COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Pharmaceutical Sciences Seminar Series

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4:00pm
NCRC Building 10 - South Atrium
Zoom

"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 improving efficacy of T cell neoantigen cancer vaccines. 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.

Recent clinical research highlights the pivotal role B cell immunity and B/CD4 T cells crosstalk in enhancing the effectiveness of immune checkpoint blockade (ICB) therapy in cancer patients. In order to activate B/CD4 T cell crosstalk in the first project, we have developed the SARS-CoV-2 B epitope-guided tumor neoantigen nanovaccine (ACNVax). ACNVax uniquely combines viral (SARS-CoV-2) B antigens and tumor-specific T neoantigens. This nanovaccine features SARS-CoV-2 B epitope-cluster configuration on its surface, crosslink with the BCR of SARS-CoV-2 B antigen specific B cells, subsequently present tumor T cell neoantigen to CD4 T cells, which fosters cross-talk between virus-specific B cells and tumor-specific CD4 T cells. The ACNVax combined with anti-PD-1 showed significant anticancer efficacy in various cancer models.

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.