While new drugs like the CDK4 inhibitors, palbociclib, abemaciclib and ribociclib, have significantly changed the landscape for women with metastatic hormone positive breast cancer, more work needs to be done. Many women are initially resistant to these therapies and others develop resistance during treatment. Thus, metastatic breast cancer remains a terminal disease. In order to continue to improve patient outcomes, novel therapies or new drug combinations must be developed. Data suggest that targeting another protein, called p27, might combat drug resistance either as a monotherapy or in combination with other CDK4 inhibitors. A p27 inhibitor would target both the driver of cancer, CDK4, and the driver of drug resistance, CDK2. This project will investigate whether p27 targeting using a new, experimental p27 targeting drug, IpY, might kill CDK4i resistant breast cancer cells and cause tumor regression in animal models. We will use several well-established models of CDK4i resistance to determine if we can inhibit metastatic tumor growth. The novelty of this project is that we are using models that resemble the disease specifically detected in drug-resistant metastatic patients, and that we are using a new therapeutic approach to target both CDK4 and CDK2. If successful, this would identify a new target and a new approach to potentially increase survival of metastatic patients.