For over a century, scientists and physicians have debated the relevance of lymph node (LN) metastasis in tumor progression. William Halsted, a turn of the 20th century surgeon, believed that tumors travel through lymphatics to LNs where they acquire additional metastatic traits that endow them with the capacity to leave LNs through lymphatics and colonize distant tissues, resulting in stage 4 disease. This framework, known as the Halstedian model, was the basis for which he pioneered radical mastectomy, a disfiguring surgical approach that sought to aggressively remove LNs from patients with breast cancer.

In contrast, recent approaches that employ new sequencing technologies have begun to suggest that distant tumors are unrelated to the tumors in LNs, inspiring scientists to suggest that LN metastasis plays no functional role in tumor progression outside of serving as a convenient biomarker of disease. By developing mouse models of LN metastasis, we uncovered an important role for LN metastasis that reconciles these two disparate models. Our model, termed Metastatic Tolerance, suggests that when tumors spread to LNs, they reeducate the immune system to be tolerant of the cancer, and that tolerance enables tumors to subsequently spread to distant tissues. Thus, LN colonization is a functionally critical step in metastatic progression, not because it serves as a cellular reservoir of distant metastases, but rather because it drives the generation of immune tolerance that allows tumors to escape the immune system while spreading to distant sites.

 Our work encompassed in this METAvivor award has begun to shed light on the mechanisms by which this tolerance is generated within LNs and spreads throughout the body. Furthermore, it has laid the groundwork for developing therapies that target these mechanisms in LNs to reeducate the immune system to attack cancers. To this end, our lab now develops new classes of immunotherapies that traffic to LNs and generate anti-tumor immunity with the express intent of curing patients with advanced metastatic disease. The support of METAvivor provided me with the opportunity to select an institution to begin my independent laboratory that I believe has the ideal set of translational resources to rapidly advance these therapies to patients. Simply put, METAvivor has been one of the most important resources I have been fortunate enough to receive in the advancement of our mission of curing metastatic disease.