TDEVELOPMENT OF ORAL PBAE-BASED NANOPARTICLE-LOADED CAPSULES SYSTEMS FOR TARGETED SIRNA DELIVERY IN COLORECTAL CANCER THERAPY

Project Summary

Precision medicine is redefining the approach to cancer therapy by enabling the delivery of therapeutic agents directly to diseased cells with high spatial and molecular specificity. This project focuses on the advanced pharmaceutical development of polymeric nanoparticles derived from proprietary poly(β-amino esters) (pBAEs), engineered to encapsulate specific small interfering RNAs (siRNAs) targeting key oncogenic or immunosuppressive pathways in colorectal cancer (CRC).

From a pharmaceutical technology standpoint, a key challenge is ensuring the nanoparticles maintain structural and functional stability throughout gastrointestinal transit while achieving site-specific release in the colon, where CRC typically originates. To this end, the nanoparticles are incorporated into oral enteric capsules that are resistant to acidic pH, disintegrating only at a pH >6.5, thereby ensuring release in the colon. This delivery system protects the siRNAs from enzymatic and chemical degradation in the stomach and small intestine, and maximizes therapeutic bioavailability at the tumor site.

The proposed nanocarriers are designed to target cells within the tumor microenvironment, including: Colorectal cancer epithelial cells expressing oncogenes such as KRAS, MYC, or β-catenin, which can be selectively silenced using siRNAs; and tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), which contribute to immune evasion and may be reprogrammed via siRNA delivery (e.g., targeting CSF1R, STAT3, or TGF-β signaling);

To enhance selective uptake, the nanoparticles can be surface-functionalized with ligands (e.g., folic acid, transferrin, hyaluronic acid) that bind overexpressed receptors on cancer or immune cells, enabling active targeting and enhanced internalization.

The project encompasses the full pharmaceutical development pipeline: Formulation and physicochemical characterization of the nanoparticles (via DLS, NTA, TEM, zeta potential), release profiling in simulated gastrointestinal conditions (SGF, SIF), stability testing within enteric capsules, and biological validation using CRC cell lines (e.g., HCT116, HT-29) and advanced 3D co-culture models to assess gene silencing efficiency, cell viability, and potential immunomodulation.

This Master's Thesis project represents a cutting-edge opportunity to work at the crossroads of oncology, RNA therapeutics, and pharmaceutical nanotechnology, contributing to the development of non-invasive, localized siRNA therapies for colorectal cancer, with high translational potential.