**Lay Summary of Outcomes**

**2021 / 2022**

- In the current reporting period, we have made great strides (despite COVID restrictions) in completing the goals of the proposal and generating highly novel data

- We have shown for the first time:

o RAGE drives metastatic progression in preclinical models

o Drugs against RAGE inhibit the growth/spread of established metastasized tumor cells

o RAGE drives unique molecular pathways in metastatic tissue compared to the primary tumor, showing new potential mechanisms of targets for metastatic breast cancer

- We will use the data from this work as part of our upcoming grant applications to the NIH and DOD.

- For our work with RAGE inhibitors, these studies will be critical towards the development of clinical trials. We have made the novel finding that RAGE inhibition prevents chemotherapy-associated cognitive impairment (so-called chemobrain) and most recently we have generated novel data that RAGE knockout reduces doxorubicin induced cardiac dysfunction. We are currently planning a clinical trial to establish whether RAGE inhibitors can impair the side-effect of common cancer therapies.

Most importantly, we have established that the RAGE inhibitor TTP488 reduces metastasis in multiple preclinical models. As the RAGE inhibitor TTP488 has already been successfully tested for safety in human clinical trials, this makes TTP488 a highly translatable and desirable small molecule to test in human BC patients.