It is estimated that 114 individuals in the US alone are dying each day from metastatic breast cancer (mBC). To the pool of mBC are contributing 4-6% of newly diagnosed patients and 30% of those who eventually metastasize. The 5-year survival for MBC is less than 25% and the triple negative breast cancer type has the worst prognosis, underscoring the need for more effective and personalized treatments. While personalized medicine in cancer has been dominated by genetic approaches, therapeutic responses have not yet been completely understood simply by a genetic deterministic manner for a significant number of patients. Even the newest immune therapies have shown dramatic effects only in a subset of patients and the differences between patients that determine responsiveness remain largely unknown and will likely require functional approaches to reveal them. This logic also applies to traditional chemotherapies, many of which are now appreciated to work, at least partly, through either inhibiting tumor protective immune suppression or increasing the immunogenicity of the tumor cells.

The proposed experiments are a trajectory of translational research from my lab initially focusing on inflammatory conditions. We have recently developed an assay, Therapeutic Response Predictor Assay (TheRPA) that can be used to screen different treatments and point out the ones more likely to benefit the individual patient. In this project, we propose to develop a similar tool for metastatic breast cancer (THeRPA-mBC). This is a functional assay that is based on Patient-Derived Explants (PDE) treated in the lab with candidate drugs instead of the patient. The advantage over existing platforms is that PDE incorporates important elements of the tumor niche (the immune microenvironment and the stroma) as well as the tumor cells themselves. In addition to the close proximity of the in vivo situation, an additional feature of our technology is that it fully assesses interpatient variability in therapeutic responses. Parallel integrated OMICs analysis of paired, treated and untreated, PDEs from the same tumor will enable us to exploit our system to detect potential biomarkers of response and possibly identify disease underlying pathways and particular cell types that are affected by treatment and might be drivers of therapeutic response or resistance to these agents. Furthermore, the maturation of the proposed ex- vivo analytical tool will enable pre-clinical testing of novel single or combination therapies designed to meld immunotherapies with other targeted and standard chemotherapeutic approaches.

We will use PDEs from 30 patients with mBC and we will treat them in-vitro with chemotherapy, immunotherapy or their combination. The effect of each treatment will be evaluated by a composite cell proliferation/cytokine-based read-out and an algorithm to distinguish responders from non-responders will be applied. The proposed studies upon their successful completion are expected to generate proof-of-concept data supporting TheRPA-mBC as a precision medicine tool for identifying patients with mBC who are more likely to respond to PD1/PDL1 inhibitors. Furthermore, our molecular analysis is expected to provide critical insights about the exact profile and activation status of the immune cell subtypes and their soluble mediators that are associated with such responses. This realization has the potential, upon its further expansion, to reveal previously unappreciated targets involved in the anti -tumor response and could potentially lead to development of new more effective treatments.

Complementing the applicability of TheRPA-mBC in advancing personalized treatments, our PDE-based technology could be applied to clinical trials in a dish with the capacity to test in parallel more than one candidate drug or combinations of drugs. Such process can substantially accelerate the development of novel treatments for mBC and at a fraction of the costs for clinical trials by enabling the best candidate drug to move forward.

Future research using THeRPA-mBC will evolve around two main pillars, personalized medicine and accelerating new treatments and will be patient-centric with the ultimate goal to improve the life of patients with breast cancer. Instrumental to the success of this endeavor and its future implementation will be the engagement of the various stakeholders, including patients, community members, health care providers, non-profit organizations and health insurers. From the early steps of project development we will continuously seek input and feedback from patients and their communities in an all-inclusive and equal representation manner. Furthermore, we will rely on patient and Foundation initiatives to further disseminate our discoveries which can potentially transform patient care.