Near-Infrared-Activated Organic Nanocomposite for Enhanced Photothermal and Photodynamic Cancer Therapy

DTPT-core A–D–A nanoparticles (DTPTTCF@TPGS) exhibit low toxicity and potent near-infrared-triggered anticancer effects, effectively suppressing tumors.

Phototherapy, including photothermal therapy (PTT) and photodynamic therapy (PDT), has emerged as a minimally invasive and selective cancer treatment, leveraging localized heating or reactive oxygen species (ROS) generation to induce tumor cell death. PTT converts light energy into heat, causing DNA damage, protein denaturation, and membrane disruption, while PDT activates photosensitizers to produce ROS, triggering oxidative damage and apoptosis. Combining PTT and PDT enhances therapeutic efficacy, particularly when using near-infrared (NIR) light, which penetrates deeper into tissues. Organic acceptor–donor–acceptor (A–D–A) molecules with strong NIR absorption are promising phototherapeutic agents due to their high molar extinction coefficients, photostability, and dual PTT/PDT potential. However, their hydrophobic nature limits direct biomedical application, necessitating encapsulation in biocompatible carriers. D-α-tocopheryl polyethylene glycol succinate (TPGS) has proven effective, forming self-assembled nanoparticles (NPs) that improve solubility, stability, and bioavailability while also inhibiting P-glycoprotein to overcome drug resistance. TPGS-based NPs demonstrate low toxicity to normal cells, induce apoptosis in cancer cells *via* ROS generation, and enhance the therapeutic effects of co-delivered anticancer agents. These features make TPGS-encapsulated A–D–A molecules a versatile and promising platform for multimodal NIR-triggered phototherapy, combining high efficacy, selectivity, and safety for potential clinical applications.

Jiashing Yu and Ken-Tsung Wong (National Taiwan University) recently initiated a collaborative study to investigate a series of A–D–A structured small molecules featuring a coplanar dithieno[2,3-d:2′,3′-d′]thieno[3,2-b:3′,2′-b′]dipyrrole (DTPT) core, a framework known for its excellent charge-transport properties and strong NIR light absorption. Although DTPT-based materials have been extensively explored for applications in organic photovoltaics and other optoelectronic devices, this study repurposes them as organic photosensitizers for cancer phototherapy. To improve biocompatibility and stability, the DTPT-based molecules were formulated into NPs using TPGS (**Fig. 1(a)**). Among the series, DTPTTCF—bearing 3-cyano-4,5,5-trimethylfuran-2(5H)-ylidene malononitrile (TCF) terminal acceptor groups—exhibited the most promising performance.

Photothermal characterization revealed that, upon 808 nm laser irradiation for 10 minutes, most DTPT-based nanoparticles (excluding DTPTCY@TPGS) exhibited a temperature increase exceeding 20 °C at a concentration of 30 ppm, whereas the control (water) showed no measurable change. Comparable heating behavior was observed in phosphate-buffered saline (PBS) (**Fig. 1(b)**), confirming the strong photothermal capabilities of these nanoparticles. To assess cytotoxicity, an *in vitro* assay was conducted on both normal (L929) and cancerous (4T1) cell lines. The results demonstrated that L929 cell viability remained above 65% even at a high concentration of 50 ppm, indicating minimal toxicity toward normal cells. Similarly, 4T1 cells treated with DTPTTCF NPs maintained over 50% viability at the same concentration, suggesting limited cytotoxic

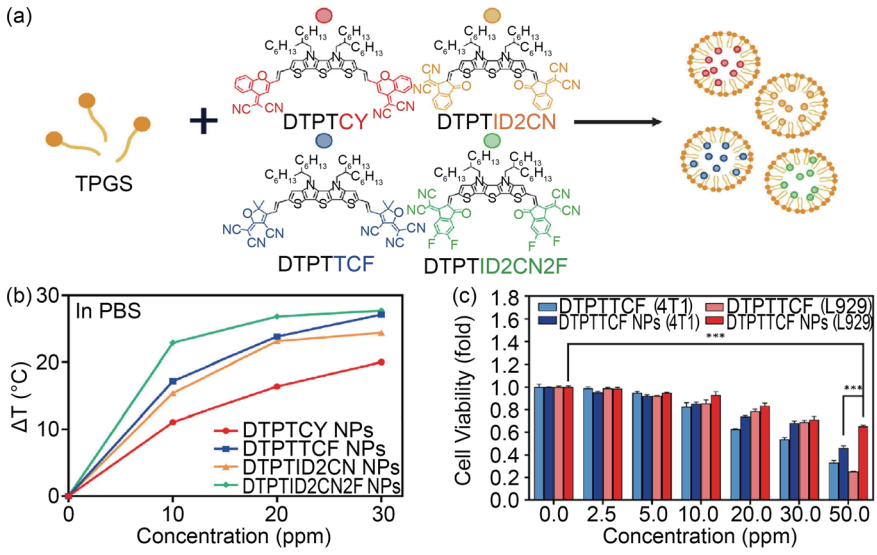

Fig. 1: (a) Schematic of tailor-made nanoparticles as photosensitizers. (b) Temperature increase of DTPT NPs in PBS after 10 minutes of irradiation with an 808 nm laser. (c) Cell viability of 4T1 and L929 cells incubated with DTPTTCF@TPGS NPs at different concentrations (mean ± SD, n = 3, $p < 0.001$ by ANOVA followed by Tukey's post hoc test). [Reproduced from Ref. 1]

effects on cancer cells. Collectively, these findings underscored the biocompatibility of DTPTTCF NPs and their low cytotoxicity toward both normal and malignant cells (**Fig. 1(c)**).

Overall, the resulting DTPTTCF@TPGS nanoparticles exhibited low inherent cytotoxicity, strong NIR absorption, enhanced photothermal conversion efficiency, and robust photodynamic activity, making them promising candidates for cancer phototherapy.

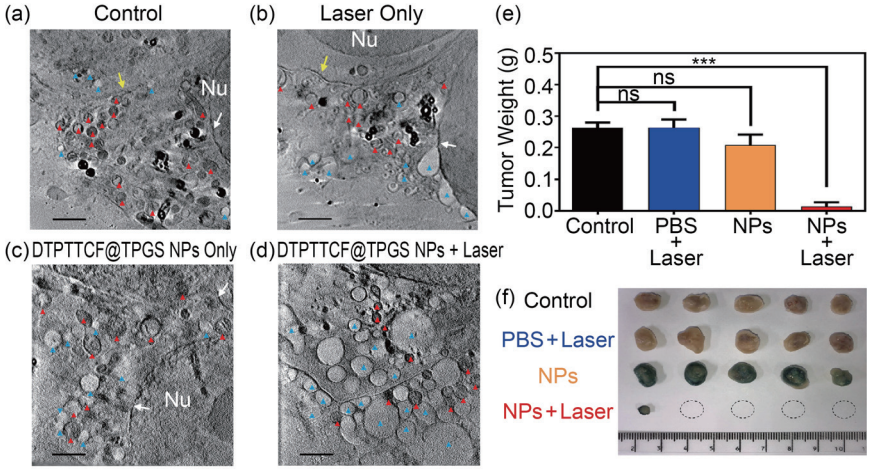

Fig. 2: Virtual slices of reconstructed Z-stack images of 4T1 cells under different treatment conditions captured *via* soft SXT: (a) control group, (b) laser-only group, (c) DTPTTCF@TPGS NPs-only group, and (d) NPs + Laser group. Nu: nucleus; mitochondria (red); vesicles (blue); nuclear membrane (white arrows); cell membrane (yellow arrows). Scale bars: 2 μm. (e) Tumor weight of mice at the end of treatments (day 14) (mean ± SD, n = 5, $p < 0.001$ by ANOVA followed by Tukey's post hoc test). (f) Photographs of tumors extracted from mice at the end of treatments (n = 5). [Reproduced from Ref. 1]

Additionally, soft X-ray tomography (SXT) at **TPS 24A** beamline was employed to visualize treatment-induced intracellular alterations with high spatial resolution (**Figs. 2(a)–2(d)**). In 4T1 cells, major organelles—including mitochondria, vesicles, nuclei, nuclear envelopes, and plasma membranes—were clearly delineated, enabling the precise assessment of morphological integrity. No appreciable structural differences were detected between the control and laser-only groups, indicating that laser irradiation alone did not perturb cellular ultrastructure. By contrast, subtle vacuolar changes were observed in a small subset of cells within the NPs-only group, suggesting limited nanoparticle-associated stress. Notably, extensive and prominent vacuolization emerged following irradiation in the NPs + Laser group, representing a marked deviation from all other conditions. Taken together, these SXT observations strongly support that the combined NPs + Laser treatment triggered pronounced intracellular disruption consistent with the initiation of apoptotic cell death.

In vivo antitumor performance was evaluated using a 4T1 tumor model established in BALB/c mice. Treatment began when tumors reached 30–60 mm^3, and mice were assigned to four groups: PBS (control), PBS with NIR laser, DTPTTCF@TPGS NPs, or NPs combined with NIR laser irradiation. Only the NPs + Laser group showed a pronounced therapeutic effect. After intratumoral injection, NIR irradiation of NPs-treated tumors rapidly increased tumor temperature to approximately 55 °C, enabling effective photothermal activity. Throughout the 14-day observation period, tumor progression differed significantly among groups: tumors in the control, PBS + Laser, and NP-only groups expanded at least four-fold from baseline. By contrast, the NPs + Laser group exhibited strong inhibition of tumor growth, with only one very small tumor remaining out of five mice (**Fig. 2(e)**). At the end of treatment, excised tumors showed dramatic reductions in tumor weight, with nearly complete tumor elimination in the NPs + Laser group (**Fig. 2(f)**). Overall, laser-activated DTPTTCF@TPGS NPs markedly reduced both tumor size and tumor weight, demonstrating excellent photothermal antitumor efficacy.

In summary, a long-wavelength-responsive phototherapeutic delivery system was developed based on DTPT-centered A–D–A-type conjugated molecules. These molecules exhibited strong absorption, efficient reactive oxygen species generation, and pronounced photothermal effects. Utilizing the self-assembly properties of amphiphilic TPGS, biocompatible DTPTTCF@TPGS nanoparticles with high loading efficiency were formulated. *In vitro* assays demonstrated controlled and effective cytotoxicity against cancer cells, while high-resolution imaging revealed significant intracellular damage under NIR irradiation. Overall, these results underscored the potential of DTPTTCF@TPGS nanoparticles as robust and precise phototherapeutic agents for cancer treatment. (Reported by Zi-Jing Lin)

This report features the work of Jiashing Yu, Ken-Tsung Wong and their collaborators published in Adv. Healthcare Mater. ***14****, 2404418 (2025).*

TPS 24A Soft X-ray Tomography

- Soft X-ray Imaging, SXT
- Biomedical/Biological Science, Biomedical Engineering, Materials Science, Environmental Science

Reference

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