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Smart Polymeric Nanocarriers for miRNA Delivery Against Triple Negative Breast Cancer

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The most typical malignancy in women is breast cancer. This translates to almost 2.3 million women who have been diagnosed with the illness, which, according to the World Health Organization (WHO), resulted in more than 685,000 fatalities globally in 2020. Additionally, 8 million women have received a breast cancer diagnosis in the past five years, making breast cancer the most prevalent cancer worldwide [1]. Additionally, triple-negative breast cancer (TNBC) is a subtype of breast cancer that lacks the human epidermal growth factor receptor 2, progesterone receptor, and oestrogen receptor. Furthermore, TNBC is known for its drug resistance, aggressiveness, and metastatic properties [2]. Even though radiotherapy and chemotherapy are two therapeutic modalities for the treatment of breast cancer, they have had limited effectiveness in clinics due to a number of limitations, such as the emergence of drug resistance throughout therapy. Gene therapy offers a promising avenue to overcome these challenges. MicroRNAs (miRNAs) are significant factors in the development, metastasis, and advancement of breast cancer [3]. The oncogenic transcription factor Forkhead Box M1 (FOXM1) is engaged in processes that are thought to be cancer hallmarks [4]. In a previous study Zuhal Hamurcu et.al claimed that the results of the miRNA expression profile in two distinct TNBC cells, miRNA was downregulated after FOXM1 was knocked down. Also, they conducted KEGG pathway analysis and GO enrichment analysis for miRNA, and these analyses revealed that this miRNA is connected to the cell cycle, AMPK, p53, and NF-kB signalling pathways, as well as the formation and progression of cancer [5]. However, a few barriers, including miRNA instability, unfavourable off-target effects, and non-specific activation of the immune system's natural defences, prevent RNAi-based techniques from operating to their full potential. Delivery of miRNA into cells is further restricted by endothelial cell resistance, inability to achieve endosomal escape, which prevents the miRNA from reaching the location of cytosolic action. The development of nanocarriers addresses almost all these problems. To make complex and transport miRNA to breast cancer cells, we developed “smart” polymeric nanocarriers. Also, smart polymeric nanoparticles provide a protective shield, shielding miRNAs from enzymatic degradation and enhancing their bioavailability. Inhibitor miRNA and smart nanocarriers are complex at a 2/1 N/P ratio. Additionally, mimic miRNA and negative miRNA form an 8/1 complex with smart nanocarriers. Finally, with a 16/1 N/P ratio, FAM-labelled negative miRNA and smart nanocarriers are complex. Furthermore, the percentage of cells encapsulating miRNAs in cells analysed using flow cytometry was determined. Accordingly, the import percentages of BT-549 and MDA-MB-231 cells are over 35% and 55%, respectively. The fluorescence microscopy results obtained show that our FAM-labelled miRNAs reach the inside of the cell within 4 hours. As a result of this experiment, it was observed that miRNA could be transported to the cell without any enzymatic digestion. Our results demonstrated the potential of polymeric miRNA delivery systems showcasing promising outcomes in preclinical for triple-negative breast cancer treatment. These advances hold immense promise in improving the precision, efficacy, and safety of breast cancer

treatments. To enable efficient delivery and controlled release of miRNA, the physicochemical characteristics of the smart nanocarriers, including size, charge on the surface, and stability, are optimized.

Keywords: Breast cancer, miRNA, Gene delivery, Gene therapy, Nanomedicine, Nanocarriers

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