPI-9—with the model antigen ovalbumin (OVA), into PLGA microparticles. Microparticles are synthesized via single emulsion solvent evaporation. DLS and SEM analysis validate the formation of microparticles with a diameter of ~3µm—an optimal size for phagocytosis by DCs. An extraction protocol of drugs and proteins is developed and analyzed via HPLC and micro BCA (bicinchoninic acid) assays, confirming the loading of therapeutic agents. Release kinetics are observed over the course of one month, then modelled against established release profiles, exposing a first-order, diffusion-driven release process. To evaluate tolerogenic potential, monocyte-derived DCs are co-incubated with loaded microparticles and analyzed for tolerogenic markers via flow cytometry. Microparticle treated DCs exhibit high expression of PD-L1 and low expression of CD86, confirming their tolerogenic effect. By integrating a drug delivery system within the PPI framework, these results advance the strategy towards achieving controlled and sustained immunomodulation, hallmarks of an efficient autoimmune therapy.