**Lay Description of Important Outcomes**

Addressing the challenge of improving outcomes for Stage IV breast cancer patients will require safe treatments that can target metastases at multiple sites in the body leading to their regression and, ideally, elimination. Advances in image-guided radiotherapy suggest that for many patients, it may soon be possible to safely treat almost any metastatic site, but the safety margin will limit the doses to levels that may be ineffective on their own. As such, we and others have sought a means to enhance the effects of radiation on tumors without increasing toxicity to normal tissue. Here, using radiation to enhance an anti-tumor immune response appears to be a highly promising strategy. Indeed, once an effect immune response can be induced, it may be possible to eliminate not only the treated tumors but other tumor sites, micrometastases and quiescent tumor cells. Based on promising initial results, our concept was to use radiation, at an otherwise ineffective dose, to open the blood vessels within the tumor, allow antibody drugs circulating in the patient to leak into the tumors, and to thereby deliver immunotherapy drugs into the tumors where it could then mediate a beneficial effect. However, in dissecting our results, we found that while radiation does indeed improve delivery of immunotherapy antibodies to tumors, a different mechanism determined whether the combination of radiation and immunotherapy would eliminate tumors. We found that the underlying mechanism was due to so-called "adaptive resistance", in which irradiation of tumors leads to a characteristic sequence of events. First, the tumor is damaged and releases inflammatory signals. Then immune cells exit the circulation to respond to the injury. These immune cells then release signals that have both positive and negative impacts. In particular, the release of interferon gamma can be sensed by tumor cells as a signal to activate anti-inflammatory, immunosuppressive genes, particularly the checkpoint protein PD-L1. As a result, while a dose of radiation can initiate an anti-tumor immune response, the tumor can then rebound, activate PD-L1, restore immunosuppression and return to growth. As such, our focus has shifted during this project period to interrupting this rebound immunosuppression and thereby enabling radiation to drive an anti-tumor immune response unopposed by adaptive resistance. This work led to a striking observation that treatment with veliparib, a drug that inhibits the enzyme poly-ADPribose polymerase, better known as PARP, could prevent the activation of adaptive resistance in irradiated tumors. Instead of inducing PD-L1 and restoring immunosuppression after radiation, the immune infiltrate persists and remains activated, eliminating the tumor. A manuscript is in preparation and a grant proposal is pending. This strategy appears practical to test in patients in the near term. In some stage IV breast cancer patients with only one or up to a handful of metastases, it may be possible to treat each of their tumors by irradiating them individually at a safe dose while the patients are being treated with an oral PARP inhibitor such as veliparib. This may allow the patient's immune system to target the irradiated tumors as well as eliminate microscopic tumors to prevent further metastatic growth. For other breast cancer patients, their metastases may be spread too widely or located where radiation cannot be used safely. To address this situation, we have developed a strategy to modify cancer cells to form a personalized vaccine that once injected into the patient, can drive an anti-tumor immune response. These vaccines can be used to suppress tumor growth on their own or combined with radiation or other treatments to eliminate tumors. We recently published a paper describing forming novel cancer vaccines and treating mice, but more needs to be done before this approach might reach patients. Grant proposals are pending. However, once this work is completed, we anticipate breast cancer cells obtained by biopsy of a metastasis could then be converted to a vaccine for that patient. When combined with other treatments, the vaccine might help drive a strong anti-tumor immune response that could prevent further growth or even eliminate metastatic tumors.