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Atypical Retinoid ST1926 Nanoparticle Formulation Development and Therapeutic Potential in Colorectal Cancer

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Abstract : Nanomedicine, the application of nanotechnology to medicine, is an emerging discipline that has gained significant attention in recent years. Current breakthroughs in nanomedicine have paved the way to develop effective drug delivery systems that can be used to target cancer. The use of nanotechnology provides effective drug delivery, enhanced stability, bioavailability, and permeability, thereby minimizing drug dosage and toxicity. As such, the use of nanoparticle (NP) formulations in drug delivery has been applied in various cancer models and have shown to improve the ability of drugs to reach specific targeted sites in a controlled manner. Cancer is one of the major causes of death worldwide; in particular, colorectal cancer (CRC) is the third most common type of cancer diagnosed amongst men and women and the second leading cause of cancer related deaths, highlighting the need for novel therapies. Retinoids, consisting of natural and synthetic derivatives, are a class of chemical compounds that have shown promise in preclinical and clinical cancer settings. However, retinoids are limited by their toxicity and resistance to treatment. To overcome this resistance, various synthetic retinoids have been developed, including the adamantyl retinoid ST1926, which is a potent anti-cancer agent. However, due to its limited bioavailability, the development of ST1926 has been restricted in phase I clinical trials. We have previously investigated the preclinical efficacy of ST1926 in CRC models. ST1926 displayed potent inhibitory and apoptotic effects in CRC cell lines by inducing early DNA damage and apoptosis. ST1926 significantly reduced the tumor doubling time and tumor burden in a xenograft CRC model. Therefore, we developed ST1926-NPs and assessed their efficacy in CRC models. ST1926-NPs were produced using Flash NanoPrecipitation with the amphiphilic diblock copolymer polystyrene-b-ethylene oxide and cholesterol as a co-stabilizer. ST1926 was formulated into NPs with a drug to polymer mass ratio of 1:2, providing a stable formulation for one week. The contin ST1926-NP diameter was 100 nm, with a polydispersity index of 0.245. Using the MTT cell viability assay, ST1926-NP exhibited potent anti-growth activities as naked ST1926 in HCT116 cells, at pharmacologically achievable concentrations. Future studies will be performed to study the anti-tumor activities and mechanism of action of ST1926-NPs in a xenograft mouse model and to detect the compound and its glucuroconjugated form in the plasma of mice. Ultimately, our studies will support the use of ST1926-NP formulations in enhancing the stability and bioavailability of ST1926 in CRC.

Keywords : nanoparticles, drug delivery, colorectal cancer, retinoids
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