Signed details of the excellence in research work for which the Sun Pharma Research Fellowship is claimed, including references & illustrations (Max. 2.5 MB). The candidate should duly sign on the details *

27th August 2024.

Breast Cancer occurrence is on the rise in the Indian population and is expected to double within the coming twenty years. There are subtypes of breast cancer that are treated differently, and the ones with the most optimal targeted treatment strategy are entirely curable. However, about 20-25% of breast cancers in India do not have any targeted therapies. These subsets of breast cancers are TNBCs – triple-negative breast cancers, negative for ER, PR, and HER2. The systemic treatment options that are currently available for TNBC show unpredictable responses in terms of tumor regression, and hence, a high frequency of TNBC patients recur within two to three years. With rising incidence rates of breast cancer in India, TNBCs are going to pose a huge clinical challenge with a lack of better treatment options and recurrent disease burden.

TNBC in India presents with high frequency:

We documented variability and reasons for the variability in TNBC prevalence across 34 studies in India with a meta-analysis to conclude that despite the variability and diagnostic advancements, TNBC presents with a high prevalence of up to 27%, compared to that of western populations, where TNBC prevalence is 10-17% (Figure 1). In India, TNBC occurs at a higher frequency, shows up at a significantly younger age, and has aggressive features (**Kulkarni et al., 2020**). The meta-analysis systematically documents the highly prevalent and highly aggressive TNBC subtype in Indian Ethnicity compared to that of the Western population in the SEER data collected in the US, where diagnostic methods and time to diagnosis are equal for both Indian and non-Indian patients. The data brings out the urgency we need to exercise to tackle the clinical challenge specific to the Indian ethnicity.

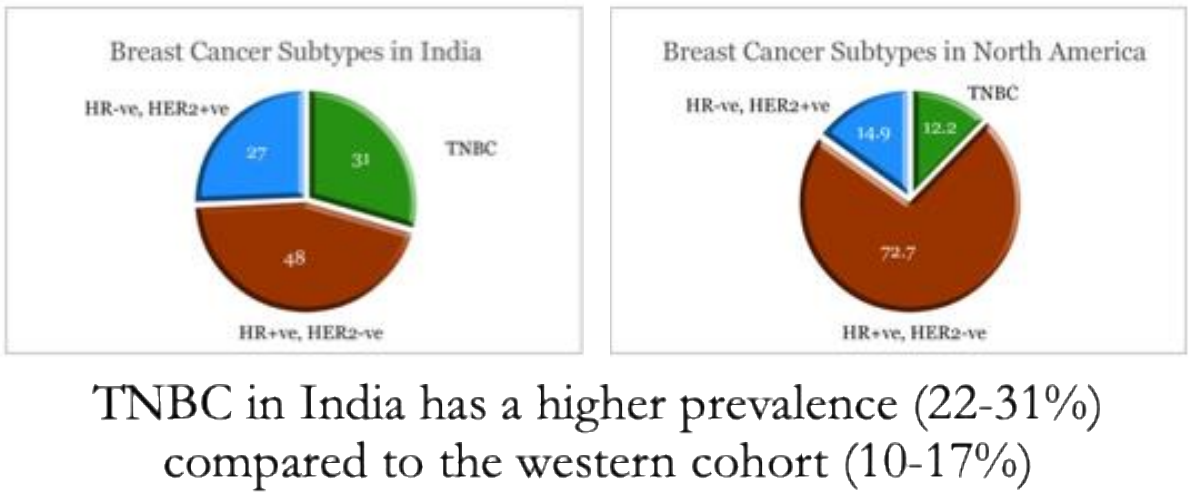

Figure 1: Comparative prevalence of breast cancer subtypes in India vs in North America.

To tackle this challenge, there is a need to have directed efforts to find casual genetic and molecular alternations underlying aggressive TNBCs within India. Molecular determinants that are responsible for non-responsiveness and progressive TNBCs need to be identified with cellular and molecular profiling of the breast cancer cohort from India in large numbers. The array of cellular and molecular markers that are strongly associated with the treatment response can be

developed as prognostic markers for Indian patients. Further, these can be developed into targeted therapies.

To aid the study of profiling TNBCs in an Indian cohort, I set up a FFPE tumor biobank at PCCM with a cohort of 1600 patient samples for breast tumors along with over 700 parameters to cover clinical features and treatment details, with follow-up information for 82%, and an average follow-up of 3 years. A detailed audit of the biobank is published in a peer-reviewed journal, Cancer Treatment and Research Communication, **Busheri et al. 2021**. This biobank also includes a vast amount of high-resolution image data from whole slide scans of H&E and IHC slides for over 500 patients to aid digital pathology studies.

How do we profile the biobank samples:

The flow chart below shows how we plan to profile the TNBC tumors to investigate the underlying causes for aggressive features and ultimately develop prognostic and targetable markers. The 1st off-shoot, cellular marker profiling, has already been published (**Vaid et al. 2022**), where we identified salient features of tumor immune infiltrates that present differently compared to that reported for western patients.

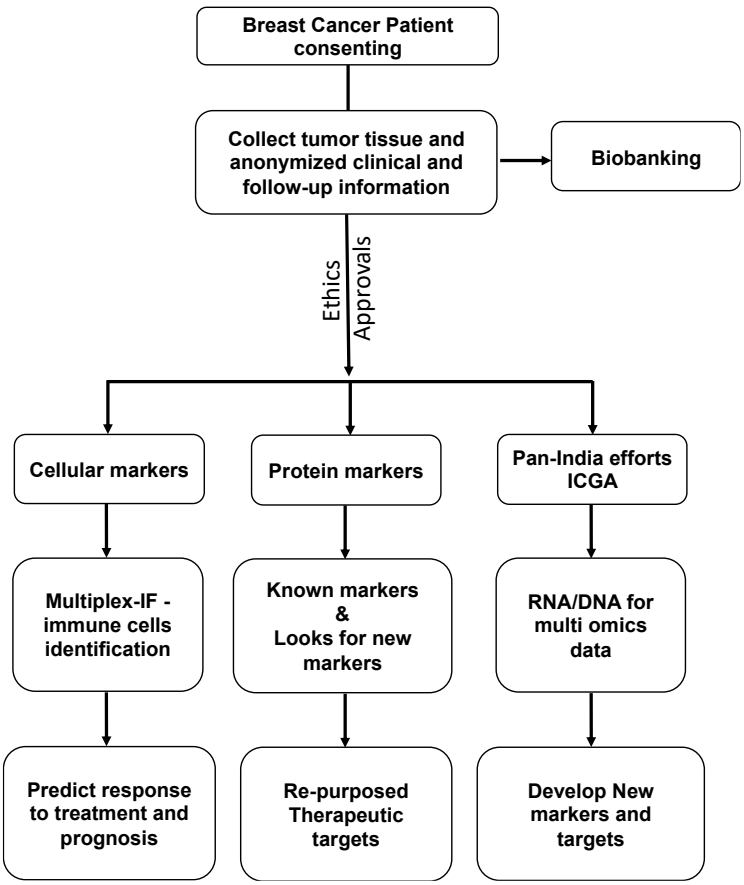

Figure 2: Workflow for profiling breast cancer patients to identify India-specific differences and targetable makers.

The study reported a correlation of treatment response with tumor-infiltrating lymphocytes (TILs), specifically in Triple Negative Breast Cancers from an Indian cohort of 250 breast cancer (IDC) cases, **Vaid et al 2022**. TNBC subtype showed the highest proportion of patients with high degree

of immune infiltrates which co-related with better treatment response and significantly better outcomes of the patients (Figure 3). We also observed breast cancer patients of Indian ethnicity presented with a higher proportion of intra-tumoral tills compared to that reported for Western cohorts. The international TILs working group decided to disregard intratumoral TILs since the proportion was noted to be less than 5 percent and had no implications for patient prognosis. In the paper, we propose that such cut-offs need to be re-investigated for the Indian ethnic population, as our observations showed a significant impact of intra-tumoral TILs on patient prognosis.

This is a first-of-kind study for breast cancer patients in India and provides a proof-of-principle for larger cohort analyses for TILs as a cost-effective marker that will aid in identifying TNBC patients who may benefit from the chemotherapy from the ones who may not.

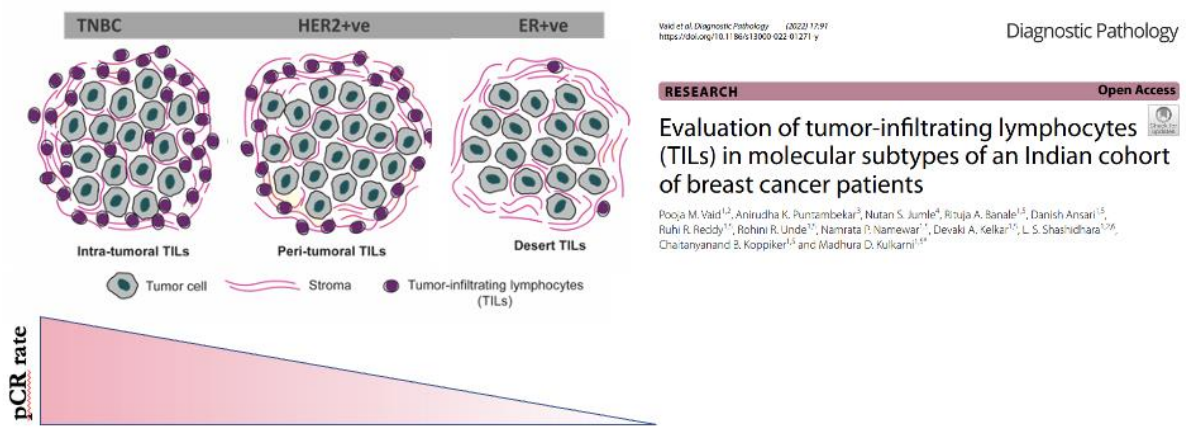

Figure 3 represents our findings on how differential infiltration of immune cells in the tumor and stroma manifest in treatment response and patient outcomes in an Indian cohort of breast cancer patients.

Following up on the study, we are now profiling infiltrating lymphocytes based on functional subgroups using multiplex imaging (Vaid et al., in preparation) with respect to the stromal environment and BRCA1/2 mutation status. We are also looking at the contribution of the extracellular matrix in regulating TILs infiltration.

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