6. Contributions and scope of the work
Since there is inadequate prognostic markers available for prediction of future metastasis of patients primarily diagnosed with breast cancer, it is utmost important to find newer markers which can efficiently help clinicians to estimate future possibilities. Established markers are routinely used to set the treatment protocol. However, most of them are standardized in western population. Therefore, sometimes, patients fail to respond to therapies.

We aimed to find novel markers of breast cancer metastasis by investigating patients from eastern India. This study is one of the very few reports from Indian sub-continent that deciphers novel prognostic markers and therapeutic targets of human breast cancer metastasis.

Our study is effective because it not only proposes CXCR5-CXCL13 co-expression and CCL17 and/or CCL22 expression as markers of poorer prognosis, rather, it also deciphers the intracellular signaling of CXCL13-CXCR5 axis. We have demonstrated that RelA is a common TF for both cxcl13 and cxcr5. Besides, this is the first report where we have shown that M2 macrophages are a probable source of intra-tumoral CXCL13. Thus, blocking M2 macrophage-trafficking may also inhibit elevated CXCL13 expression and associated disease progression. This study is unique on its part where it has highlighted that breast cancer cell line-conditioned medium is able to promote M2 polarization and CXCL13 expression.

We are first to identify RANKL in the signaling axis of CXCL13. RANKL is known to promote lung metastasis. Thus, increased RANKL expression is the answer for our observation of increased LNM in CXCL13-CXCR5 co-expressing patients.

Nonetheless, we have also highlighted the tumor suppressive function of Nrf2. Involvement of Nrf2 in tumor progression is still debated. Our finding of negative regulatory function of Nrf2 supports its’ function as tumor suppressor rather than an oncogene.