CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180712

Project Title:
Rational Combination Treatment Options to Reverse Resistance in Hormone Receptor-Positive Breast Cancer Refractory to Standard Therapy

Award Mechanism:
Multi-Investigator Research Awards (Version 2)

Principal Investigator:
Hunt, Kelly

Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

Approximately 266,120 new cases of invasive breast cancer and 40,920 deaths due to breast cancer are expected to occur in 2018. Recent advances in gene expression profiling have revealed multiple breast cancer subtypes with differing outcomes. The majority of the newly diagnosed breast cancers are hormone receptor-positive and HER2-negative. Among the estimated 3.5 million men and women in the US with a history of breast cancer, 20-30% of these individuals experience a recurrence of their breast cancer and thus, represents a tremendous problem for patients and clinicians. The risk of recurrence in HR+ cases is typically lower over the first 5-10 years using conventional adjuvant systemic therapy, but the annual hazard rates for recurrence over time remain constant, at least for 15-20 years and HR+ cancers are the leading cause for deaths. The most effective and preferred form of initial treatment is endocrine therapy for metastatic HR+ breast cancer. Although most of these patients will derive benefit from endocrine therapy, disease progression is inevitable as the patients develop resistance to endocrine therapies which could be either due to intrinsic or acquired resistance after a period of initial response to treatment. Patients with acquired resistance have a low probability of responding for extended periods to further endocrine treatments, thus, there is a need to investigate new treatments that target other vulnerabilities in metastatic breast cancer. The main validated mechanisms of endocrine resistance are upregulation of escape survival pathways, such as growth factor receptors. The goal in our proposal is to understand the biology of resistance to endocrine treatment and to develop combinatorial therapies which are personalized to the individual patient's tumor and the risk of recurrence.

Our proposal presents a coordinated program to link what we learn from laboratory studies of tumor samples from patients receiving standard of care therapies to identify biological reasons for resistance. From that research we can identify and test new treatments to overcome resistance. We will extensively study the tumor samples from the basic building blocks of DNA, RNA and protein. We will also transplant a portion of the resistant tumors into a mouse model (patient derived xenografts, PDX), so we can study and treat these resistant tumors with newly discovered treatments. All the research projects study resistance, different reasons and pathways for resistance, and each project has a strong lead for overcoming that resistance. One of the projects will assess the risk of recurrence and develop a model that can be applied to all patients with HR+

breast cancer so that treatment plans can be modified based on the level of risk. Our three cores function to support the integrated research program. One core has the critical role of supporting the projects with specimens that are acquired from various ongoing clinical trials. They will coordinate all of the activities between the clinics and the patients to support this research program. The second core is for evaluation of histopathologic features and application of standardized parameters in interpretation of tumor samples by experienced breast pathologists. They will ensure a high level of accuracy and provide assistance in the development and interpretation of new assays by individual MIRA project investigators generated from combinations of novel drugs in the experimental models. This will allow the research teams to test their biological hypotheses of how to overcome the specific types of resistance. Our third core will be providing the statistical support required to ensure that the study design and outcomes are carefully evaluated and interpreted.

This overall project is highly innovative and very interactive amongst the projects and cores. It engages scientists with expertise in key areas of cancer biology and therefore as a whole, has a great potential to advance knowledge. Importantly, the real life responses to standard therapy will inform us about the shortcomings of these treatments and unlock new opportunities to improve therapy with personalized treatments. It will be a window into real human biology and therefore overcome one of the important limitations in cancer research - that laboratory research models may not exactly reflect the patient's situation. The "deliverables" of this project include new predictive biological signals (or biomarkers) that can be used to identify patients who may need a specific additional therapy or those at lower risk where we can de-escalate therapy.

The basic scientists will work closely with the clinical scientists to gain a greater understanding of their work in the context of real patients' samples from ongoing clinical trials, and the clinicians will gain tools to help in assessing who is at risk for resistance and how to adjust treatment to overcome that resistance. Additionally this knowledge will benefit the team to focus on development of new clinical trials to advance different treatment strategies. Therefore, this program should lead to greater success in personalizing treatment based on biology and risk of recurrence and increase the probability of long-term survival for patients with HR+ breast cancer.