COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

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

Lukasz Ochyl
Pharmaceutical Sciences, Ph.D. Candidate
(Mentor: Dr. James Moon)

Monday, April 2, 2018
1:00 pm
NCRC Building 10, Room G063/064

"Preparation and Characterization of Cell Membranes for Cancer Immunotherapy"

Abstract: Cancer immunotherapy has advanced rapidly over the past decade leading to clinical approval of immune checkpoint blockade and adoptive cell transfer therapies. Further efforts into development of therapeutic vaccines had generated promising results in pre-clinical and clinical studies. Here, we demonstrate novel methodology for preparation of cell membranes into nano-sized vesicles and the development of characterization methods via nanoparticle flow cytometry. Cancer cell membranes from murine melanoma cell line expressing model antigen, ovalbumin, were used for generation of PEGylated vehicles (PEG-NPs), which efficiently delivered endogenous membrane-associated cancer antigens to the draining lymph nodes after subcutaneous administration. PEG-NPs were efficiently taken up by dendritic cells and, when dosed with a potent adjuvant, led to antigen-specific T cell activation and proliferation. In combination with immune checkpoint blockade (anti-PD-1 treatment), our vaccination approach led to therapeutic cure of 63% of mice and persistent memory responses rejecting additional tumor rechallenge. We further utilized our nanoparticle platform by using adjuvant-matured dendritic cells (DCs) generating MPLA-activated dendritic cell membrane vesicles ((MPLA)DC-MVs). This preparation led to nanoparticles carrying T cell activation ligands (CD80 and CD86) and promoted their proliferation in vitro. In addition, (MPLA)DC-MVs, but not unstimulated DC-MVs, resulted in activation of immature dendritic cells in vitro. Administration of this formulation in vivo together with OVA peptide epitope led to expansion and maintenance of antigen-specific T cells in mice that received adoptive cell transfer or had established OVA-expressing tumors. These studies had demonstrated the use for cell membranes in immunotherapy as vaccine vehicles, but further characterization and optimization could allow for improved efficacy, prompting us to adopt flow cytometry methods aimed at nanoparticle analysis. The technique was established by analysis of lipid-based synthetic formulations focused on demonstrating effective fluorescence detection and separation of individual particle populations. Proof of concept studies were used to confirm presence of ovalbumin on membrane-derived vesicles with antibody staining. Finally, we had utilized this technique to examine antigen display on hepatitis virus C vaccine formulation in order to determine if broadly neutralizing antibodies can bind efficiently and thus if they can be raised in mice immunized with these formulations. Taken together, this work has generated a foundation for further research into the use of cell membranes as nanoparticles for immunotherapeutic approaches and techniques necessary for their characterization.

Defenses are open to the public.