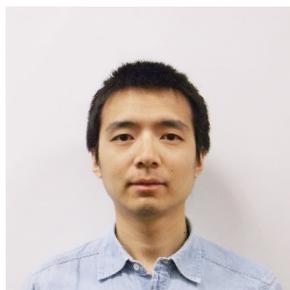




COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

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



Rui Kuai
Pharmaceutical Sciences, Ph.D. Candidate
(Mentors: Dr. James Moon and Dr. Anna Schwendeman)

Tuesday, December 5, 2017
10:00 am
NCRC Building 10-G064

***“Synthetic High Density Lipoprotein Nanodiscs for
Cancer Immunotherapy and Chemoimmunotherapy”***

Abstract: Despite the tremendous potential of peptide-based cancer vaccines, their efficacy has been limited in humans. Recent innovations in tumor exome sequencing have signaled the new era of personalized immunotherapy with patient-specific neoantigens, but a general methodology for stimulating strong CD8 α ⁺ cytotoxic T-lymphocyte (CTL) responses remains lacking. Here we demonstrate that synthetic high density lipoprotein-mimicking nanodiscs (sHDL) coupled with antigen (Ag) peptides and adjuvants can markedly improve Ag/adjuvant co-delivery to lymphoid organs and sustain Ag presentation on dendritic cells. Strikingly, nanodiscs elicited up to 47-fold greater frequencies of neoantigen-specific CTLs than soluble vaccines and even 31-fold greater than perhaps the strongest adjuvant in clinical trials (i.e. CpG in Montanide). Moreover, multi-epitope vaccination generated broad-spectrum T-cell responses that potently inhibited tumor growth. Nanodiscs eliminated established MC-38 and B16F10 tumors when combined with anti-PD-1 and anti-CTLA-4 therapy. These findings represent a new powerful approach for cancer immunotherapy and suggest a general strategy for personalized nanomedicine. We also sought to develop alternative approaches for cancer therapy. For example, we demonstrated that by simply incorporating a hydrophobic anticancer drug withalongolide A-4,19,27-triacetate (WGA-TA) in sHDL nanodiscs, we could enhance the therapeutic outcome of WGA-TA and reduce the side effects due to the improved tumor targeted delivery of nanodiscs. In addition to direct killing of tumor cells, some chemotherapeutic drugs can cause immunogenic cell death and induce antitumor T cell responses, which also contribute to the anticancer efficacy and prompt a number of clinical trials on combination chemoimmunotherapy. However, it remains unclear how to achieve potent immune activation with traditional chemotherapeutics in a manner that is safe, effective, and compatible with immunotherapy. Here we show that high-density lipoprotein (HDL)-mimicking nanodiscs loaded with doxorubicin (DOX), a widely used chemotherapeutic agent, can potentiate immune checkpoint blockade in murine tumor models. Delivery of DOX via nanodiscs triggered immunogenic cell death of cancer cells and exerted antitumor efficacy without any overt off-target side effects. Importantly, “priming” tumors with DOX-carrying nanodiscs elicited robust antitumor CD8⁺ T cell responses while broadening their epitope recognition to tumor-associated antigens, neoantigens, as well as intact whole tumor cells. Combination chemoimmunotherapy with nanodiscs plus anti-PD-1 therapy induced complete regression of established CT26 and MC38 colon carcinoma tumors in 80-88% of animals and protected survivors against tumor recurrence. Our work provides a new, generalizable framework for utilizing nanoparticle based chemotherapy to initiate antitumor immunity and sensitize tumors to immune checkpoint blockade.

Defenses are open to the public.