



## Scientific Abstract

### SU2C Breast Cancer Dream Team:

## **“An Integrated Approach to Targeting Breast Cancer Molecular Subtypes and Their Resistance Phenotypes”**



*[This abstract was provided by the scientists when their application was accepted.]*

Our understanding of the molecular basis of breast cancer probably exceeds that of any other epithelial cancer. Yet, women still succumb to the disease. This occurs despite targeted therapies that, based upon current molecular markers, have the potential to be effective in up to 50-75% of patients at initial diagnosis.

Our Dream Team brings together 7 outstanding members dedicated to improving the initial and long-term effectiveness of targeted breast cancer therapies and of identifying other critical targetable pathways.

Currently, most breast cancers fall into three therapeutic categories: tumors that are positive for estrogen receptor (ER) expression and that thus have the potential to be sensitive to anti-hormone therapy, tumors that are positive for Her-2 and that might respond to antagonism of this receptor, and tumors that lack ER and progesterone receptors as well as the HER2 alteration, “triple negative” (TN) tumors.

In general, we will take staged, highly interactive approaches to each disease class with the goals of having clinical impacts in the short term (12-18 months), the mid-term, and the long term.

Targeted therapies exist for both ER- and HER2-positive disease. These are effective in many appropriately classified patients; however, a large number of tumors fail to respond (*de novo* resistance), and in many initially responsive patients, treatments eventually lose potency (acquired resistance). We feel that the greatest immediate impact can be made for both of these treatment classes by reversing *de novo* and acquired resistance.

Short-term impacts will be realized through scientifically based, rational strategies for combination therapies (rather than the traditional empiric approaches) that will be translated into the clinic within the first 12-18 months. Impact in the mid and long term will emerge from unbiased, genome-wide studies designed to understand the nature of resistance pathways and mechanisms, which may include new driver pathways. We will carry out comprehensive genomic, epigenomic, proteomic, and functional genetic screens as well as probe the contribution of normal-tumor cell interactions and cancer stem cells to therapy resistance and disease recurrence.





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Triple-negative disease presents a special challenge, as no truly targeted approach is yet available for this tumor class. Here we will focus on targeted blockade of DNA repair mechanisms (PARP inhibitors) as they have shown clear promise in treating BRCA mutant tumors.

By understanding the determinants of resistance and the contributions of tumor cell environment and of cancer stem cells, we may develop immediately applicable biomarkers for predicting *de novo* resistance and for identifying patients most at risk for acquired resistance.

The ultimate goal is to build upon genetic and genomic studies to design new rational therapies that selectively eliminate breast tumor cells in a predictable fashion based upon the mutations that sustain their growth and survival.