**Lay Summary**

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.

Over the last year, using METAVIVOR funding, we have demonstrated that IpY is able to inhibit the growth of and kill breast cancer cells that contain many of the same genetic mutations found clinically in drug resistant breast cancer patients. This suggests that when palbociclib stops working, IpY, can go to work to reduce tumor burden for these patients. We presented some of this work at the prestigious annual meeting of the American Association of Cancer Research in New Orleans in April 2022, and are continuing to work on this project to test this hypothesis in animal models, which more closely resemble the human disease condition.

A more advanced version of IpY, called IpY.20, is being developed by the biotech company Concarlo Therapeutics. IpY.20 has a smaller, more stable version of the therapeutic peptide, which most importantly can be manufactured using the linear peptide synthesizer, making it a more commercially viable product. Concarlo Therapeutics is currently in manufacturing with IpY.20, with the goal of

performing IND-enabling safety/toxicity studies in 2023, with the goal of FIH Phase 1 clinical trials for palbociclib-resistant metastatic breast cancer patients in 2024. Thus, the work from this METAVIVOR project has direct clinical applications, as it will help to justify the use of IpY.20 in drug resistant breast cancer.