JOHNS HOPKINS
MEDICINE
THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER

STING and Immune Checkpoint Blockade Combination Improves Treatment Response

With the support of the Breast Cancer Research Foundation, Dr. Emens and her team have been able to examine to what extent pre-existing antigen tolerance influences the efficacy of a potent STING-activating agent, called ADU S-100, against HER-2^+ breast tumors. Her team found that the agent caused lasting tumor clearance in antigen intolerant – or immune competent – mice, while the same efficacy was not seen in antigen *tolerant* mice, for whom the agent resulted in tumor clearance in only 10% of the animals. In an effort to find a way to improve treatment efficacy in the tolerant mouse group, Dr. Emens and her team discovered that modulating the signaling of certain receptors, such as PD-L1, in combination with the administration of ADU S-100, enhanced the ability of the agent to clear tumors, increasing the clearance level from 10% of the mice to 40%. These findings indicate for the first time that combining STING agonists, like ADU S-100, with immune checkpoint blockade such as PD-L1 could allow clinicians to overcome immune tolerance to induce tumor regression and improve treatment outcomes for patients receiving immunotherapy.

While STING-activating approaches alone have already shown efficacy in melanomas, colon tumors, breast tumors, and pancreatic tumors in mice, the advances revealed in Dr. Emens' most recent work have defined an important role for STING signaling in promoting adaptive tumor immunity, allowing patients' immune systems to recognize tumors as dangerous and take steps towards defeating them. The use of STING agents to promote the priming of tumor-specific immune cells represents a potentially novel cancer therapy approach. ADU-S100 in particular has been evaluated in preclinical models as an intratumoral injection (STINGIT), as part of

certain vaccines (STINGVAX), and in combination with radiation therapy. However, these previous studies are limited by the absence of tumor-specific immune tolerance in the models utilized.

A unique strength of Dr. Emens' model is the ability to evaluate the impact of immune tolerance on cancer immunotherapy strategies, and develop strategies for overcoming this tolerance. These findings have implications for future clinical studies of ADU-S100-based therapies in cancer patients, where established immune tolerance to tumor antigens presents a major challenge to the efficacy of immunotherapies. A clinical trial testing single agent intratumoral ADU-S100 in advanced cancer patients with solid tumors and lymphomas is already underway, but Dr. Emens' data supports combining ADU S100 with relevant immune checkpoint modulation, such as PD-L1, to boost its clinical efficacy, ensuring that more patients with difficult cancers have the opportunity to benefit from the promise of immunotherapy.