

## **Developing effective combination therapies for metastatic TNBC by co-targeting epigenetic and oncogenic enzymes.**

Amy Schade, PhD; Brigham & Women's Hospital

**Background and Significance:** Triple negative breast cancer (TNBC) is an aggressive subtype of breast cancer, which represents ≈15% of cases. TNBC tumors frequently recur and metastatic disease is incurable. The current standard of care for most TNBCs includes chemotherapy. There is an urgent, unmet clinical need for effective therapies for metastatic TNBC. We have identified a promising new therapeutic combination that is effective in TNBC tumor models. We propose to extensively test this drug combination in metastatic TNBC models, deconstruct the mechanism by which it functions, and identify biomarkers to help select patients that are likely to respond. However, we also hypothesize that these agents will also improve the efficacy of immunotherapies by promoting immune recognition and (together with immunotherapies) will trigger more durable responses.

The basis of our novel therapeutic strategy involves combining an agent that inhibits an epigenetic enzyme with one that inhibits a classic cancer-causing oncogene. It is becoming increasingly clear that epigenetic enzymes play an important role in regulating a cell's identity or "state" which is directly related to its ability to divide and/or survive. Therefore, we hypothesized that if we were able to shift the state of TNBCs with drugs that target an important epigenetic enzyme, they might become sensitized to more classic oncogenic inhibitors. In fact, we found a unique drug combination that does just that. Moreover, both of these drugs are in late stage clinical trials and are well-tolerated.

Our preliminary data showed that the combination of inhibition of an epigenetic enzyme with inhibition of the oncogene can induce the death of tumor cells in the laboratory. While treatment with one inhibitor alone resulted in slowing of cell proliferation, combination treatment converted that response into cell *death*, an important indicator that this combination could induce tumor *shrinkage*. Importantly, we indeed found the drug combination induced tumor shrinkage in a model of human breast cancer in immunocompromised mice, a key finding that distinguishes our combination from other potential investigational therapies that only slow tumor growth. Our preliminary data have further revealed a possible mechanism by which the combination kills tumor cells and potential biomarkers that may predict which patients would benefit most strongly from this treatment.

**Research Plan:** Given our strong preliminary data, we propose to further develop this therapeutic strategy for the treatment of metastatic triple negative breast cancer. In our first aim, we propose to establish the efficacy of combined these agents in metastatic TNBC models. First, we will assess the effects of these agents in *metastatic (TNBC) PDX* models. We will also use orthotopic mouse metastatic models so that we may examine the effects of these agents on tumors in immunocompetent mice. In our second aim, we propose to elucidate the mechanism by which this drug combination induces tumor regression. In our third aim, we propose to determine how these agents affect the immune system and will determine whether the therapeutic response can be further enhanced by the addition of an immunotherapy. Importantly, a positive result would signal a chemotherapy free treatment option for metastatic TNBC.

**Impact:** This project has the potential to change the standard of care for TNBC. Importantly, our combination kills tumor cells (as opposed to slowing tumor growth) and has the potential to activate the immune system to prolong treatment response and reduce chances of recurrence. Our therapeutic approach is particularly exciting because this combination is comprised of clinically advanced and/or approved drugs and our preliminary data are quite compelling. Importantly, based on Phase III studies of each drug in other indications, it is likely that the side effects of each drug in combination will be well tolerated in people with few serious adverse side effects. Finally, we have designed these studies in collaboration with clinical and pharmaceutical company colleagues so that we will be prepared able to rapidly translate these findings into clinical trials which could be developed for metastatic TNBC in the very near future.