LAY ABSTRACT

In the U.S. alone, more than 40,000 people die from breast cancer each year. The vast majority of those deaths are due to that fact that we don't have curative treatments for metastatic breast cancer (MBC); the tumors eventually become resistant to all therapies that are given. Remarkably, at least 37 different therapies are currently FDA-approved for MBC but they are largely given on a trial-and-error basis: there is no way to know if a particular therapy will be effective for an individual's cancer and no way to try them all before complete resistance occurs or cumulative toxicity takes its toll. This lack of precision manifests as ineffective treatments for many patients - frequently coupled with severe, potentially lethal side effects. Use of one drug after another can also cause overall drug resistance.

Through a strong translational research collaboration, we propose to individualize treatment for MBC patients with a novel clinical trial that will personalize therapy early in the course of metastatic disease. Our strategy is to grow individuals' tumor cells from a biopsy and directly test the ability of available drugs to kill the tumor, using a novel three-dimensional culture and drug screening system. We will evaluate FDA-approved drugs and drugs for which there are clinical trials available. In tandem, we also conduct FDA-approved genomic analysis to identify key mutations in the tumor, and integrate those data with drug response data to identify the best therapies. These personalized results will then be returned to the treating physician using an IRB-approved disclosure. Using IRB-approved surveys, we will determine how often our data leads to a treatment recommendation that is different than the physician's original plan, and how often treatment was actually changed based on the precision oncology results. Finally, we will determine the progression-free survival times of patients on "precision-directed" versus standard treatment regimens to determine if a larger trial is warranted.

Our preliminary data already suggests our precision oncology strategy can select effective drugs for patients and increase survival time. Based on our positive data so far, we believe this project will have immediate impact for patients with metastatic disease. We expect that early selection of effective drugs will improve survival, while also eliminating toxicity from ineffective therapies. We request METAvivor funding to support this concept as a first-step (and first of its kind!) clinical trial.

If this small feasibility trial is successful, we will be able to compete for funding for a larger trial to test whether this strategy can in fact extend survival and quality of life for MBC patients. Moreover, there is an important opportunity for new discoveries as a result of this project: the precious MBC patient-derived tumor samples collected in this trial will be grown as long term MBC models and used to discover and test new, *hopefully curative,* therapies for MBC.