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Nanostructured Perylene Diimide Oligomers with Ultra-high Photothermal Conversion Efficiency for Tumor Therapy

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Abstract: Developing one agent with high stability and ultra-high photothermal conversion efficiency for near-infrared (NIR) photothermal cancer treatment is very challenging but highly desirable. Herein, we developed a new perylene diimide(PDI)-based oligomer (**OPDI**), which depicts greatly red-shifted absorption at NIR region compared with monochromophoric PDIs. More importantly, the self-assembled **OPDI** nanoparticles not only exhibit high stability and preferable biocompatibility but also possess an ultra-high PTCE (up to 79.8 %, higher than most photothermal agents reported before). This **OPDI** photothermal agent has been demonstrated to exhibit excellent therapeutic effects. Our research would provide a new platform for the development of new photothermal agents with ultra-high PTCE.

Photothermal therapy (PTT), has been demonstrated as a promising and effective modern therapeutics due to its outstanding advantages such as precise targeting, deep penetration and minimal invasiveness through tissue to healthy tissues in cancer treatment..^[1] Although numerous near-infrared (NIR, 670-900 nm) photothermal compounds have been reported for cancer PTT,^[2] the agents with stable and ultra-high NIR photothermal conversion efficiency (PTCE) is rare.^[3] Thus, developing new materials to address this issue is highly desirable.

Among all reported photothermal agents, PDI-based compounds have caused many scientists' interest due to their adjustable optical or photothermal properties as well as

preferable biocompatibilities.^[4] For instance, monomeric PDI (**MPDI**) derivatives, exhibited preferable photothermal performance, have been reported in cancer PTT.^[5] Unfortunately, most of the monomeric PDIs generally showed lower photothermal conversion efficiency (PTCE), and their stabilities have never been mentioned which greatly impedes their applications in cancer PTT. Such issue might be solved through covalently bonding two or more monomeric PDI cores together to form larger conjugated PDI derivatives, because these oligomers can achieve NIR absorption with high stability and high PTCE. Beside this, PDI-based molecules have already been demonstrated to self-assemble into ultra-small nanoparticles in water containing biocompatible surfactant^[4f,6] which have great potential for biological applications.

Herein, we firstly developed a novel PDI-based oligomer (**OPDI**), in which the neighboring PDI units are bridged by an imine group via palladium catalyzed coupling reaction of dibromo perylenediimide (PDI-2Br) and diamino perylenediimide (PDI-2NH₂) (Figure 1a). The optical properties of this multi-chromophoric **OPDI** can be tuned, e.g. evidently red-shifted absorption and emission compared with monochromophoric PDIs, blue-black color in solid state and weak fluorescence. All these features may make **OPDI** more suitable for tumor therapy. Moreover, the **OPDI** can self-assemble into nanoparticles (NPs) in aqueous dispersion in the presence of Pluronic F127 (Figure 1b). Most impressively, the unprecedented **OPDI** NPs demonstrate distinct advantages: 1) Ultra-high PTCE of 79.8 %. This value is higher than that of most photothermal agents reported so far;^[5g,7] 2) Quite stable performance. The as-fabricated **OPDI** NPs show no evident changes in dimension, morphology and photothermal properties in aqueous dispersion after aging for 5 months; and 3) Preferable biocompatibility. Effective PTT has been demonstrated *in vitro* and *in vivo* (Figure 1b).

other isomers are listed in Figure S10-S12. The GPC analyses revealed that the **OPDI** sample has a number-average molecular weight (M_n) of 4086 as well as a narrow polydispersity indices (PDI) of 1.03 (Figure 2e), which are well consistent with above-mentioned MS results. The optical properties of **OPDI** solution (in THF) were investigated through UV-vis absorption and photoluminescence (PL) spectroscopy (Figure 2f and S13a). Evidently, the maximum absorption of **OPDI** was broadened and red-shifted compared with that of the monochromophoric PDI-2Br and **MPDI** (Figure 2f), which suggests the formation of an expanded rigid backbone within **OPDI**. More importantly, the **OPDI** solution in THF demonstrates preferable absorption in the region of 680 ~ 800 nm (Figure 2f), which lays the foundation for the following photothermal conversion and treatment. Furthermore, **OPDI** can readily self-assemble into small nanoparticles (NPs) in aqueous solution ($\sim 5 \text{ mg mL}^{-1}$) containing F127 as a protection surfactant. The **MPDI**-based NPs were also prepared via the same methods.

Figure 2. a-d) MALDI-TOF MS analysis of **OPDI** (matrix: 1- cyano-2-(4- hydroxyphenyl) acrylic acid), full spectrum (a), applied spectra of trimer (b), tetramer (c) and pentamer (d). e) GPC curve of **OPDI** (THF, PS standard). f) The UV absorption of PDI-2Br, **MPDI** and **OPDI** in THF, the inset shows the photos of corresponding solutions (0.1 mg mL^{-1}).

After self-assembly, the maximum absorption peak of **MPDI** NPs appears at about 645 nm (Figure 3a), which is consistent with the color (blue) of the corresponding

aqueous dispersion (inset in Figure 3a). In contrast, the **OPDI** NPs show an evident absorbance at NIR region compared to **MPDI** NPs (>760 nm, Figure 3a), which suggests that the **OPDI** NPs may possess the photothermal conversion capability under the irradiation of NIR light. Accordingly, the color of aqueous dispersed **OPDI** NPs shifts to black (inset in Figure 3a), which should be attributed the greatly enlarged rigid backbone after coupling reaction. It is also noted that both **MPDI** and **OPDI** NPs behave superb dispersibility in aqueous phase containing F127 (Inset in Figure 3a). The morphologies of **MPDI** and **OPDI** NPs were studied by transmission electron microscopy (TEM). The **MPDI** NPs exhibit irregular nanoparticles with an average diameter of 38 ± 12 nm (Figure 3b), where the **OPDI** NPs possess a much more regular morphology with an average diameter of 37 ± 7 nm (Figure 3c). The dimensions of two kinds of NPs were further confirmed by dynamic light scattering (DLS, inset in Figure 3b and 3c).

Figure 3. a) The absorption of **MPDI** and **OPDI** NPs in pure water ($200 \mu\text{g mL}^{-1}$), the inset shows the photos of corresponding dispersions ($200 \mu\text{g mL}^{-1}$). b) The representative TEM image of **MPDI** NPs, the inset shows the DLS. c) The representative TEM image of **OPDI** NPs, the inset shows the DLS. d) Thermal images of PBS, **MPDI** and **OPDI** NPs in PBS solutions ($200 \mu\text{g mL}^{-1}$) after laser irradiation at different time. e) The effects of irradiation time on the temperature changes of PBS, **MPDI** and **OPDI** NPs in PBS solutions ($200 \mu\text{g mL}^{-1}$). f) The effects of irradiation time on the temperature changes of PBS, **OPDI** NPs in PBS solutions ($200 \mu\text{g mL}^{-1}$) prepared after 1 or 5 months. 808 nm laser irradiation was used at 1.5 W cm^{-2} for 5 min. g) The effects of irradiation time on the temperature changes of and **OPDI** NPs in PBS solutions ($200 \mu\text{g mL}^{-1}$) under different irradiation powers. h) The effects of irradiation time on the temperature changes of and **OPDI** NPs in PBS solutions ($0\text{--}300 \mu\text{g mL}^{-1}$) under the same irradiation powers (1.5 W cm^{-2}). 808 nm laser irradiation was used for 5 min.

The excellent dispersibility of the ultra-small NPs in aqueous phase encourages us to investigate the photothermal conversion capability of the **OPDI** and **MPDI** NPs. The aqueous dispersions of **MPDI** and **OPDI** NPs as well as the PBS control were irradiated by a NIR laser with $\lambda = 808$ nm, and the system temperature was recorded via thermal imaging (detailed in Supporting Information: SI). As shown in Figure 3d and 3e, the phosphate buffer solution (PBS) shows almost no temperature change under the irradiation of 808 nm laser. As expected, the **MPDI** dispersion ($200 \mu\text{g mL}^{-1}$) exhibits inconspicuous increase (only about 4°C) in the system temperature. In contrast, profiting from the considerable absorption in the NIR region, an entirely different photothermal conversion result can be investigated for the **OPDI** NPs dispersion. For instance, a distinct temperature increase (reached 53°C within 300 s) of the **OPDI** NPs dispersion ($200 \mu\text{g mL}^{-1}$) was observed after the treatment of the same NIR laser power (1.5 W cm^{-2}), which is consistent with our former hypothesis. Moreover, the extremely weak fluorescence emission of **OPDI** NPs (Figure S13b) suggests that the vibrational relaxation may play a dominant role in furnishing a useful photothermal effect.^[5g] Since the **OPDI** NPs dispersion demonstrates an greatly enhanced absorbance at NIR region, an effective conversion from photo energy into thermo within the **OPDI** NPs dispersion upon NIR irradiation can be seen. Moreover, the **OPDI** NPs exhibits superb-stable morphology. Even after aging for 5 months (Figure 3f and Figure S14), the as-fabricated **OPDI** NPs still displayed preferable photothermal performance without any change in morphology.

Interestingly, our **OPDI** NPs also exhibited laser power- and concentration-dependent photothermal conversion effect. For instance, the photothermal heating effect of the dispersion was enhanced not only with the increase of light power, but also with the **OPDI** NPs concentrations (Figure 3g and 3h, Figure S15 and S16). Meanwhile, the study of photothermal cycle performance (Figure S17a) indicated that, the **OPDI** NPs still show excellent photothermal performance (after 10 cycles irradiation). This result suggests that **OPDI** NPs can be acted as the efficient photothermal agent, in cancer cells/tumor PTT. Furthermore, a steady-state temperature was recorded through the heating and cooling profiles (Figure S17b). The

PTCE (η) of the **OPDI** NPs was calculated to be 79.8 % (inset in Figure S17b), which is higher than the values of most reported organic photothermal agents.^[5g,7]

Profited from above-mentioned excellent photothermal performance, the **OPDI** NPs have been utilized in photothermal therapy of cancer *in vitro*, where the **OPDI** NPs dispersion possess low cytotoxicity in dark (Figure S18) even at a higher concentration ($200 \mu\text{g mL}^{-1}$), indicating a preferable biocompatibility. Notably, the **O-**

Figure 4. a) MTT results of 4T1 cells treated with different concentrations of **OPDI** NPs without or with laser irradiation (808 nm at 1.5 W cm^{-2} for 10 min). b) The effects of irradiation power on the 4T1 cell viability treated with $200 \mu\text{g mL}^{-1}$ of **OPDI** NPs or without **OPDI** NPs (808 nm for 10 min). c) The effects of irradiation time on the 4T1 cell viability with $200 \mu\text{g mL}^{-1}$ of **OPDI** NPs or without **OPDI** NPs (808 nm at 1.5 W cm^{-2}). d-f) Co-staining of live and dead 4T1 cells: d) cells only; e) cells irradiated with laser only; f) cells treated with $200 \mu\text{g mL}^{-1}$ of **OPDI** NPs. 808 nm laser irradiation at 1.5 W cm^{-2} was used for 10 min . The scale bars in (d-f) are $200 \mu\text{m}$.

PDI NPs displayed efficient PTT against cancer cells under the laser irradiation (Figure 4a), i.e. the **OPDI** NPs exhibited greatly enhanced photo cytotoxicity toward 4T1 cells with the increasement of its concentration. Similarly, the photo cytotoxicity also shows the laser power- and illumination time-dependent behaviors (Figure 4b and 4c). It should be noted that the illumination time (10 min) could lead to the efficient lethality to cancer cells. Thus, the following illumination time for all cells experiments kept at 10 min . Live/dead staining further supports above PTT results, where live and dead 4T1 cells were differentiated by co-staining with PI (red fluorescence; dead cells) and calcein AM (green fluorescence; living cells) after laser irradiation. Almost all the cells were positive for red fluorescence after laser

irradiation, indicating the extinction of cancer cells (Figure 4d-4f). All results suggest that this novel photothermal agent possesses superior biocompatibility and efficient PTT effects.

To investigate the PTT of cancer *in vivo*, the ability of photothermal imaging was firstly studied. After intra-tumor injection (4T1 tumor-bearing mice were used and the 4 h post-injection as the optimum treatment time) of **OPDI** NPs, the temperature inside the tumor is much higher than that of mice injected by PBS solution (Figure 5a), and the temperature can reach about 60 °C after irradiation for only 2 minutes, which is much fast (Figure 5a and 5b) comparing to other agents. These results suggest that the new photothermal agent possess excellent photothermal imaging and quick temperature elevation performance. Subsequently, four groups were established: (1) PBS administration (50 μ L, intra-tumor injection); (2) only laser irradiation administration (1.0 W cm⁻²); (3) only **OPDI** NPs administration (50 μ L, 0.5 mg mL⁻¹, intra-tumor injection); (4) **OPDI** NPs administration (50 μ L, 0.5 mg mL⁻¹, intra-tumor injection) combined with laser irradiation (4 h post-injection was also chosen here). During the subsequent 14-days observation period, the situations of mice in the above four groups were observed (Figure S19). There is no tumor outburst after the initial elimination in group (4) (Figure S19 and 4c-4e), and the corresponding anatomized tumor displays the lowest values in size and weight. On the contrary, the tumors from the other three groups show consistently higher growth rates, further suggesting that the PTT induced by the **OPDI** NPs can significantly eliminate the tumor. More importantly, during the 14-day observation period, the treated mice didn't display any abnormalities in the daily behaviors and the weight values of the monitored body were stable (Figure S19 and 4f). Meanwhile, the eosin (H&E) staining was applied to estimate the biosafety of **OPDI** NPs *in vivo* (healthy mice were used here). At 14-day post-injection, the major organs were harvested from the mice treated with **OPDI** NPs (50 μ L, 0.5 mg mL⁻¹, intravenous injection) and PBS as a control, respectively. No obvious damages or inflammations of the organs (Figure S19) were observed,

suggesting that the OPDI NPs can be removed from the mice body through a proper way without any biotoxicity *in vivo*.

Figure 5. (a) Representative time-dependent photothermal images of PBS (50 μ L) and **OPDI** NPs (Intra-tumor injection of 50 μ L of 0.5 mg mL⁻¹, 808 nm laser at 1.0 W cm⁻²) injected 4T1 tumor-bearing mice. (b) The effects of irradiation time on the tumor temperature of 4T1 tumor-bearing mice (The injection and laser irradiation conditions are same as Figure 5a). (c) Photos of tumors collected from the mice in different groups at the end of PTT. (d) The relative tumor volume of mice in different groups at 0-14 day post-injection. (e) The tumor weights of tumors collected from the mice in different groups at the end of PTT. (f) The body weights of mice in different groups at 0-14 day post-injection. Injection and treat conditions in Figures c-f: mice were intra-tumor injected by 50 μ L of 0.5 mg mL⁻¹ **OPDI** NPs, after 4 h, the 808 nm laser (1.0 W cm⁻², irradiated for 10 min) were used for temperature elevation.

In summary, we have successfully synthesized a novel perylene diimides (PDI)-based oligomer (**OPDI**), which can be self-assembled into nanoparticles in the presence of F127. The as-fabricated **OPDI** NPs not only exhibit high stability and preferable biocompatibility, but also possess ultra-high photothermal conversion efficiency (up to 79.8 %), which makes them as promising photothermal agents for cancer therapy. Our research also indicated that this novel photothermal agent can display the proper clearance from the body without biotoxicity and suppress cancer growth *in vitro* and *in vivo* through photothermal therapy. This investigation would provide us a new strategy to develop new photothermal agents for photothermal therapy and biomedical applications.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: perylene diimide oligomer, self-assembly, photothermal agent, photothermal conversion efficiency, phototheranostics

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Table of Content