Lay Abstract (1 page)

In January 2018, the first biologically targeted drug for metastatic triple negative breast cancer (TNBC) was approved by the FDA, the PARP protein inhibitor (PARPi) olaparib. This approval represents a significant step forward in treatment of a disease which has historically inferior outcomes and standard treatments limited largely to cytotoxic chemotherapy. While some patients derive significant survival benefit from this drug, others do not benefit, even in the population with germline *BRCA1/2* mutations, where the drug was originally approved. Pathologic assays have not been able to reliably predict patient response, possibly because they are not representative of the entire tumor. Only a small fraction of the tumor is sampled during a biopsy and breast cancer is invariably biologically mixed.

To overcome this, we have developed an imaging companion diagnostic that can assess whole tumor PARP protein levels. Foundational results have been published (Makvandi, M. J. Clin. Invest. 128:2116, 2018) demonstrating that this test measures *in vivo* PARP expression. In this application we will test the premise, supported by early results, that the presence of increased tumor PARP protein, as measured by a PARP-PET imaging test, correlates to response to PARPi. We will also show the extent to which successful PARPi treatment engages with the target protein PARP-1. We will enroll any patients with metastatic breast cancer, regardless of tumor receptor profile or germline tumor mutations. Our initial results have shown that whole tumor PARP expression can be high in around a third of patients, independent of tumor hormone status and germline BRCA mutations.

Funding this application will allow us to take the first step toward validating a tool for personalized PARPi treatment decisions. ***If successful, this has the potential to expand the population of patients who are candidates for PARPi treatment and reduce the possibility that a patient will receive this drug without benefit.*** Thus, our research has high translational impact by better selecting and potentially increasing the numbers of patients who will benefit from this new targeted drug.