COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Pharmaceutical Sciences Seminar Series

Wednesday, March 27, 2024
4:00pm
NCRC Building 10 South Atrium
Zoom

"Co-delivery of Manganese-Drug Combinations in PLGA Delivery Systems for Enhanced Cancer Immunotherapy"

Presented by:

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Abstract The cGAS-STING pathway is a key regulator of innate immune sensing of cancer and is currently a hot target for cancer immunotherapy. Activation of cGAS-STING can promote dendritic cell (DC) activation and T-cell recruitment, converting "cold" tumors to "hot" tumors. However, clinical translation of STING agonists has been challenging due to poor pharmacokinetic properties and off-target toxicities. We have previously demonstrated that nutritional metal ions, such as manganese, can synergize with innate sensing inflammatory pathways and elicit an amplified IFN-I response that triggers innate and adaptive immune responses against cancer. In this work, we develop poly(lactic-co-glycolic acid) (PLGA) milli-cylinder implants co-loaded with a commercially available STING agonist, ci-di-AMP (CDA), and manganese ion that we can translate as a therapy for hard-to-reach tumors or maintenance treatment post surgical resections to prevent tumor reoccurrence. We show that CDA & Mn^{2+} can be efficiently loaded into PLGA implants and release continuously over a course of 3-4 weeks. Using a subcutaneous murine colon carcinoma model (CT26), we show that these implants demonstrate anti-tumor effects, can successfully perform similarly to a multi-dose treatment, and promote an immunogenic tumor microenvironment. In parallel, we sought to discover other cancer agonists that can also synergize with manganese ion. We demonstrate that 3M-052, small molecule TLR7/8 agonist, in combination with manganese ion can also amplify Type I immunity against cancer. We have formulated PLGA nanoparticles that can encapsulate 3M-052 and manganese ion and we hope to show efficacy of this therapy both as an intertumoral and intravenous administration. The success these new "metalloimmunotherapies" can broaden clinical indications of STING/TLR-targeted cancer immunotherapy and may provide a patient-centric solution that can promote patient comfort and adherence.