COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Department of Pharmaceutical Sciences
Ph.D. Dissertation Defense Seminar

Friday, March 15, 2024
12:00pm
NCRC Building 10, Room ACR2
HTTPS://UMICH.ZOOM.US/J/96576929601
PASSCODE: 747730

"Immuno-therapeutics modulating B immunity against cancer"

Presented by:

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Abstract: Our immuno-therapeutics are designed to promote B/CD4 T cell crosstalk or eliminate B regulatory cells, enhancing efficacy of cancer immunotherapy. We used two different approaches to achieve these goals. First, we've engineered a SARS-CoV-2 B epitope-guided tumor neoantigen nanovaccine to promote B/CD4 T cell crosstalk for improving cancer immunotherapy. Second, we used a dual functional albumin nanomedicine, targeting of STING and PI3Kγ, to eliminate regulatory B cells to overcome STING resistance for cancer immunotherapy.

Neoantigen cancer vaccines using peptide or mRNA have shown promising anticancer efficacy in melanoma, colon and pancreatic cancer patients. Their efficacy is achieved through dendritic cell-mediated antigen presentation to activate CD4/CD8 T cell antitumor immunity. Most recent studies discovered that tumor infiltrating B cells are positively associated with better responses to anti-PD-1 immunotherapy in patients with various cancer types. However, it is unclear whether traditional B cell immunity or other B cell functions are crucial for its beneficial anticancer efficacy, while B/CD4 T cell crosstalk is essential for CD4/CD8 T cell antitumor immunity. Yet, current neoantigen vaccines using CD4/CD8 T epitopes are unable to promote B/CD4 T cell crosstalk. We designed SARS-CoV-2 B epitope-guided neoantigen cancer vaccines using peptide or mRNA to promote the crosstalk between SARS-CoV-2 B cells and tumor CD4 T cells, through B cell-mediated antigen presentation, for improving cancer immunotherapy.

In addition, the immune suppression in tumors and lymph nodes, regulated by suppressive myeloid cells and regulatory B (Breg) cells, hinders the effectiveness of immunotherapy. Although STING agonists activate myeloid cells to overcome immune suppression, it expands Breg cells, conferring STING resistance in PDAC. In the second project, we discovered that blocking PI3Kγ during STING activation abolished IRF3 phosphorylation to eliminate Breg cells, while PI3Kγ inhibition sustained STING-induced IRF3 phosphorylation to preserve STING function in myeloid cells. Therefore, we developed a dual functional compound SH-273 and its albumin nanoformulation Nano-273, which stimulates STING to activate myeloid cells and inhibits PI3Kγ to eliminates Breg cells overcoming STING resistance. Nano-273 achieved systemic antitumor immunity through intravenous administration and preferential delivery to tumors and lymph nodes, which decreases Breg cells and remodels microenvironment. Nano-273, combined with anti-PD-1, extended median survival of 200 days in transgenic KPC PDAC mice (KrasG12D-P53R172H-Cre), offering potential for PDAC treatment.