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Superiority of aromatase inhibitor and cyclooxygenase-2 inhibitor combined delivery: Hyaluronate-targeted versus PEGylated protamine nanocapsules for breast cancer therapy

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Abstract:

Despite several reports have revealed the beneficial effect of co-administration of COX-2 inhibitors with aromatase inhibitors in managing postmenopausal breast cancer; no nanocarriers for such combined delivery have been developed till now. Therefore, protamine nanocapsules (PMN-NCs) have been developed to co-deliver letrozole (LTZ) that inhibits aromatase-mediated estrogen biosynthesis and celecoxib (CXB) that synergistically inhibits aromatase expression. Inspired by the CD44-mediated tumor targeting ability of hyaluronate (HA), we developed HA-coated PMN-NCs (HA-NCs) via electrostatic layer-by-layer assembly. Moreover, multi-compartmental PEGylated phospholipid-CXB complex bilayer enveloping PMN-NCs (PEG-NCs) were designed for conferring biphasic CXB release from the phospholipid corona and oily core as well as enabling passive-targeting. The NCs demonstrated excellent stability, prolonged circulation and could be scaled up with the aid of spray-drying technology. Hemolysis, serum stability and cytotoxicity studies confirmed the superiority of combined LTZ-CXB nano-delivery. Mechanistically, the NCs especially HA-NCs and PEG-NCs demonstrated precious anti-tumor effects in vivo revealed as reduction in the tumor volume and aromatase level, increased apoptosis, as well as inhibition of VEGF, NF-κB and TNF-α augmented by

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histopathological and immunohistochemical studies. Overall, our approach provided for the first time a potential strategy for targeted LTZ-CXB combined therapy of hormone-dependent breast cancer via singular nanocapsule delivery system.

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