TNBCnano: Novel Layer-By-Layer Nanoparticles for Systemic Combination Delivery of MRP1 siRNA and Doxorubicin for Triple-Negative Breast Cancer Treatment

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Every minute, four women are diagnosed with Triple Negative Breast Cancer (TNBC). Yet, TNBC remains the only subtype of breast cancer without an approved biological treatment, with an average life expectancy of 10.2 months. Neoadjuvant treatments are proven unsuccessful due to rapid tumor drug resistance, cell heterogeneity, and lack of precise receptor targeting. This research developed a novel dualfunctional doxorubicin encapsulated layer-by-layer (LBL) nanoparticle uniquely designed for drug-resistant protein knockdown by gene silencing, and controlled drug delivery to TNBC tumors. Molecular docking was achieved through Autodock Vina to identify hyaluronic acid and MRP1 siRNA as candidates biocompatible with Cancer Stem Cells. The nanoparticle design used amphiphilic interactions to encapsulate doxorubicin in Poly(lactic-co-glycolic acid) via double emulsion solvent evaporation, further coated with layers of MRP1 siRNA, chitosan, and hyaluronic acid using LBL opposite electrostatic deposition assembly. Transmission electron microscopy confirmed a 100 nm anhydrous size core and 150 nm with layering, showing enhanced permeability and retention. Nanoparticle morphology displayed distinct layering further validated by zeta potential analysis. Further doxorubicin release and human body compatibility was assessed by incubating nanoparticles in a replicated human plasma environment using phosphate buffered saline. Nanoparticles exhibited 60% doxorubicin release over 24 hours, followed by gradual release. siRNA release in the mimicid environment held a controlled linear release (%) relationship over 72 hours. Produced particles are cost-effective (<$50 batch), providing accessible, targeted treatment that displays clinical potential in developing future TNBC therapies.