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Near Infrared Boron Dipyrromethene Nanoparticles for Optotheranostics

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Abstract

Boron dipyrromethene (BODIPY) is a class of important emerging fluorescent dyes. Due to their unique chemical and optical properties, near infrared (NIR)-emitting BODIPY dyes containing nanoparticles have recently been developed for a wide array of cutting-edge cancer optotheranostic applications. These nanoparticles not only have robust photostability and tunable photophysical properties, but they can also be flexibly tailored to a multitude of functional uses. Based on these outstanding characteristics, such nanoparticles have shown great promise in diagnosis as biological sensors, as well as in their utilization in advanced imaging and photomedicine for cancer treatment. In particular, here, this study first discusses their use as photoswitchable fluorescence probes toward in vitro single-molecule imaging. Second, this study takes a look at their opportunities for photoacoustic imaging utilization. Third, approaches are discussed to construct new NIR-absorbing BODIPY nanoparticles for photodynamic therapy (PDT). Fourth, this study delves into the new approach to use such nanoparticles as an emerging version of triplet-triplet annihilation upconversion (TTA-UC) and their biological uses, such as their photoactivation prodrug therapy (PAPT) for cancer. Finally, new biological sensors based on NIR BODIPY nanoparticles are introduced.

Keywords

BODIPY; cancer; near infrared; optotheranostics

1. Introduction

In recent years, near infrared (NIR)-BODIPY-loaded nanoparticles (NIR BODIPY NPs) have attracted considerable attention due to their unique chemical and physical properties, such as their intense absorption ability in the NIR region and robust photostability.^[1–4] Compared to other dye-doped nanoparticles, NIR BODIPY NPs are one of the most promising candidates for biomedical applications, as the synthesis and modification of BODIPY are quite facile and readily controlled.^[5–7] Since their molecular structure, and concomitant physiochemical and optical properties are also flexible, they are easily tailored.

Conflict of Interest

The authors declare no conflict of interest.

Meanwhile, BODIPY nanoparticles (BODIPY NPs) are typically nontoxic and biocompatible to living organisms.^[8,9] Therefore, NIR BODIPY NPs provide a vast opportunity as a versatile foundation for cancer optotheranostic applications.

Cancer has long been and remains one of the leading causes of death in the world^[10–13] and early diagnosis and effective therapy can both improve cancer survival rates and reduce patients' suffering.^[14–16] Although quite significant advances have been achieved in cancer diagnosis and therapeutic technologies, effective treatment protocols are inadequate due to the low efficacy and/or high toxicity of existing therapeutics.^[17–19] In the past few years, with the tremendous development of optical methods and biophotonic materials in the biomedical field, increased attention has been paid to the diverse applications possible with respect to luminescence nanoparticles for light-mediated diagnosis/treatment or "optotheranostics."^[20–22]

Here, we will focus on the design and synthesis of the emerging NIR BODIPY luminescent organic nanoparticles, along with their applications in cancer optotheranostics. There are five sections, which are shown in Scheme 1. In the first section, we will present a strategy to prepare NIR BODIPY NPs as reversibly photoswitchable fluorescent probes. In the second, we will present recent advances in the use of NIR BODIPY as deep-tissue photoacoustic imaging (PAI) agents due to their intense absorption ability in the NIR region. In the third section, we will discuss recent progress in the design of new NIR BODIPY NPs as therapeutic agents in photodynamic therapy (PDT). In this section, we will take a look at how to enhance and broaden the absorption of BODIPY photosensitizers in the NIR region, and we will illustrate the consequent enhancement in singlet oxygen generation in NIR BODIPY and their concomitant treatment effect in vivo. In the fourth section, we combine BODIPY-based photosensitizers with annihilators to prepare organic upconversion nanoparticles as new phototransducers to activate the prodrug in vivo. Finally, we will introduce the design and use of NIR-BODIPY NPs as potential tumor reducing microenvironment detectors.

2. NIR BODIPY NPs in Photoswitchable Imaging

Due to their numerous potential applications, there has been widespread investigation into photoswitchable materials in the past several decades, ranging from rewritable data storage, display development, and super-resolution fluorescence imaging.^[23–26] In previous studies, photoswitchable nanoparticles were developed by co-doping photochromic and fluorophore units in one nanoparticle.^[27–30] In such photoswitchable nanoparticles, when the fluorophore unit is excited, fluorescence resonance energy transfer (FRET) occurs from the fluorophore to the photochromic moiety, leading to fluorescence quenching. Upon long-wavelength light excitation, the molecular structure of the photochromic moiety can change accordingly, leading to the blueshifting of the respective absorption wavelength. Consequently, the FRET effect between the fluorophore and the photochromic moiety disappears, resulting in the ability to recover bright fluorescence.^[27–30] For example, green-emission BODIPY and spiropyran molecules were encapsulated together with poly(ethylene glycol)–poly(methyl methacrylate) (PEG–PMMA). Within these nanoparticles, the photoreversible transformation of closed state spiropyran into the corresponding open state

leads to the fluorescence quenching of BODIPY.^[31,32] However, the emission wavelength of most reported photoswitchable nanoparticles is limited to the visible region. In contrast, the NIR emission of photoswitchable nanoparticles has quite a few advantages compared to visible light, such as reduced biological autofluorescence, as well as better tissue penetration.^[33,34] Recently, as shown in Figure 1, Huang et al. selected an NIR-emitting BODIPY dye (B-1) as the fluorophore and 1,2-dithienylethene (DTE) as a photochromic moiety to construct the NIR-emitting photoswitchable nanomaterial.^[35] By the use of an amphiphilic polymer coating, small, photostable, and biocompatible photoswitchable nanoparticles co-doped with B-1 and DTE (DTE-B-1-NPs) were obtained. The DTE-B-1-NPs showed robust reversible photoswitching ability in their NIR emission. Moreover, reversible NIR-emission photoswitching was demonstrated via these DTE-B-1-NPs in live cells.^[35] This study presents a new way to reversibly modulate the NIR emission of dyes for numerous future advanced biophonic applications, such as super-resolution fluorescence imaging in biological applications.

3. NIR BODIPY NPs in Photoacoustic Imaging

NIR-BODIPY-based nanoparticles can be used not only to construct reversible NIR-photoswitchable materials for in vitro and ex vivo applications, but they can also achieve deep-tissue photoacoustic imaging. PAI is a newly emerging and rapidly growing noninvasive biomedical imaging technology.^[36–40] In brief, in PAI, nonionizing laser pulses are delivered into biological tissues, producing ultrasonic waves. The ultrasonic energy that is absorbed is then used to reconstruct the optical absorption distribution in the tissue.^[36–40] Compared to light, ultrasonic waves are generally two to three orders of magnitude less scattered in biological tissue. Hence, photoacoustic imaging not only possesses the high sensitivity and specificity of optical imaging, it also offers high spatial resolution at great depths of up to several centimeters. It is important to note that the latter is challenging via conventional pure-optical-imaging technologies. In addition, as the axial resolution of photoacoustic imaging comes at the time of arrival of the ultrasonic signals, this enables depth-resolved 3D images to be taken without the need to mechanically scan in a vertical direction. Moreover, photoacoustic imaging has provided an unprecedented opportunity to link complex biological systems from organelles to organs at multiple scales with consistent optical absorption contrast, and this has the potential to facilitate the study of system biology. The key to success, with respect to the application of PAI in vivo, is the development of new and robust NIR-absorbing endogenous biomaterials.^[36–40] To date, numerous photoacoustic contrast agents have been developed, such as carbon nanotubes,^[41,42] and gold nanomaterials,^[43–45] as well as small-molecule dyes.^[46–48] However, the nonbiodegradability, potential long-term toxicity, and poor metabolism in the body of the aforementioned nanoparticles has hindered their clinical transition. The biocompatible small-molecule dye, indocyanine green (ICG),^[49,50] which has been approved by the U.S. Food and Drug Administration for patient use, suffers from intrinsic optical instability and is difficult to modify. Hence, the exploration of novel NIR dyes with intense absorption ability, high biological compatibility, and good photostability is highly desirable for PAI in vivo.

Wu and co-workers also recently reported the facile synthesis of a more flexible naphthalene-fused BODIPY dimer (ND-BDP) (Figure 2). In addition, such an ND-BDP

molecule presents an intense NIR absorption, much better photostability, and higher photoacoustic activity in vitro compared to ICG, making it an excellent candidate to be a PA contrast agent. Moreover, applications for the ND-BDP-loaded BSA-protein-based nanoparticles for PAI in vivo were also demonstrated with respect to a mouse model with liver cancer. In this study, a significant PA signal was able to be observed in the tumor region 24 h postinjection due to the accumulation of the ND-BDP-loaded BSA NPs (Figure 2).^[51]

Not only can NIR-BODIPY-based imaging contrast be efficiently achieved with high-resolution tumor photoacoustic imaging, it also offers a unique opportunity to probe the given biological analysis in its native environment with minimal disruption as an in vivo detector.^[52] For example, H₂S has been proven to be a physiological gas transmitter with robust cytoprotective action in multiple organ systems, including playing a regulatory role in the cardiovascular system and modulation of the central nervous system.^[53] In this regard, Zhao and co-workers presented the development of a PA nanoparticle (Si@BDP) to specifically detect H₂S based on NIR BODIPY as the chromophore (Figure 3). In Si@BDP, a H₂S-responsive PAI sensor was designed based on the modulation of the electronic density of the substituents to redshift the absorption of BODIPY dye to the near-infrared region in order to produce PA signals. That was done by employing the feasible thiol-halogen nucleophilic substitution to a monochlorinated hybrid dye with H₂S. Indeed, when BDP reacts with H₂S, BDP-SH will be produced inside the Si@BDP nanoparticles, resulting in high NIR absorption around 780 nm. Thus, the Si@BDP can lead to a strong photoacoustic signal output in the NIR region. More importantly, Si@BDP has been able to photoacoustically track endogenous H₂S generation in real time in an HCT116 (human colon cancer cells) tumor-bearing mouse model.^[37]

4. NIR BODIPY NPs in Photodynamic Therapy

Photodynamic therapy has received emerging attention in cancer therapy due to its minimally invasive nature, fewer side-effects, and less damage to marginal tissues than conventional cancer treatments, such as chemotherapy and radiotherapy. Generally, PDT contains three essential factors: a photosensitizer, molecular oxygen, and light. The photosensitizer can sensitize molecular oxygen via light, which results in singlet oxygen species to treat the malignancy in the targeted tissue.^[54–60] In recent years, NIR-mediated PDT has been receiving increasing attention since NIR light has much deeper tissue penetration than visible light. The development of NIR-mediated PDT has great promise with respect to the treatment of deep-seated tissue tumors, such as brain cancer or the peritoneal metastasis of ovarian cancer, especially where regular cancer treatment is inaccessible.^[61–64] In this regard, the absorption intensity and singlet-oxygen generation efficiency in the NIR region are essential to the design of successful photosensitizers. These key factors are particularly important in the treatment of tumors at a deep tissue level, as these factors greatly improve the efficiency of PDT, thus reducing the dosage of PS molecules and lowering the power of the excitation light required.^[65–67]

In order to achieve NIR-mediated PDT in deep-seated tumors, several highly efficient NIR-absorbing BODIPY-based photosensitizers have recently been developed. For example, Huang et al. designed a biocompatible and highly effective NIR-light-absorbing carbazole-

substituted BODIPY (Car-BDP) (Figure 4).^[63] Due to the outstanding π - π conjugation between carbazole and BODIPY, Car-BDP possesses an intense, broad NIR absorption band (600–800 nm) and a high singlet-oxygen quantum yield ($\Phi = 67\%$). After being encapsulated in tumor-targeting biodegradable poly(lactic acid)-poly(ethylene glycol)-folic acid (PLA-PEG-FA) polymers, Car-BDP is able to form small, uniform organic nanoparticles that are both water-soluble and tumor-targetable (Car-BDP-TNM). By utilizing an exceptionally low power density and cost-effective lamp-light, such nanoparticles offer an unprecedented tumor-targeting photodynamic therapeutic effect at a deep-tissue level. In addition, due to their excellent NIR fluorescence properties ($\lambda_{em} = 770$ nm), Car-BDP-TNM can be simultaneously traced in vivo. This study appears to be a major step forward in PDT via the development of a new class of ultralow-power lamp-light-operable NIR-absorbing biocompatible organic nano particles for the noninvasive effective targeting and treatment of deep-tissue tumors.^[63]

Alternatively, as shown in Figure 5, a resonance energy transfer (RET) mechanism was utilized to construct a novel dyad photosensitizer that is able to dramatically boost NIR photon utility and enhance singlet-oxygen-species generation (Figure 5).^[68,69] In this study, the energy-donor moiety (distyryl-BODIPY) was connected to a photosensitizer (i.e., diiododistyryl-BODIPY) to form a dyad molecule (RET-BDP). The resulting RET-BDP showed significantly enhanced absorption and singlet-oxygen efficiency than that of the acceptor moiety of the photosensitizer alone (diiodo-distyryl-BODIPY) in the NIR range. After being encapsulated with biodegradable copolymer Pluronic F-127-folic acid (F-127-FA), RET-BDP molecules can form uniform and small organic nanoparticles that are both water soluble and tumor targetable. Used in conjunction with an exceptionally low-power NIR LED light irradiation, these nanoparticles show superior tumor-targeted therapeutic PDT effects against cancer cells both in vitro and in vivo relative to that found for unmodified photosensitizers.^[70] This study offers another new method to expand the options for the design of NIR-absorbing photosensitizers for future clinical cancer treatments.

Moreover, Ju et al. reported on a newly designed NIR-responsive pH-activatable aniline-substituted Azo-BODIPY as a multifunctional photosensitizer to realize specific targeting imaging, for efficient PDT and therapeutic self-feedback through encapsulating such molecules in cRGD-functionalized nanoparticles (Figure 6).^[64] By regulating the pH effect, the diethylaminophenyl-substituted groups can efficiently modulate NIR fluorescence and singlet-oxygen (1O_2) generation. Meanwhile the bromophenyl molecule promoted the intersystem crossing (ISC) effect in order to increase 1O_2 generation efficiency in the Azo-BODIPY.^[71,72] After being encapsulated by an RGD-modified amphiphilic polymer, the nanoparticles (Azo-BDP-NPs) can specifically target cancer cells in PDT. Since the absorption of Azo-BDP-NPs is beyond 800 nm, this significantly improves imaging sensitivity and increases the penetration depth of the PDT. By monitoring the fluorescence decrease in the tumor region after PDT, the therapeutic efficacy was demonstrated in situ and in real time. This provides a valuable and convenient self-feedback function for PDT efficacy tracking.^[64]

In regard to PDT, another major challenge is that of avoiding PDT-induced hypoxia, as this can lead to the recurrence and progression of cancer through the activation of various

angiogenic factors, significantly reducing treatment outcomes.^[73,74] In order to address this issue, Kim and co-workers reported an interesting acetazolamide (AZ)-conjugated NIR BODIPY photosensitizer (AZ-BDP) that reduces the effects of PDT-based hypoxia by combining the benefits of anti-angiogenesis therapy with that of PDT (Figure 7).^[75] AZ-BDP showed a specific affinity to aggressive cancer cells that overexpress carbonic anhydrase IX (CAIX), thus leading to enhanced photocytotoxicity. Moreover, AZ-BDP presented enhanced in vivo efficacy in a xenograft mouse tumor regrowth model that is relative to BDP in a PDT-induced ROS generation and CAIX knockdown. Finally, AZ-BDP displayed efficient targeting and therapeutic effects in clinical samples collected from breast-cancer patients. This study exhibited an attractive therapeutic approach to the targeting of CAIX-overexpressing tumors.^[75]

As demonstrated by preclinical and clinical studies, it is often difficult to treat deep-seated tumors with PDT alone, as severe local hypoxia tumor tissues and frequently encountered residual tumor cells surviving from PDT treatment are present, thereby resulting in unsatisfactory photoinduced anticancer efficiency.^[76–78] In order to increase the therapeutic effect of PDT and reduce its significant side effects, a new field that would link the combination of PDT with other therapeutic techniques is highly desirable.^[76–78] Photothermal therapy (PTT) has been proposed for the effective treatment of advanced-stage cancer that has relatively minor side effects. This relies on heat generation in NIR responsive biomaterials upon near-infrared (NIR) photoexcitation and the subsequent destruction of cancer cells by excessive local heating.^[79–82] More importantly, as PTT does not depend on the concentration of oxygen in a tumor, it can efficiently treat hypoxia cancer using this advanced cancer treatment method.^[79–82] NIR BODIPY photosensitizers not only can efficiently generate singlet oxygen upon NIR light irradiation, but they can also produce a thermal effect via nonradiative transition from an excited state to a ground state. As shown in Figure 8, by combining such special PTT and PDT features of the NIR BODIPY, Chen et al. rationally designed a platinum (Pt)-substituted NIR BODIPY photosensitizer (Bodiplatin). In this molecule, Pt as a heavy atom promotes rapid ISC from a single to a triplet state. PEG substitution can further enhance the water solubility of photosensitizers and reduce the nonspecific interaction with proteins in the systematic circulation. After Bodiplatin is self-assembled in water, the bifunctional nanoparticles (Bodiplatin-NPs) can efficiently treat cancer with low-power-intensity NIR light irradiation. Bodiplatin-NPs can produce both remarkable singlet oxygen and photothermal effect through their preferential triplet-excited-state-to-ground-state transition and nonradiative decay, thereby generating abundant singlet oxygen to inhibit the growth of a tumor. Moreover, Bodiplatin-NPs exhibit enhanced resistance to photobleaching, negligible dark toxicity, and effective intracellular translocation from the lysosomes to cytoplasm, as well as preferable tumor accumulation in vivo, facilitating remarkable photoinduced cancer cells, tumor-tissue treatment, and subsequent synergy between PDT and PTT for treatment.^[83]

5. NIR BODIPY NPs in TTA-UC-Based Prodrug Activation

Light-induced prodrug activation has received a great deal of attention in recent years due to its noninvasive operation and high spatiotemporal controllability.^[84–86] In such a strategy, small-molecule drugs are typically modified and protected via the use of light-sensitive

photomasks, such as coumarin, 2-nitrobenzyl, and 7-nitroindoline.^[87,88] However, the absorption of these photomasks is typically located in the deep blue (≈ 435 nm) or phototoxic UV (≈ 365 nm) region. Moreover, these prodrugs are limited at a poor tissue-penetration depth in their in vivo application.^[87,88] To address these issues, long-wavelength light in the therapeutic window (600–900 nm) has deep-tissue penetration owing to its minimal absorption by the tissue. In previous reports, lanthanide-ion-doped inorganic upconversion nanoparticles (UCNPs) were used to convert tissue-penetrable NIR light (980 or 800 nm) into high-energy short-wavelength photons (i.e., 365 nm) to trigger prodrug activation.^[89,90] However, there are serious challenges with regard to the use of inorganic UCNPs. For instance, due to the intrinsically small cross-sections of absorption and emission of the contained lanthanide ions, such UCNPs have quite low quantum yields that typically require relatively high-power density laser excitation. In addition, the long-term in vivo toxicity and systematic clearance of inorganic lanthanide ions inside such UCNPs is unclear.^[91] These key limitations have led to the exploitation of a more biocompatible upconversion strategy, particularly with respect to the emerging organic-chromophorebased triplet–triplet annihilation upconversion (TTA-UC).^[92,93] In previous studies, green-to-blue TTA-UC nanomicelles (palladium octaethylporphyrin (PdOEP) as the sensitizer and 9,10-diphenylanthracene (DPA) as the emitter) were fabricated in order to trigger the uncaging of blue-light-sensitive coumarin-group-modified peptides, thus enabling better subsequent cell targeting. Nevertheless, such green excitation light is limited in tissue penetration in vivo.^[94,95] In addition, a red-to-blue TTA system containing mesotetraphenyl-tetrabenzoporphine palladium (PdTPBP, sensitizer) and perylene (emitter) can upconvert 635 nm laser light to 475 nm photons. This red-to-blue TTA system was used for the photodissociation of ruthenium polypyridyl complexes from PEGylated (PEG = poly(ethylene glycol)) liposomes in water.^[96] However, the existing system has limitations with respect to its in vivo applications due to its suboptimal efficiency and relatively high excitation power density.^[96] In addition, the anti-Stokes-shifted emission with a wavelength of 475 nm is not compatible with the typical deep-blue/UV operation wavelengths for biologically used caging groups.^[94,95] Therefore, it was highly desirable to develop a new TTA system with dramatically improved anti-Stokes shifting ability from far-red to deep-blue light, as well as robust brightness properties.

In order to achieve TTA-UC-based prodrug activation for cancer therapy, as shown in Figure 9, Han et al. developed a new TTA system that has robust brightness and the longest anti-Stokes shift (far red to deep blue). In this TTA-UC system, a metal-free iodized BODIPY dimer (BDP-F) molecule was utilized as a highly far-red-sensitive photosensitizer due to its long triplet excited lifetime and intense absorption in the red region. Owing to its high fluorescence quantum yield in the deep blue region, 9-phenylacetylene anthracene (PEA) was used as the deep-blue emitter. This TTA-UC system showed a high upconversion quantum yield ($\Phi_{UC} = 3.1\%$) upon irradiation with 650 nm light. In addition, core–shell-structured prodrug delivery capsules were developed. These capsules contained mesoporous silica nanoparticles preloaded with TTA molecules as their core, and amphiphilic polymers encapsulating anticancer prodrug molecules as their shell. When stimulated by far-red light, the intense TTA upconversion blue emission in the system activated the anticancer prodrug molecules. As shown in Figure 9, the new TTA-UCNPs can efficiently photocleave the

prodrug to treat cancer upon low-power far-red LED irradiation. This work paves the way to new organic TTA upconversion techniques that are applicable to in vivo photocontrollable drug release and other biophotonic applications.^[97]

6. NIR BODIPY NPs in Biogenic Thiol Detection

Biogenic thiols (e.g., glutathione (GSH) and cysteine (Cys)), which are important in maintaining the redox status of biological systems,^[98–100] are essential endogenous antioxidants that play a central role in cellular defense against toxins and free radicals.^[98–100] Their abnormal levels of homeostasis in living cells can lead to severe health problems.^[98–100] Therefore, an efficient method to detect such biogenic thiols under physiological conditions is highly desirable.^[101–104] Fluorescence-based biosensors can be used to trace the pathway of biogenic thiols within the cells, to in situ evaluate the concentration and biofunctions of biogenic thiols, and to provide further information regarding the relationship between biogenic thiols and disease.^[98–100] The ideal fluorescent sensors should selectively light up due to interaction with biogenic thiols and present the concentration change of biogenic substrates within the cells in real time.^[98–104]

In order to achieve such goals, different types of fluorescent thiol sensors have been developed according to two significant characteristic properties of thiols (i.e., strong nucleophilicity, as well as their high binding affinity toward metal ions).^[98–104] In recent years, diverse types of visibly emitting fluorophores have been designed as fluorescent sensors for biothiol moieties, such as coumarin,^[105] fluorescein,^[106] pyrene,^[107] rhodamine,^[108] luminescent transition-metal complexes (Ru (II) and Ir (III)),^[109,110] dicyanomethylene-4H-pyran,^[111] and diketopyrrolopyrrole.^[112] Fluorescent biogenic thiol sensors based on BODIPY derivatives have been developed. For instance, Zhao and co-workers prepared BODIPY-based green- and red-emitting thiol sensors.^[113,114] Later, Chen and co-workers developed an OFF to ON NIR-emission thiol sensor that used azo-BODIPY as the fluorophore.^[115] In addition, Yang and co-workers synthesized a chlorine-substituted BODIPY molecule that can distinguish between GSH, Cys, and Hcy.^[103] However, the emission of the abovementioned fluorescent thiol sensors is usually located in the visible region.^[98–104] Meanwhile, these fluorescent thiol sensors are hydrophobic and not readily water soluble, hampering their development in living systems.^[98–103] It is therefore of great importance to develop general, cost-effective, highly selective, NIR-emitting, water-soluble biogenic thiol sensing systems.

In order to address these drawbacks, as shown in Figure 10, Huang et al. prepared an NIR-emitting fluorescence thiol sensor (B-2). In B-2, distyryl-BODIPY was chosen as the NIR-emitter and 2, 4-dinitro benzene sulfonate (DNS) was used as the fluorescence quencher as it is strongly electron withdrawing and is high selective for biothiols. After encapsulation with poly(lactic acid)–poly(ethylene glycol) (PLA–PEG), ultrasmall and uniform nanomicelles were formed (B-2-DNS). The nanomicelles were photostable and chemically stable in a broad range of pH media, and had low cytotoxicity. In the absence of thiols, the B-2-DNS was nonfluorescent. With cleavage of the DNS moiety molecule by thiols, NIR emission at 665 nm was switched on with a significant emission enhancement. Moreover, the B-2-DNS was successfully used for the fluorescence imaging of thiols inside the living cells. These

results will be useful to design other related NIR-emitting nanomicelles for the specific detection of thiols in cellular environments and has the potential to be applied in vivo.^[104]

7. Conclusion

In summary, NIR-BODIPY-based nanomaterials have been extensively explored for their potential application in cancer optotheranostics. As discussed here, these NIR BODIPY (e.g., distyryl-BDP, Azo-BDP, ND-BDP, and BODIPY dimer)-based nanomaterials, have shown outstanding potential with regard to the development of next-generation theranostics agents for cancer treatment and diagnosis. Their unique features offer various advantages, such as: a) owing to the high fluorescence quantum yield in the NIR region, as well as their low toxicity with respect to the associated organism, NIR-BODIPY fluorescence can improve detection sensitivity, with regard to cancer, which is vital for early cancer diagnosis; b) the intensive absorption, and high singlet-oxygen quantum yield in the NIR region, as well as the excellent photostability of NIR BODIPY photosensitizers, provide outstanding platforms to develop a new strain of photodynamic drug molecules; c) additionally, NIR-BODIPY-based TTA-UCNPs can convert long-wavelength light to short-wavelength emissions, which can be exploited and used as a new methodology to treat cancer via prodrug activation. Thus, the unique chemical and optical properties of NIR BODIPY nanoparticles provide a versatile solution to aid in the development of a range of novel cancer optotheranostics methods.

Although there have been numerous exciting advances in this field, a number of challenges remain in regard to the use of these NIR-BODIPY-based nanomaterials. For example: a) The ideal cancer treatment can destroy cancer cells while leaving normal cells unaffected. Therefore, NIR-BODIPY-based nanomaterials can be further upgraded with antibody conjugation as well as self-feedback properties that are suitable to the cancer microenvironment. The new system will efficiently prevent both over and under treatment, thus reducing the damage done to normal tissue, as well as the side effects for the respective patients. b) The pharmacokinetic/pharmacodynamic (PK/PD) profiles of these NIR BODIPY nanomaterials will need to be systematically evaluated in larger animals and nonhuman primates in order to translate them toward their future preclinical and clinical trials applications. Overcoming each of these challenges will provide new transformational opportunities from the bench to the bedside for cancer optotheranostics that use such biocompatible organic nanoparticles.

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Biography

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Gang Han received his B.Sc. and M.Sc. degrees in chemistry from Nanjing University. He obtained his Ph.D. at the University of Massachusetts Amherst. He then became a postdoctoral researcher working at the Molecular Foundry of the Lawrence Berkeley National Lab. He joined the faculty of University of Massachusetts Medical School (UMMS) in 2010 and is currently an associate professor in the Biochemistry and Molecular Pharmacology Department at UMMS. His current research includes the investigation of luminescent molecules and nanoparticles in biophotonic and photonic applications.

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Figure 1.

a) A schematic illustration of the nanoparticle structure of DTE-B-1-NPs. b) The proposed mechanism for the fluorescence switching for B-1. c) The molecular structures of B-1 and DTE structures. d-f) The fluorescence imaging of DTE-B-1-NPs with HeLa cells: d) DTE-B-1-NPs only; e) DTE-B-1-NPs + ultraviolet (UV) light irradiation; f) DTE-B-1-NPs + visible-light irradiation. Reproduced with permission.^[35] Copyright 2017, Wiley-VCH.

Figure 2.

Left: the molecular structure of ND-BDP. Right: A single-wavelength PAI from the anatomy of a Hep-G2-tumor-bearing mouse at 700 nm. a) Time-dependent in vivo photoacoustic images at the same position with respect to the mouse after intravenous injection of ND-BDP NPs. b) A 3D rendering of the scan area before injection and 24 h postinjection, (laser wavelength: 700 nm). Reproduced with permission.^[51] Copyright 2016, The Royal Society of Chemistry.

Figure 3.

Upper: The molecular structure of BDP, BDP-SH and the mechanism to detect H_2S with PAI. Lower: The in vivo PAI of tumor-bearing mice using Si@BDP under diverse conditions: a) the tumor region for saline-treated mice; b) the normal sites for probe-treated mice; c) the tumor regions for probe-treated mice; d) mice pretreated with: d) 100 nmol amino-oxyacetic acid (AOAA) and e) 300 nmol S-adenosyl-L-methionine (SAM) for 12 h, were subcutaneously injected with Si@BDP in the tumor regions. f) PA intensities as a function of time post-injection of Si@BDP. (laser wavelength: 780 nm). Reproduced with permission.^[37] Copyright 2017, The Royal Society of Chemistry.

Figure 4.

Left: a) A schematic illustration of NIR-mediated PDT, Car-BDP-TNM construction and b) the molecular structures of Car-BDP, PLA-PEG, and PLA-PEG-FA; Right: a) A schematic illustration of Car-BDP-TNM-mediated PDT in a deep tumor. b) Tumor growth inhibition by Car-BDP-TNM-mediated PDT in 4T₁ tumors. c) The average weight of the tumors at day 10. The mice were sacrificed and their respective tumors were isolated in order to be weighed. d) The H&E staining of mice tumor-tissue sections from different treatment groups 10 d after treatment; the scale bar represents 50 μm. Reproduced with permission.^[63]

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Figure 5.

Left: A schematic illustration of RET-photosensitizer-mediated PDT and the molecular structure of RET-BDP. Right: a) Tumor-growth inhibition by RET-BDP-TNM-mediated PDT in 4T₁ tumors. b) Digital photos of tumors for the four groups of mice. c) H&E staining of tumor-tissue sections from different treatment groups after 10 d of treatment, where the scale bar represents 50 μm. Reproduced with permission.^[70] Copyright 2017, Wiley-VCH.

Figure 6.

The structure, characterization, and optical properties of cRGD-NEt₂Br₂BDP NPs. a) The structures and pH-activatable generation of fluorescence and ¹O₂ by cRGD-NEt₂Br₂BDP NPs. b) A TEM image of cRGD-NEt₂Br₂BDP NP. c) The normalized UV–VIS–NIR absorption spectra of cRGD-Br₂BDP NPs, cRGD-NMe₂Br₂BDP NPs, and cRGD-NEt₂Br₂BDP NPs. d) The NIR fluorescence spectra of cRGD-NEt₂Br₂BDP NPs at different pH levels. e) The pH titration curves with respect to the fluorescence intensity of cRGD-Br₂BDP NPs at 685 nm, cRGD-NMe₂Br₂BDP NPs at 910 nm, and cRGD-NEt₂Br₂BDP NPs at 925 nm. f) ¹O₂ generation of cRGD-Br₂BDP NPs, cRGD-NMe₂Br₂BDP NPs, and cRGD-NEt₂Br₂BDP NPs at pH 5.0 and 7.4, determined by the SOSG fluorescence intensity at 525 nm. Reproduced with permission.^[64] Copyright 2015, The Royal Society of Chemistry.

Figure 7.

a) A schematic representation of the synergistic anticancer effect by AZ-BPS targeted to CAIX. b) Representative images of nude mice 8 weeks after intravenous tail-vein injection of AZ-BPS followed by 660 nm laser irradiation. c) The tumor volume of the mice in the BPS or AZ-BPS groups with, or without, PDT treatment. Reproduced with permission.^[75] Copyright 2017 American Chemical Society.

Figure 8.

a) A schematic illustration of bifunctional self-assembled nanoparticles of platinated BDP. b) A tumor growth profile of the mice treated with Bodioplatin-NPs. c) A photograph of the tumors extracted from the mice bearing 4T₁ tumors at 30 d postirradiation. d) An image of H&E-stained tumor sections harvested from the mice treated with Bodioplatin-NPs.

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Figure 9.

a) A Jablonski diagram of the photophysical process of the triplet photosensitizers and the TTA upconversion exemplified with BDP-F as the triplet photosensitizer and PEA as the emitter. b) The molecular structure of BDP-F and PEA. c) The TTA-UC-mediated photoactivation prodrug (Cou-C) process. d) An illustration of the photocleavage drug release by TTA-UC. e) Tumor-growth inhibition by TTA-CS-mediated drug release in 4T₁ tumors. f) H&E staining of tumor-tissue sections from different treatment groups 9 d after treatment; scale bar: 50 mm. g) Representative digital photos of tumors for the four groups of mice. Reproduced with permission.^[97] Copyright 2017 Wiley-VCH.

Figure 10.

a) A schematic illustration of the nanoparticle structure of B-2-DNS and the fluorescence recovery process of B-2-DNS in the presence of thiols. b) The molecular structure of B-2-DNS and B-2. Fluorescence imaging of c) B-2-DNS incubation with only HeLa cells; d) B-2-DNS + DTT; and e) HeLa cells pretreated with *N*-methylmaleimide + B-2-DNS. Reproduced with permission^[104] Copyright 2016, Wiley-VCH.

Scheme 1.

A schematic illustration of the basic photophysical process of NIR BODIPY NPs in optotheranostics.