PUBLIC/LAY ABSTRACT

An effective therapeutic strategy for metastatic breast cancer is urgently needed. Recently, clinical trials of an immunotherapy that targets metastatic triple-negative breast cancer (mTNBC) showed that there are mixed results as patient responses vary. To maximize the benefit of immunotherapy, it is critical to understand molecular mechanisms of how cancer cells evade immune surveillance and to develop a novel treatment plan to suppress cancer cell immune evasion.

Cell mechanical properties, or mechanotype, are implicated in various cellular behaviors and functions including stem cell differentiation, drug resistance, immune cell-mediated cancer cell death, and cancer metastasis. Especially, changes in cell deformability and contractility are associated with cancer cell invasion, and deformability of immune cells regulate immune synapse formation, which is critical for T cell function. Nonetheless, the regulatory roles of cell mechanotype in cancer treatment are still poorly understood. It is especially critical to fully understand the role of mechanobiology in immunotherapy because immunotherapy offers promising prognosis in metastatic cancer patients including stage IV metastatic breast cancer patients.

I have developed a high-throughput cell mechanotyping tool called parallel microfiltration (PMF) that measures whole cell deformability, one of the most important features of cellular mechanotype. I recently completed a small-molecule library screen of 1,280 FDA-approved compounds using PMF to identify mechano-regulating molecules and successfully identified 6 candidate molecules. In this proposal, I will test how those candidate drugs can be used as a novel target to enhance T cell-mediated cytotoxicity and to recruit T cells into tumor tissues. I will also determine additional biochemical and mechanical factors from the tumor microenvironment that regulate cell mechanotype and immune evasion of cancer cells.

By understanding how cell mechanotype impacts immune evasion, findings of this study will provide a detailed understanding of the mechanisms regulating tumor cell immune evasion and ultimately provide the foundation to design more effective immunotherapies for highly metastatic breast cancer patients. Specifically, I anticipate that the results from the proposed study will serve as the basis of future preclinical studies using clinically relevant mouse models and ultimately provide foundation for human clinical trials. As I will test small molecules that are already approved by the FDA, the re-purposing of these drugs will expedite future clinical trials and offer immediate benefits to metastatic breast cancer patients.