# Development of BMX siRNA Lipid Nanoparticles Using Novel Ionizable, and Cleavable Lipids Discovered through AI and Experimentation for Cancer Therapy

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## Abstract

**Purpose:** This study aims to design, synthesize, and characterize novel ionizable and cleavable lipids that are derived from the γ-T3 isomer of vitamin E. The designed two lipids are used in the lipid nanoparticles (LNPs) structure to enhance BMX siRNA delivery for protein silencing and act as active anticancer agents.

**Methods:** In this work, the delivery system used is composed of negatively charged siRNA encapsulated into a multi-component structure that contains DOPE, 1,2-dioleoyl-3-trimethylammonium propane (DOTAP), Cholesterol, and Phosphatidylcholine. To further enhance the activity of the BMX siRNA lipid nanoparticle compositions, two novel lipids, a cleavable PEGylated lipid and an ionizable cationic lipid, were synthesized and characterized by our team (Abu-Fayyad and Nazzal 2017) and then added to the formulation.

**Results:** The designed and optimized novel BMX siRNA LNPs were physicochemically characterized and exhibited the desired characteristics. Furthermore, AI-based tools were used to predict potential interactions between the novel, ionizable lipid and the BMX siRNA, yielding promising forecasted results. The optimized BMX siRNA LNPs exhibited a preferred particle size and zeta potential values of 151 nm and 30 mV, respectively. The novel and optimized BMX siRNA LNPs showed acid-based release of the active therapeutic agent. An in-vitro cell culture study against prostate cancer cell lines further supported the idea that these novel LNPs would be potent and more active compared to control formulas.

**Conclusion:** In summary, the current work showed a successful development and characterization of anticancer novel LNPs for targeting the novel and emerging target BMX as a second option of therapeutics development, after the initial reported work our group published recently on small molecule therapeutics development (Elsanhoury, Alasmari et al. 2023).