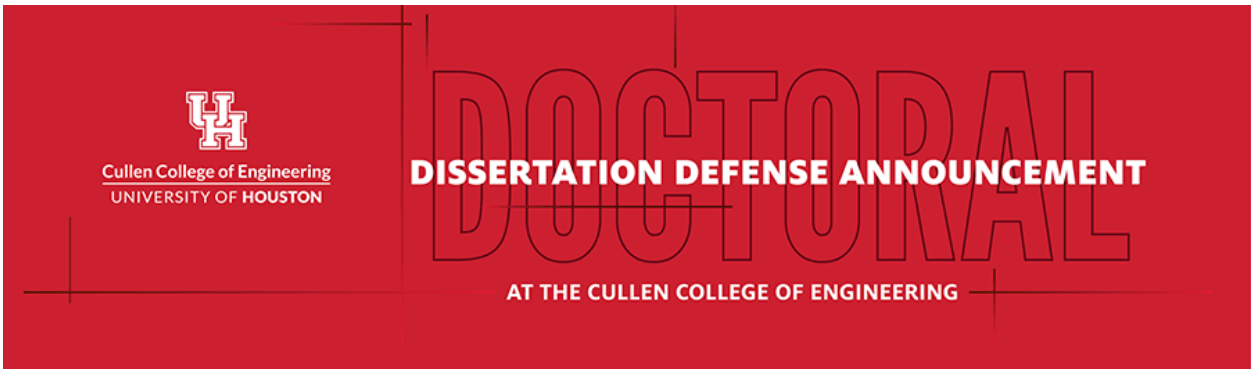

Spleen-Targeted Lipid Nanoparticles in The Treatment of Autoimmune Diseases

Shu Zhang

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Location: E220

Microsoft Teams: Link

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Abstract

Autoimmune diseases, once considered rare, now affect 3–5% of the global population according to recent epidemiological studies. The complex mechanisms underlying these diseases present significant challenges for researchers. Traditional treatments have relied on immunosuppressive drugs, which, despite their effectiveness, lack specificity and often cause severe side effects. This has driven a shift towards developing targeted therapies. Nucleic acid-based therapeutics have gained increasing attention for their potential to address diseases at the genetic level. Lipid nanoparticles (LNPs) have emerged as a superior delivery system for these therapeutics due to their biocompatibility, biodegradability, and efficient encapsulation capabilities. Given the spleen's pivotal role in immune processes, this study comprises two main projects aimed at developing spleen-targeted LNPs in the treatment of autoimmune diseases. The first project involves utilizing spleen-targeted LNPs encapsulating disease-specific antisense oligonucleotides (ASOs) to mitigate autoimmune phenotypes in an autoimmune

mouse model (B6.Mecp2^{Tg1}). Spleen-targeted LNPs were developed and characterized for their size, polydispersity index (PDI), and encapsulation efficiency, with their spleen-targeting behavior evaluated via *in vivo* imaging and their knockdown efficiency assessed through western blotting and flow cytometry. Therapeutic effects on spleen-related autoimmunity were comprehensively analyzed, including immune cell populations, autoantibody levels, cytokine profiles, and disease-related protein expressions, with therapeutic effects extending to other tissues due to decreased IgG deposition, resulting in alleviated proteinuria and neuropsychiatric deficits. The second project focuses on developing mannosylated spleen-targeted LNPs with enhanced transfection efficiency. In this study, mannose was introduced to LNPs to target receptors abundantly expressed on macrophages and dendritic cells, which are important cell subsets for maintaining immune homeostasis and crucial for endocytosis. The prepared LNPs demonstrated uniformity, elevated *in vitro* transfection efficiency, spleen-targeting activity, and enhanced transfection efficiency in the spleen. Flow cytometry confirmed their high uptake by antigen-presenting cells. Overall, these studies explored the potential of spleen-targeted LNPs for nucleic acid delivery and peripheral immune system modulation, presenting an innovative approach to treating autoimmune diseases.