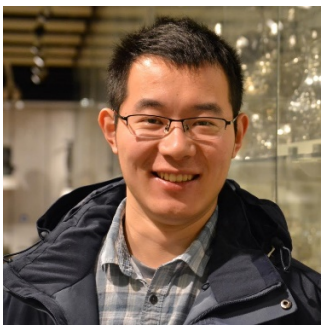
COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

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



Xiaoqi (Kevin) Sun
Pharmaceutical Sciences, Ph.D. Candidate
Mentor: Dr. James Moon

Thursday, September 2, 2021
1:00 PM
Join Zoom Meeting
https://umich.zoom.us/j/92388328693
Passcode: 216991

Developing Novel STING-activating Metalloimmunotherapy

Nutritional metal ions play critical roles in many important immune processes. Hence, effective modulation of metal ions may open up new forms of immunotherapy, termed as metalloimmunotherapy. In the first project, I discovered cobalt (Co^{2+}) and manganese (Mn^{2+}) metal ions could substantially augment Stimulator of Interferon Genes (STING) agonist activity, wherein Mn^{2+} promoted a 12- to 77-fold potentiation effect across the prevalent human STING haplotypes. In preclinical study, CDA + Mn^{2+} combination significantly amplified STING activation and induced antigen-specific T cell response, leading to complete regression of 80% CT26 tumors after IT injection. The survivors also formed a long-term immune memory against tumor rechallenging.

In the second project, I demonstrate a prototype of effective cancer metalloimmunotherapy using cyclic dinucleotide (CDN) STING agonists and Mn^{2+} in an optimized pharmaceutical formulation. Notably, I have found Mn^{2+} coordinates with CDNs to self-assemble into a nanoparticle (CDN-Mn^{2+} particle, CMP) that effectively delivered STING agonists to immune cells. CMP administered by either local intratumoral or systemic intravenous injection initiated robust anti-tumor immunity, achieving remarkable therapeutic efficacy with minute doses of STING agonists in multiple murine tumor models, including the immune checkpoint blockades-resistant tumors. In a benchmark study, CMP also performed significantly superior therapeutic efficacy than the leading STING agonists in clinical trials.

In the third project, I highlighted coordination interaction as a new mechanism for CDN formulation because the available formulation technologies relying on encapsulation and charge absorption are inefficient and/or unstable. I screened different metal ions and found interesting crystal structures formed between zinc ion (Zn^{2+}) and cyclic di-adenosine monophosphate (CDA). To design an efficient nanoparticle formulation, I also introduced Mn and $(histidine)_{33}$-polyethylene glycol (H33-PEG) in the coordination system given the potentiation effect of Mn on STING activation and the ionizable property of H33-PEG for endosome escape. By simple one-pot synthesis, I got homogeneous nanoparticles, CDA-Zn/Mn@H33-PEG (CZMP). In animal studies, CZMP not only induced higher immune activation for cancer immunotherapy but also could function as an effective vaccine adjuvant/delivery system for COVID-19 vaccine.

Overall, this dissertation presents the concept of ‘metalloimmunotherapy’and demonstrates, for the first time, the powerful potential of nanomedicine-based cancer metalloimmunotherapy. As nutritional metal ions play crucial roles in various immune processes, metalloimmunotherapy may be broadly applicable to other immune-related diseases.