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MULTIFUNCTIONALIZED BIOCATALYTIC P22 NANOREACTOR FOR COMBINATORY TREATMENT OF ER+ BREAST CANCER

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Breast cancer is a leading cause of mortality in females worldwide. Tamoxifen continues to be the standard endocrine therapy, which requires metabolic activation by cytochrome P450 enzymes (CYP). However, the lower and variable concentrations of CYP activity at the tumour remain major bottlenecks for the efficient treatment, causing severe side-effects. Combination nanotherapy has gained much recent attention for cancer treatment as it reduces the drug-associated toxicity without affecting the therapeutic response. The principle of combination therapy in cancer is to use approaches that work by different mechanisms of action. Here we show the modular design of P22 bacteriophage virus-like particles for nanoscale integration of virus-driven enzyme prodrug therapy and photodynamic therapy. The estrogen receptors (ER) are the major role players in the initiation and progression of breast cancer and represent a potential site for directing receptor-mediated cellular uptake. Thus, in our approach we have functionalized biocatalytic P22 with the well-known photosensitizer, protoporphyrin IX (PpIX) and the estradiol derivative for achieving targeted inhibition of ER+ breast tumour cells. The final nanoparticles, P22CYP-PpIX-PEG(EST) are characterized by TEM, DLS, zeta potential and photo-physical analysis. These functionalized nanoparticles are recognized by and internalized into ER^+ breast tumour cells increasing the intracellular CYP activity and showing the ability to produce reactive oxygen species (ROS) upon UV_{365nm} irradiation. The generated ROS in synergy with enzymatic activity drastically enhanced the tamoxifen sensitivity *in vitro*, leading to a strong inhibition of tumour cells, which may allow the reduced toxicity owing to the lower drug concentration, and may overcome the tumour reoccurrence limitation. Thus, the targeted combinatory treatment using multifunctionalized biocatalytic P22 represents the effective nanotherapeutics for ER^+ breast cancer.

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