

## Lay Abstract

Amongst individual breast cancer subtypes, those classified as triple-negative breast cancers (TNBCs) are especially lethal due to their highly metastatic behavior and propensity to rapidly recur. As a group, TNBCs lack expression of hormone receptors (ER- $\alpha$  and PR) and ErbB2/HER2. These molecular deficits have prevented the development of FDA-approved targeted drug therapies to treat this breast cancer subtype. Likewise, recurrent TNBCs quickly acquire resistance to standard-of-care chemotherapeutic agents through mechanisms that remain incompletely understood. Information derived from our highly innovative and medically relevant studies will *(i)* provide valuable information on what drives TNBC development, metastasis, chemoresistance and disease recurrence; and *(ii)* determine the therapeutic impact of a novel small molecule inhibitor, in combination with chemotherapy to alleviate metastatic TNBCs. Importantly, our findings will significantly impact the treatment of metastatic TNBCs, thereby improving the clinical outcome for patients bearing this deadly disease.

Our studies have shown that aberrant activity of YB1, a multifunctional gene, contributes to the activation of several oncogenic pathways, such as dysregulation of cell cycle, which is critical for orderly cell division, as well as the activation of cancer stem cells, that are known to contribute to tumor recurrence, metastasis, and therapy resistance. The proposed basic molecular studies will shed the light on how aberrant activity of YB1 contributes to the aggressiveness of metastatic TNBC tumors and help us understand the molecular underpinnings of the YB1-associated oncogenic pathways.

More importantly, with our small molecule inhibitor in hand (SU056), that we found to specifically target and inhibit YB1, we will use this drug as a therapeutic treatment to target metastatic TNBC. Our preliminary findings have already established the efficacy of the SU056 drug to inhibit the progression of metastatic TNBC tumors in small animal models. Our next step will be to assess the synergistic efficacy of combining SU056 with standard of care therapies on metastatic TNBC tumors in small animals. This will provide the long-awaited for opportunity to initiate clinical trials with patients with stage IV metastatic TNBC disease to test this novel combination therapy. Therefore, the potential benefits cannot be understated, and we truly believe that the anticipated clinical benefits to patients with stage IV metastatic breast cancer are of great significance.