CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP160710

Project Title:
A Randomized Clinical Trial Platform with Translational Studies to Overcome Resistance in Triple Negative Breast Cancer

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

Principal Investigator:
Symmans, William

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

Lay Summary:

One in six women with breast cancer, and one in three African American women with breast cancer, have triple negative breast cancer (TNBC) – a particularly aggressive type that grows very quickly and lacks the hormone and HER2 receptor targets for some of our most effective treatments. Our best modern chemotherapy is highly effective for nearly half of TNBCs. Indeed, many with TNBC now receive their chemotherapy before surgery (Neoadjuvant Chemotherapy – NACT) so that tumor shrinkage can occur and their surgery can be more conservative. Indeed, those women with TNBC who have complete (or nearly complete) disappearance of their cancer when the pathologist studies the response to NACT will have excellent chance of long-term cure. But if TNBC does not respond well to chemotherapy, there is significant risk of the cancer returning. That is because of the TNBC's resistance to chemotherapy. Therefore, studies using the NACT approach can improve our understanding the effectiveness of treatments for TNBC and the biological science behind resistance, so that we can learn how to improve the treatment and outcomes of patients with TNBC. This program is really focused on predicting when, understanding why, and innovating new approaches to prevent and treat TNBC that does not shrink in response to NACT. We consider a significant amount of residual cancer burden (RCB) remaining after the NACT to represent resistance to chemotherapy. This happens in 30% - 50% of patients with TNBC and indicates a high (>50%) risk of the cancer returning somewhere else in their body (relapse). Importantly, we have developed a reliable gene expression test of the cancer to predict response from a small sample of the tumor whether or not there will be an excellent response to chemotherapy, based on a probability score from 0 - 1. We will also monitor the initial response to chemotherapy using ultrasound imaging, to confirm that the originally predicted response seems right. If necessary, we will then make adjustments to the remainder of the chemotherapy treatment plan to improve the response. This clinical trial serves as the basis for our MIRA research program to understand and overcome resistance to treatment. Our proposal presents a coordinated program to link what we learn from laboratory studies of tumor samples from patients in the clinical trial to identify biological reasons for resistance. From that research we can identify and test new treatments to overcome resistance to standard chemotherapy treatments. We will extensively study the tumor samples and transplant a portion into a mouse model (PDX), so we can study and treat these mouse models with newly discovered treatments. If a patient's tumor is not shrinking during treatment, we will also have the option to provide

another sample, so that the scientists can create a second mouse model and learn what changed in the resistant cancer, and how to prevent that change. While it is possible TNBC may demonstrate resistance due to various reasons, we focussed our effort on three major areas. The first is to understand and target the internal cellular clock driven by p53, which tells a normal cell to stop and die. Abnormality of the p53 gene is the most common gene mutation in TNBC. This project will study and discover reasons for the development of resistance to chemotherapy among TNBCs and test the role of mutations in p53 gene and its role in preventing the tumor cells from dying when they experience severe damage from chemotherapy while they are trying to divide and populate (mitotic catastrophe). In fact, our first data-driven project addresses the hypothesis that addition of drugs to block Chk1 will kill these resistant cancer cells. In addition to the major p53 pathway, immune cells also try to stop cancer from growing. But, somehow, TNBCs develop ways to escape the immune system, in particular to the T-cells, which usually extend the killing of cancer cells that chemotherapy begins. In our second project, we uncovered ways to enhance some of the existing drugs to unmask the tumor and make them sensitive to T-cells mediating greater killing of tumor cells. In fact, our data suggest that addition of these drugs to chemotherapy will re-expose the cancer cells to the immune T-cells and improve the response to chemotherapy. Recent findings demonstrate that not all cancer cells are the same, and a subpopulation of cancer cells called cancer stem cells, that not all cancer cells are the same, and a subpopulation of cancer cells called cancer stem cells, contribute to the development of resistance to chemotherapy. Our scientists, and others have demonstrated that a significant fraction of TNBCs are enriched with therapy-resistant cancer stem cells. Moreover, TNBCs can reactivate an embryonic program known as an epithelial-mesenchymal transition, which play a pivotal role during embryo development. Cancer cells not only develop ways to pump out chemotherapy drugs but also gain the ability to hide from T-cell mediated killing. We have a new drug that targets cancer stem cells to switch them back to a state that is more vulnerable to chemotherapy. So while all the research projects are studying resistance, they study different reasons for resistance, and each project has a strong lead for overcoming that resistance. Our three cores function to support the integrated research program. One core has the critical role of running the clinical trial and coordinating all of the activities between the clinics and the patients to support this research program. The second core is a state-of-the-art facility for testing multiple combinations of novel drugs in the experimental models that our researchers use. This will allow the research teams to test their biological hypotheses of how to overcome the specific types of resistance, and to screen a huge number of drugs very quickly to find the combinations that will maximize the effect of treatment. Our third core will be comprehensively studying the profiles of tens of thousands of molecules in all the TNBC samples from patients in the clinical trial, and from all the mouse tumors that grow from them. This core will carefully categorize each TNBC and model the information to learn how to predict when the new treatments in the clinical trial will work best. 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, it is based on a clinical trial, where the real life responses to standard therapy will inform us about the shortcomings of these treatments and unlock new opportunities to improve it 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 that can be used to identify patients who may need a specific additional therapy, the elucidation of biological defects in the area of cell growth control, tumor immunology and stem cell biology that cause resistance and can be addressed with new therapies, and the actual testing of new experimental therapies designed to help patients with TNBC live longer and healthier lives. The basic scientists will work closely with the clinical scientists to gain greater understanding of their work in the context of real patients' samples from a real clinical trial, and the clinical researchers will learn who is at risk for resistance and how to adjust treatment to overcome that risk. When we can predict who won't fully benefit from our effective standard chemotherapy treatments, we can focus our best clinical trials on those who stand to benefit from a different treatment. Furthermore, when we know why a particular type of TNBC is likely to develop resistance to chemotherapy, and have worked out new treatment combinations that can overcome that resistance, then we will be able to make significant clinical advances. Therefore, this program should lead to greater success in advancing

treatment options and the proba bility of long-term survival for patients with TNBC, and indirectly for those with other aggressive forms of cancer, especially for those who most urgently need more effective treatments to overcome resistance to chemotherapy.