



2022 Jawsome Shark Tank – Multidisciplinary Pilot Project Program

Investigation of the humoral B-cell response to chemoradiation therapy and checkpoint blockade immunotherapy in locally advanced cervical cancer

Jyoti Mayadev, MD

Andrew Sharabi, MD, PhD

Sangwoo Kim, MD

Scientific Abstract:

Node-positive cervical cancer remains a clinical unmet need as recurrences after standard chemoradiation therapy (CRT) occurs in up to 40% of patients. This study will add to the understanding of recurrence based on long-term follow up of an NCI-funded, GOG 9929, phase I trial that studied the addition to ipilimumab (anti-CTLA-4) to standard CRT, which critically has completed its long term follow up, allowing for correlative science. Prior analyses focused on evolution of T cell phenotype and antigen specificity; however, B cell-focused analyses have been sparse. Our team's published data utilizing microarray technology to characterize sera of patients treated with checkpoint blockade immunotherapy have revealed that patients who respond to therapy have a distinct humoral response profile from those patients who progress. Our study team has access to the samples from GOG 9929 which collected serum at key time points (pre-CRT, post-CRT, and post-ipilimumab). We will analyze these patients' sera using proteomic microarray technology to characterize the evolution of a patient's antibody repertoire, and correlate this with their clinical outcomes. We will also identify targets or pathways targeted by a patient's antibodies that are shared across patients. Next, we will utilize a murine model of cervical cancer to study the effects of CTLA-4 blockade and RT on B cell phenotype in both the tumor microenvironment and tumor-draining lymph nodes. Overall, this project allows for an in-depth examination of the humoral immune response in cervical cancer to improve prognostication and explore novel treatment combinations.

Lay Abstract:

Patients with cervical cancer that has metastasized to the lymph nodes have a high risk of disease recurrence after standard of care therapy, which includes combination chemotherapy and radiation therapy. GOG 9929, which was a clinical trial testing the addition of ipilimumab, an immunotherapy designed to activate a patient's own anti-tumor immune response, to the standard of care therapy, was conducted and has now finished its long-term clinical follow up. With this project, we will use novel technologies to study a patient's serum, and specifically the antibodies in the serum, to evaluate whether the presence of specific antibodies can help clinicians predict which patients are at a particularly high risk of recurrence, and conversely, which patients harbor a lower risk. Importantly, this project allows for us to study how our current therapies shape the evolution of a patient's anti-tumor immune response from the unique perspective of a patient's antibodies. Recognizing the heterogeneity of disease

outcomes, this project will critically allow for clinicians to better guide patients and their families through treatment by giving personalized estimates of the risk of recurrence. Furthermore, we will use mouse models of cervical cancer to examine how our therapies affect the function of immune cells, specifically looking at antibody-producing cells. Overall, this project allows for us to explore a unique aspect of the immune system in cervical cancer to identify *patients who are at high risk of disease recurrence* with the goal to formulate innovative ways to target this disease.