

HBKU Thematic Research Grant 2nd Cycle– Project Highlight

Project Title: CRISPR-Cas9 functional screen to identify novel prognostic and therapeutic lncRNA targets in triple negative breast cancer



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Executive Summary

Cancer is the second leading cause of death worldwide, while breast cancer is the most diagnosed malignant diseases among women. While the bulk of research has focused on protein coding genes, past decades have witnessed increased interest in deciphering the function of noncoding RNAs (ncRNAs), representing the bulk of transcribed RNAs, in human cancers. Our group has recently employed the CRISPR-Cas9 genome editing system to target the transcription start site (TSS) of various lncRNAs and characterized the biological functions of selected lncRNAs in breast cancer. In this proposal, we aim to functionally characterize the role of ~ 1000 commonly expressed lncRNAs in triple negative breast cancer (TNBC), using pooled CRISPR-Cas9 lentiviral library screen system in 3-dimensional (3D) spheroid models exhibiting resistance to standard chemotherapies. A customized paired-guide RNA (pgRNA) lentiviral library targeting ~ 1000 lncRNAs loci, including lncRNA transcripts currently annotated in the GENCODE, in addition to numerous novel lncRNA transcripts will be used in the screen. Therapeutic potential of the identified lncRNAs from this study will be tested using Anti Sense Oligos (ASO) in TNBC models. The prognostic value of identified lncRNA transcripts with potential role in driving chemotherapy resistance will be validated in breast cancer transcriptome data.

Expected Outcome

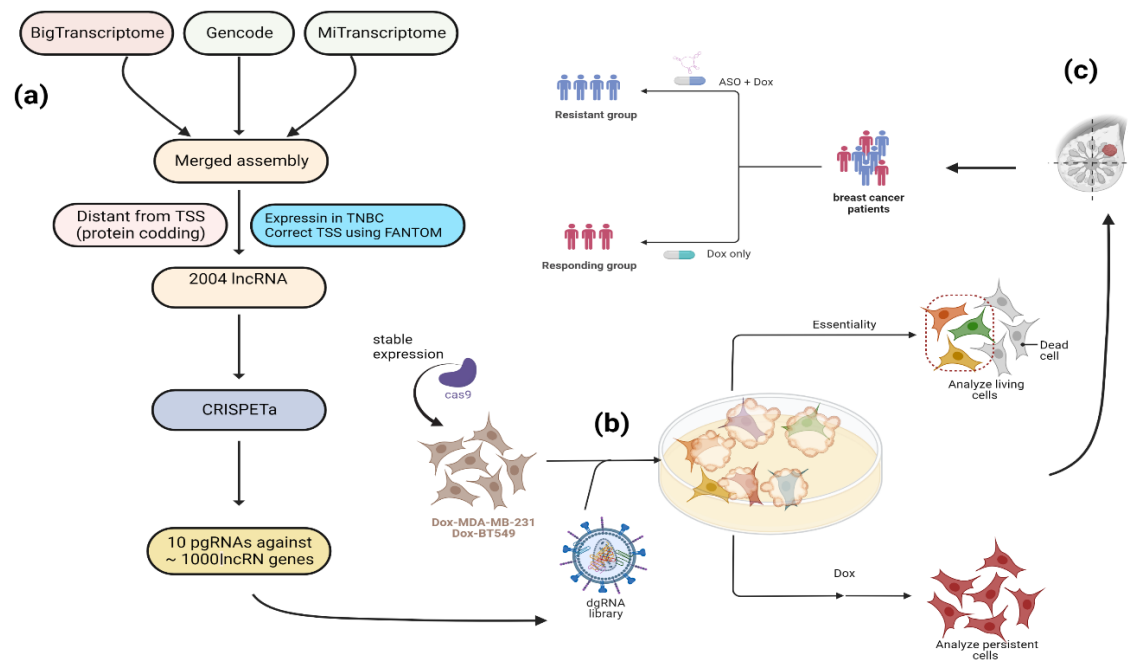
- Identification of prognostic and therapeutic lncRNAs
- Potential intellectual property disclosures
- High impact publications
- Technology transfer to HBKU and capacity building

Collaborating HBKU Entities:

Dr. Tanvir Alam – College of Science and Engineering, HBKU

Dr. Omar Albagha – College of Health and Life Sciences, HBKU

Schematic presentation of CRISPR-Cas9 screen strategy and its clinical impact



(a) pgRNA lentiviral library construction strategy where only unique lncRNA loci with no overlap with protein coding genes are retained. **(b)** CRISPR-Cas9 screening strategy in 3D culture followed by computational analysis. **(c)** Prognostic value of identified lncRNAs in breast cancer patients in relation to patient prognosis and survival in multiple cohorts.