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# Erythrocyte membrane-camouflaged carrier-free nanoassembly of FRET photosensitizer pairs with high therapeutic efficiency and high security for programmed cancer synergistic phototherapy

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ABSTRACT

Phototherapy has been intensively investigated as a non-invasive cancer treatment option. However, its clinical translation is still impeded by unsatisfactory therapeutic efficacy and severe phototoxicity. To achieve high therapeutic efficiency and high security, a nanoassembly of Forster Resonance Energy Transfer (FRET) photosensitizer pairs is developed on basis of dual-mode photosensitizer co-loading and photocaging strategy. For proof-of-concept, an erythrocyte-camouflaged FRET pair co-assembly of chlorine e6 (Ce6, FRET donor) and 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindotricarbocyanine iodide (DiR, FRET acceptor) is investigated for breast cancer treatment. Notably, Ce6 in the nanoassemby is quenched by DiR and could be unlocked for photodynamic therapy (PDT) only when DiR is photobleached by 808-nm laser. As a result, Ce6-caused phototoxicity could be well controlled. Under cascaded laser irradiation (808–660 nm), tumor-localizing temperature rise following laser irradiation on DiR not only induces tumor cell apoptosis but also facilitates the tumor penetration of NPs, relieves tumor hypoxia, and promotes the PDT efficacy of Ce6. Such FRET pair-based nanoassembly provides a new strategy for developing multimodal phototherapy nanomedicines with high efficiency and good security.

## 1. Introduction

Breast cancer seriously threatens women's health [1,2]. Although most early-stage breast cancer can be effectively cured, triple negative breast cancer (TNBC) is still a great challenge in clinic [3,4]. TNBC is a subtype of breast cancer with negative estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) [1]. The clinical features of TNBC mainly include poor sensitivity to chemotherapeutics drugs, high risk of remote metastasis, and poor prognosis of patients [5–9]. Therefore, the clinical treatment of TNBC with chemotherapy is still far from satisfactory [5,10]. Moreover, most chemotherapeutics agents have narrow therapeutic windows, resulting in serious side effects [11–13]. In addition to systemic chemotherapy, tumor-localized photodynamic therapy (PDT) and photothermal therapy (PTT) have also been extensively investigated as non-invasive cancer therapeutics for TNBC treatment [14].

PTT and PDT induce the apoptosis and/or necrosis of tumor cells via local temperature rise and reactive oxygen species (ROS) generation under laser irradiation, respectively [15,16]. Given that the therapeutic mechanisms of PTT and PDT are independent of the expression of specific cell receptors, phototherapy has been considered as ideal treatment regimen for TNBC [17,18]. However, the therapeutic efficacy of mono-phototherapy (PTT or PDT alone) is far from satisfactory [19–21]. PTT, with spatial heterogeneous distribution of temperature rise within tumor tissues, is not sufficient to completely eliminate the tumor cells [22–24]. Moreover, the production of ROS by most photosensitizers (PSs) for PDT heavily depends on oxygen. As a result, the tumor hypoxia has posed a big obstacle for PDT [16,25]. Notably, the combination of

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