COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

The Department of Pharmaceutical Science is pleased to announce the
Ph.D. Dissertation Defense Seminar of

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(Mentor: Dr. James Moon)

"Development and Optimization of Synthetic High-Density Lipoprotein Vaccine Nanodiscs for Immune Modulation"

Abstract: Cancer immunotherapy is a novel, attractive approach for cancer treatment. Cancer immunotherapy based on vaccines has shown promising results, but suffers from poor immunogenicity. This lack of efficacy can be attributed to the inefficient delivery of antigens and adjuvants to immune activation sites, resulting in weak cytotoxic T lymphocyte (CTL) responses. With profound advances in nanotechnology and biomaterials in recent years, researchers have shown the promise of nanoparticles designed to co-deliver antigens and adjuvants to antigen-presenting cells (APCs) for improving immunogenic responses of cancer vaccines.

Cancer stem cells (CSC) are a subpopulation of cancer cells that can proliferate extensively and drive tumor metastasis and recurrence. Despite intensive research, it remains challenging to specifically target and eliminate CSCs. In the first project, I report a novel approach to target CSCs by vaccination against aldehyde dehydrogenase (ALDH), which is highly up-regulated in CSCs. I have developed synthetic high-density lipoprotein (sHDL) nanodiscs co-loaded with ALDH peptide antigen and CpG (a Toll-like receptor (TLR)-9 agonist) adjuvant. Nanodisc vaccination combined with αPD-L1 immune checkpoint blocker led to significant induction of CTL responses against ALDH, leading to inhibition of D5 melanoma and 4T1 breast cancer. Overall, I have shown that nanodisc vaccination against ALDH in combination with αPD-L1 immunotherapy can exert strong anti-tumor efficacy.

In the second part of my project, I have optimized sHDL vaccine nanodiscs for the treatment of colon cancer. We have optimized sHDL nanodiscs that can efficiently deliver cancer antigens to lymph nodes and elicit strong anti-tumor T-cell responses against colorectal cancer. Overall, I have shown that polyICLC (a potent TLR3 agonist) admixed with sHDL can form a powerful adjuvant system (sHDL+polyICLC) that can be readily combined with an antigen. sHDL+polyICLC induced robust activation of dendritic cells, and sHDL+polyICLC generated strong anti-tumor immune responses, exerting strong anti-tumor efficacy in the MC-38 colon cancer model. Furthermore, I have shown that non-human primates vaccinated with sHDL+polyICLC elicited potent T-cell responses. Overall, these results show that immunotherapy based on sHDL+polyICLC can generate potent anti-tumor T-cell responses.

In the third project, I have developed sHDL-based immunotherapy for inducing antigen-specific immune tolerance. Multiple sclerosis (MS) is an autoimmune disease caused by autoreactive lymphocytes against axons and myelin sheaths of the central nervous system (CNS), leading to axonal loss and demyelination. Current treatments for MS are mainly based on immunosuppressive therapies that have unintended side effects on global immune responses and cause significant toxicity. To address these issues, I have developed synthetic high-density lipoproteins (sHDL) designed for the delivery of tolerogenic MS antigens and tested them in a murine model of experimental autoimmune encephalomyelitis (EAE), a widely accepted pre-clinical model of MS. sHDL-MOG considerably inhibited the symptoms of EAE, whereas treatments with blank sHDL, sHDL-M30, PBS, or free MOG peptide had no significant impact. Overall, inverse vaccination with sHDL carrying tolerogenic peptide antigens is effective against EAE and warrants further research as the basis for immunotherapy against MS and other autoimmune diseases.

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