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Abstract Submission Form

Poster Title: **Pharmacological Targeting of The YB1 is a Potential Therapeutic Strategy for the Treatment of Triple Negative Breast Cancer Tumors**

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Category: **Cancer Biology**

Metastatic breast cancer (BC) is the 2nd leading cause of death in women in the US, annually accounting for more than 43,000 deaths and 281,000 new cases of invasive BC. Amongst genetically distinct BC subtypes, those classified as being "triple-negative" (TNBC) are especially devastating due to their highly metastatic behavior, their propensity to recur rapidly, and their low response to standard-of-care therapies. In fact, the acquisition of chemoresistant phenotypes represents the main cause of disease recurrence, metastasis, and death in TNBC patients. Currently, the molecular mechanisms that regulate TNBC progression and metastasis remain unknown, as does the way these metastatic tumors acquire resistance to standard-of-care therapies. We recently established YB1 as a novel driver of these deadly TNBC activities, doing so by stimulating the cancer stem cell phenotype that promotes chemoresistance and TNBC metastasis.

YB1 is a multifunctional protein that acts as a transcription factor of cancer stem cell genes Nanog, Oct and Sox. Moreover, aberrant activation of YB1 contributes to the metastatic progression of several cancers, including TNBC. Our investigations revealed a major role of YB1 in the regulation of several hallmarks of cancer that drive TNBC tumors progression and metastasis, both in vitro and in preclinical mouse models of TNBC tumors. In extending these discoveries, we now show that aberrant YB1 expression activates oncogenic signaling leading to the dysregulation of cell cycle progression through the regulation of the Cyclin D/CDK4/6 complex signaling and the RB pathway.

We also report the identification of a novel small molecule inhibitor, SU056, that specifically targets YB1 and inhibits its oncogenic activity in TNBC cell lines. We further show that the SU056-mediated inhibition of YB1, in combination with standard of care chemotherapies, has a significant impact (synergistic effect) on inhibiting TNBC tumor progression and metastasis, compared to single arm treatment.

Mechanistically, our studies revealed that genetic or pharmacologic targeting of YB1 inhibits TNBC tumor progression and metastasis through the regulation cyclin D-CDK4/6-RB pathway and blockade of cell cycle progression.

Ongoing experiments are focused on investigating the effect of CDK4/6 inhibitor and SU056, either as monotherapy or in combination therapy, on the progression and metastasis of TNBC tumors in animal models.

Together, our data support the notion that targeting YB1 represents a potential therapeutic option for the treatment of TNBC, which could be enhanced when combined with standard of care treatment modalities.