**Lay Description of Important Outcomes**

Resistance to breast cancer therapies remains a significant and fundamental obstacle to clinical care. Unfortunately, all metastatic breast cancers develop resistance to therapy resulting in disease progression. This is particularly true of inflammatory breast cancers, an aggressive subtype of breast cancer associated with increased likelihood of therapeutic resistance and increased propensity for development of metastatic disease. We have used a new method to grow three-dimensional patient tumors in the lab to develop models of inflammatory breast cancers. We used these tumor models to test hundreds of compounds for their ability to reverse resistance to chemotherapy, identifying candidate therapies that may more effectively treat metastatic disease. Furthermore, these models were used to assess biomarkers of therapeutic response and resistance that can potentially guide challenging treatment decisions. Finally, we collaborated with Dr. Nadav Ahituv at UCSF and used these models to test a potential cell-based therapeutic, modification of fat cells, to effectively treat metastatic cancer by taking advantage of metabolic vulnerabilities of cancer cells, demonstrating the potential of these three-dimensional tumor models for preclinical testing of new therapies.