In order to make progress in understanding the biology of breast cancer, and to develop new drugs against the disease, we must find ways to experiment with tumor cells in the most physiologically relevant way possible. The most common method is to grow the cells on a plastic dish, as tissue cultures. However, growing tumor cells in isolation, outside of their normal environment, causes changes in the behavior and genetic makeup of the cells that could lead to misinterpretation of results. Growing human breast cancer cells in mice avoids many of the problems that occur in cultures, and allows for collection of more reliable data. However, the most common models for breast cancer research and drug discovery are made by injecting these cultured cancer cell lines into mice. Thus, the irreversible genetic and behavioral aberrancies that arose in culture remain, resulting in models that are poor predictors of metastasis and drug effectiveness. Dr.Lum and his collaborators have generated exciting new models of breast cancer, where tumors are taken directly from patients and grafted into mouse mammary glands. Previous METAvivor funding facilitated their discovery that tumor grafts from a single patient grown in mice were able to retrospectively (in hindsight) predict the actual response of the patient's tumor to therapy, including eventual chemo-resistance and relapse. The essential next step in this study is to address the questions of (1) whether development of chemo-resistance in chemo-treated mice with individualized tumor grafts could be used to predict relapse events in patients *before they happen*, and (2) whether personalized chemo-resistant tumor grafts can predict the most effective alternative therapy in the case of relapse.

The goal of this METAvivor proposal is to determine the value of patient-derived tumor grafts as models of chemotherapy resistance observed in patients with metastatic breast cancer. Do tumor grafts acquire chemo-resistance in a manner that mimics what occurs in the tumors of patients? Do the chemo-resistant tumor grafts then give us a model in which to predict the most effective alternative therapy? All new drugs must go through pre-clinical testing in animal models prior to clinical trials. The ability to improve predictions of drug efficacy with dependable models will bring the most promising new drugs or drug delivery modalities to the clinic. These tumor graft models are particularly exciting because they are individualized, and recapitulate the original tumor remarkably well particularly with respect to metastasis - the real problem in breast cancer. Dr. Lum envisions a future where we can preemptively generate tumor grafts from patients with aggressive breast cancer and treat the mice with the same standard therapy given to the patients, in order to enrich or select for chemo-resistant tumor cells as a preemptive, individualized relapse model.