**Lay Description of Important Outcomes**

Steroid hormone receptors (SRs) are known to interact extensively in cancer cells but the impact of these interactions is unknown. A complete understanding of the significance of SR cooperation as well as their interactions with abnormal and elevated signaling pathways in cancer cells is urgently needed if we are to improve upon existing treatment strategies for metastatic breast cancer. We recently discovered that progesterone receptors (PRs) interact with estrogen receptors (ER) to promote specific gene programs associated with breast cancer cell survival, dissemination, and metastasis. In particular, we showed that PRs drive breast cancer stem cell self-renewal or “stemness” phenotypes, a process believed to be required for the formation and maintenance of new metastatic tumors. Relative to hormone-responsive (luminal A type) primary breast tumors, we find that the controlled “yin and yang” relationship between ER and PRs is disrupted in advanced metastatic breast cancer. Instead, these receptors adapt and acquire new roles, in which PRs co-opt a potent GO signal, especially when ER is therapeutically blocked. We hypothesize that PRs “feed” metastatic ER+ breast cancers, allowing them to renew themselves and maintain a therapy resistant state. The goal of this proposal is to uncover how PRs support, maintain, and renew the metastatic cascade in ER+ breast cancer. An important novel finding of our recent work (Aim 1) is that in breast cancers harboring mutant active ERs, PR is required for the activation of a unique signaling pathway known as the Unfolded Protein Response (UPR). This exciting finding reveals new biomarkers (i.e. proteins we can detect in tumors) we can use to signify which tumors will respond to drugs that block the UPR in metastatic breast cancers. We are thrilled by this novel finding:

**Impact:** The studies have already yielded a better understanding of PR actions and the associated abnormal signaling events (activation of the UPR during tumor progression) that can be collectively targeted in the clinic as part of new modernized endocrine therapies that account for SR interactions between ER and PRs. New biomarkers have been discovered to identify the subset of women whose metastatic breast cancers are primarily PR-driven. We can use the information gained from these studies to block uncontrolled and abnormal signaling events that fuel phosphorylated PRs in ER+ metastatic breast cancer. We anticipate that the addition of PRblocking strategies to existing standard-of-care therapies will dramatically improve health and extend lifespan for women suffering from metastatic ER+ breast cancer. In summary:

• These findings reveal that progesterone receptors (PR) are essential partners of estrogen receptors (ER) that drive ER+ breast cancer metastasis via activation of cellular stress pathways that circumvent existing cancer therapies by increasing the ability of breast cancer cells to survive and adapt.

• The clinical relevance of these findings is that they provide a strong rationale for the inclusion of antiprogestins (and inhibitors of cellular stress signaling) as part of new future therapies aimed at preventing the development of recurrent/endocrine resistant breast cancer metastasis.