

Triple negative breast cancer (TNBC) involves any breast cancer that does not express the genes for estrogen, progesterone and epidermal growth factor receptor 2. An estimated 1 million cases of breast cancer are diagnosed annually worldwide and of these, 1,70,000 are of TNBC phenotype. Most of the deaths with TNBC are due to the metastatic disease, referred to as metastatic TNBC (mTNBC or Stage IV). Across the United States, approximately 50,000 women die every year due to mTNBC, one of the most lethal in the breast cancer spectrum. Importantly, the population-based studies show that the overall breast cancer incidence rates are highest among White American women but younger African Americans are disproportionately affected by mTNBC. Consequentially, a 5-year survival rate for mTNBC in AA patients is only 14% compared to 36% in non-African American women. It is contentious whether survival differences are due to inequalities in access to health care treatment or due to a genetic component underlying the susceptibility to TNBC. But irrespective of the cause, the differences in the mTNBC burden of African American represent one of the most notable examples of disparities in cancer related to racial identity.

Unfortunately, the only available treatment options for TNBCs patients include surgical removal of tumor followed by intensive and cytotoxic chemotherapy, mainly due to lack of targeted therapies. While many patients respond to these treatments, the disease prognosis is very poor and up to 85% of recurrent cancer patients develop metastasis and eventually die. Therefore, the three milestones for achieving the promise of the “Cancer Moonshot Initiative” are: (a) to gain mechanistic understanding of TNBC metastasis; and (b) to design novel multi-faceted biological therapies with the potential to treat already metastasized TNBC; and (c) identify and characterize genetic factor that predisposes AA women to mTNBC. A major limitation in developing an effective treatment for TNBC is the lack of targetable genetic determinants of metastasis. Therefore, we opt for a candidate-based approach and provide supporting evidence that tripartite motif-containing 37 (TRIM37) plays a pivotal role in the TNBC metastasis. We have previously shown that TRIM37 is a breast cancer oncogene that transforms a normal cell into a cancer cell. Further, our new preliminary data show that TRIM37 promotes anchorage-independent growth essential for cancer cell to survive in circulation and alters expression of metastatic effectors, thereby high expression of TRIM37 accelerates metastatic growth of TNBC. Our analysis of publicly available datasets also shows that TRIM37 is highly expressed in breast tissue of AA women and consistently, is expressed at higher level in the breast cancer tissue of AA women compared to patients of other ethnicity. Together, these findings suggest that high TRIM37 level can predispose AA women to aggressive mTNBC phenotype. To this end, we carried out molecular and functional studies that provided a rationale to target TRIM37 for mTNBC, for which, we engineered a highly selective and effective targeted therapeutic strategy based on inhibiting oncogenic TRIM37, using a highly stable synthetic polymer (*Antisense oligonucleotide*). Moreover, to maximize the therapeutic efficiency, we have designed antibody-conjugated nanoparticles that carry TRIM37-ASO in the nanoparticle core. We chose to graft folate receptor 1 (FOLR1) antibody on the nanoparticles because FOLR1 is over-expressed in TNBC. As a result, we find that anti-FOLR1-conjugated nanoparticles selectively delivers TRIM37-ASO to TNBC cells and reduces metastatic growth of TNBC. We provide an important proof-of-concept in support for our therapeutic design by demonstrating that TRIM37-ASO delivered by antibody-conjugated nanoparticles inhibits TRIM37 expression in TNBC tumors generated in xenograft mouse model. *This precision targeted approach based on preliminary data (that we have generated) offers a promising path for selective and effective mTNBC treatment.* We therefore will test our selective and effective therapeutic approach for treating mTNBC in immunodeficient and immunocompetent murine models.

The inherent racial disparity in TNBC and high TRIM37 expression in AA women prompted us to hypothesize that TRIM37 polymorphism may contribute to TNBC etiology. *Our results suggest that TRIM37-associated risk variants correlate significantly with high TRIM37 in AA women; however, their functional significance and association with clinical outcome remains to be demonstrated.* Using publicly available datasets, we identified TRIM37-associated risk alleles that segregate racially and correlate with high TRIM37 expression. Therefore, we predict that functional TRIM37 SNPs may predispose AA women to aggressive TNBC. To test, we will carry out functional characterization of TRIM37 variants and confirm their association with race and mTNBC clinical outcome using patient samples available to us through UVA School of Medicine and ORIEN (please see attached letters).

This project is extremely important from investigative and translational research perspective for mTNBC. Unlike generalized chemotherapy, this targeted approach has a great potential to be clinically beneficial since toxicity will be significantly reduced. If successful, we expect that our targeted therapy design will provide disease related outcome to mTNBC patients with in 3-5 years in terms of improving metastasis-free overall-survival. In summary, our findings from the proposed project will advance the field of therapies targeting mTNBC.