

Personalized Therapy for Curing Metastatic Breast Cancer
Dr. Michael Flister, PhD
Assistant Professor, Human and Molecular Genetics Center
Medical College of Wisconsin

Over 230,000 new cases of breast cancer are diagnosed in the U.S. each year, of which 40,000 patients die annually from metastatic breast cancer that is resistant to the currently available therapies. In most cases, the mechanism(s) by which metastatic tumors resist therapy are unknown and possibly differ between individuals with different subtypes and somatic driver mutations (i.e., the acquired mutations driving the malignancy). One strategy to identify the mechanism(s) of therapy resistance has been to study a patient's transplanted tumor sample in an animal host (e.g., the NSG mouse), which is referred to as a patient-derived xenograft (PDX) model. The advantages of a PDX model is that the unique characteristics of a patient's tumor tissues can be biologically replicated across multiple animal hosts, enabling drug testing and mechanistic studies that might be used to direct that patient's clinical treatment. However, several limitations to the current strategy for PDX modeling also exist and addressing these limitations is the longterm goal of improving treatment for Stage IV metastatic breast cancer patients. One major limitation is that although estrogen receptor positive (ER+) breast cancer makes up 70-80% of cases and recurs with lethal therapy-resistant metastatic disease in 15-20% of patients, very few PDX models of ER+ breast cancer exist. The paucity of ER+ PDX models is caused by the inability of the initial tumors to engraft (<4% of the time), which prohibits studying how these tumors progress to metastatic disease that is resistant to therapy. Our solution has been to develop an animal host with improved rates of engraftment for all types of breast cancer, due to its expression of the human prolactin gene. This new PDX host is a NSG mouse, with a humanized prolactin gene (hPrl.NSG), improves the engraftment rate of ER+ tumors to >40%. Additionally, ER+ and triple negative breast cancer (TNBC) PDX tumors develop metastatic disease that is therapy resistant in the hPrl.NSG host, exactly as is observed in human patients in the clinic. Using this strategy we have already generated >20 PDX models, which include all tumor subtypes from patients at rates that match the clinical demographics of the U.S. In this Metavivor grant, we will use multiple approaches to identify the acquired DNA mutations and molecular signals that drive therapy resistance in metastatic breast cancer, which will be used to develop new therapeutic strategies for curing metastatic breast cancer.