UC San Diego
MOORES CANCER CENTER

2023 Jawsome Shark Tank – Multidisciplinary Pilot Project Program

Spatial dissection of antigen-specific B-T cell cooperation in HNSCC and NSCLC

Hannah Carter, PhD
Theresa Guo, PhD

Scientific Abstract:

Immune checkpoint inhibition (ICI) therapy has generated unprecedented responses in some cancers, however only a minority of patients respond. Understanding the factors that determine response is critical to design the next generation of immunotherapies with a higher response rate. Immune cell infiltrates have been associated with response, however it is increasingly clear that it is not the abundance of individual immune cell types, but rather how those cell types interact within the tumor microenvironment that is most strongly associated with response. Several studies have demonstrated that dense aggregates of B and T cells in functional structures called tertiary lymphoid structures (TLS) are associated with superior immunotherapy outcomes in a number of tumor types including head and neck squamous cell carcinoma (HNSCC) and non-small cell lung cancer (NSCLC). We hypothesize that there exist host and tumor associated factors that promote the formation of these TLS, and that understanding these factors will uncover new targets to promote TLS formation and improved response to ICI treatment. We propose to use spatial transcriptomic technologies to study B and T cell clusters in the tumors of ICI responsive patients and ICI non-responsive patients. Aim 1 will characterize and contrast local cellular neighborhoods and gene expression signatures of B-T clusters between responders and nonresponders to implicate drivers of B-T formation. Aim 2 will characterize B and T cell receptor clonotypes to investigate whether B-T clusters in responders are more antigen specific, and expression of key antigens such as TERT or HPV associated proteins will be investigated.

Lay Abstract:

Immunotherapy has greatly improved outcomes for a subset of cancer patients, but many do not benefit. This proposal seeks to study the characteristics of tumors that responded versus those that did not respond in order to identify putative mechanisms underlying better responses and use those to suggest new drug targets for future study. We are specifically interested in two immune cell types, B and T cells that have been found to interact in some tumors, and when they interact it has been associated with better immunotherapy responses. Because the spatial relationships between these cells in the tumor is important, we plan to use spatially resolved gene expression profiling to study them and compare their behavior in immunotherapy responders and non-responders. We will focus on determining local gene expression patterns and immune cell characteristics that are associated with formation of B-T cell clusters in immunotherapy responders but not non-responders. Our study will focus on two cancer types, head and neck squamous cell carcinoma and non-small cell lung cancer, where approximately 20~30% of

patients benefit from immunotherapy treatment. Targets implicated by this study will form the basis for follow-on grant applications to support translational studies.