**Lay Description of Important Outcomes**

Over the initial 18 months of our research endeavor, which has been generously funded by METAvivor, we have amassed compelling data that bolster the hypothesis regarding the critical role of metabolic reprogramming in the proliferation of breast cancer brain metastases. Among the noteworthy findings thus far, we highlight the following:

* RNA-seq profiling has unveiled a pronounced enrichment of OXPHOS in brain-metastatic cells.
* Untargeted metabolomics have validated the downregulation of aspartate upon OXPHOS inhibition.
* Restoration of NAD+ has demonstrated support for the proliferation of respiration-deficient cells.
* We have successfully optimized a brain interstitial fluid-mimetic culture medium (ABP) for the cultivation of brain-tropic cancer cells.
* Within the ABP medium, brain-metastatic cells have exhibited heightened sensitivity to OXPHOS inhibitors at physiologically relevant concentrations.
* Synergistic effects have been observed between OXPHOS inhibitors and inhibitors of the aspartate transporter. Looking ahead, over the forthcoming 6 months, our focus will shift towards evaluating the efficacy of drug combinations involving OXPHOS inhibitors in the treatment of brain-metastatic breast cancer using animal models.