**Lay Important Outcomes**

Our research project funded by METAvivor has yielded a large body of data indicating that metabolic reprogramming is critically important for the growth of breast cancer brain metastases. In particular, a druggable metabolic pathway termed ‘oxidative phosphorylation’ (OXPHOS) is highly upregulated in brain-metastatic relative to primary breast cancer cells, and the physiological nutrient environment of the brain potently sensitizes metastatic breast cancer cells to OXPHOS inhibitors. Some of the key outcomes from this work are as follows. • Brain-metastatic triple-negative breast cancer cells are able to proliferate using the restricted nutrient supplies available in the brain, whereas the parental breast cancer cells fail to grow under these conditions. • OXPHOS is a highly upregulated gene expression signature in brain-metastatic, relative to parental breast cancer cells. • Although brain-metastatic breast cancer cells do not show heightened sensitivity to OXPHOS inhibitors under standard (non-physiological) cell culture conditions, during growth with physiological nutrient supplies these cells become highly sensitized to drugs targeting OXPHOS. • In addition to its role in cellular energetics, an important function of OXPHOS is to provide precursors for nucleotide biosynthesis such as aspartate. We proposed, and have now demonstrated in cell culture systems, a rational drug synergism by combining OXPHOS inhibitors with clinically-approved drugs targeting nucleotide biosynthesis. We have now optimized an experimental system for evaluating this drug synergism in animal models. • This project has therefore identified a combination of two classes of drugs, each of which is already clinically approved for other indications, that has a synergistic effect against brain-metastatic breast cancer cells. • Data obtained during this project has pointed towards future studies on nutrient exchange between brainmetastatic breast cancer cells and other cell types within the brain, further shifting the research focus of our lab towards improving therapies for patients with brain-metastatic breast cancer and leading to an ongoing collaboration between cancer biologists and neuroscientists.