

1358 **NOVEL EGFR/PI3K DUAL-TARGETING NANOPARTICLES INDUCE IMMUNOGENIC CELL DEATH IN BLADDER CANCER**

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Background Bladder cancer (BCa) is one of the most common malignancies worldwide. Epidermal Growth Factor Receptor (EGFR) overexpression is seen in up to 74% of BCa tissue specimens, however, current EGFR-based target therapy shows little benefit for BCa patients as the EGFR downstream pathways could be circumvented by other receptor tyrosine kinases (RTKs). Dual targeted therapy, which can bind and inhibit the EGFR and its downstream PI3K to affect tumor progression, could be a potential strategy for BCa treatment.

Methods Herein, we identified two natural products triptolide (TPL) and hesperidin (HSP), dual targeting EGFR and PI3Kin BCa by network pharmacology and molecular modeling. By applying a succinic acid linker was added between these two products, we synthesized amphiphilic TPL-HSP-EGFR targeting prodrug (THE) which further self-assembles into nanoparticles (THE NPs). Once binding to the EGFR on BCa surface, THE NPs could be internalized into BCa cells and released into lysosome to achieve further biofunctions.

Results THE NPs harbor the high drug-loading (91.99%) and low toxicity properties in utilizing natural products as tumor therapeutics. THE NPs could target BCa cells and internalized into lysosome. After hydrolyzed in low pH environment, THE NPs could release TPL and HSP targeting and inhibiting EGFR and PI3K. Immunogenic cell death markers HMGB1 and CRT levels were evaluated both in vitro and in vivo after treatment so as to inhibit BCa proliferation and tumor growth.

Conclusions Dual targeting nanoparticle may emerge as a novel paradigm in BCa treatment, providing a new approach for inducing immunogenic cell death in BCa care.

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