INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Thesis Title: Tweaking EMT and MDR Dynamics by Co-targeting Signaling Pathways in Triple Negative Breast Cancer

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SHORT ABSTRACT

Triple-negative breast cancer (TNBC), the most aggressive subtype of breast cancer, which lacks effective targeted therapies due to lack of expression of the targetable bioreceptors. Additionally, hypoxic condition in solid tumors contributes to the epithelial to mesenchymal transition (EMT), which aggravates cancer progression, multidrug resistance (MDR), migration, and stemness of TNBC. In the **Introduction and Review of Literature** section, describes in detail the complex molecular signaling process that leads to metastasis, cancer progression, and relapse. In this section, basic biology and molecular aspects of EMT have been described. Furthermore, the role of aberrant induction of EMT in metastasis, cancer stemness, and MDR has been elucidated. **Section 2** comprises a thorough explanation of the **Materials** and **Methods** used for the experiments in the current thesis. **Section 3** In this section, firstly an attempt was persuaded to alter EMT and MDR dynamics in TNBC by co-targeting EGFR and Wnt/β-catenin signaling Given the strong implication of EGFR and Wnt/β-catenin signaling in the molecular pathogenesis of TNBC through EMT and MDR, the effect of the inhibitor combination was explored on TNBC cells by analyzing molecular changes in EMT markers in both monolayer cultures and multicellular tumor spheroids, which mimic *in vivo* conditions. In the subsequent endeavor, second approach was to alter EMT and MDR dynamics in TNBC by co-targeting Wnt/β-catenin and SQSTM1 signaling. Therefore, an effective combination therapy module was devised to target Wnt/β-catenin signaling (FH535) and SQSTM1 (siRNA), simultaneously. The effect of an inhibitor (FH535) with combination of siRNA against SQSTM1 was investigated in TNBC cells to explore molecular alterations of EMT and MDR markers. Following combination therapy, cytotoxicity tests on TNBC cells revealed a significant dose-dependent reduction in cell viability and a synergistic interaction between inhibitors. In the final part of the thesis, a nontherapeutic approach was implemented with FDA-approved drugs and biocompatible. In this work, a novel therapeutic module has been fabricated by coating a non-toxic, biodegradable PLGA nanoparticle core with D-penicillamine templated Au-Cu bimetallic nanoclusters. Further, the resultant nanomaterials were coated with recombinant transferrin protein to specifically target transferrin receptor overexpressing cancer cells. **Conclusion and Future prospects** summarizes the key findings of this current thesis. In pursuit of effective therapy, multiple critical signaling pathways underlying EMT were targeted which resulted in reversal of EMT, MDR and stemness of TNBC cells. Overall, the obtained results emphasize a potential combined application of crucial pathways inhibitors in the targeted therapy of TNBC.

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