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Review

Advances in Nanoparticle-Based Phototherapy: A precision medicine perspective

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Abstract

Nanoparticle-based phototherapy is a novel precision medicine strategy that combines nanotechnology with light-directed therapeutic modalities to deliver highly targeted, minimally invasive treatment. The most popular approaches are photodynamic therapy and photothermal therapy, which cause cellular damage by generating reactive oxygen species and inducing hyperthermia (heat) at the treatment site, respectively. The incorporation of nanoparticles significantly enhances all these processes, including light absorption, stability, biodistribution, and site-specific delivery. At the molecular and cellular levels, photoactivation of nanoparticles triggers a series of biological events, including oxidative stress, mitochondrial dysfunction, apoptosis, autophagy, and immunogenic cell death, which enable both tumor ablation and systemic immune activation. Therapeutic efficacy has also been improved by adding near-infrared (NIR-II) light, and recent advances in nanomaterial design, including MXenes, metal–organic frameworks, and upconversion nanoparticles, have further enhanced it. Besides, stimuli-responsive and theranostic nanoplatforms have been designed to enable adaptive therapy and real-time monitoring, paving the way for personalized medicines. Despite these advances, challenges such as nanoparticle toxicity, tumor heterogeneity, limited light penetration, and poor scalability for clinical translation remain. The review discusses in detail the molecular mechanisms of nanoparticle-based phototherapy technologies, as well as the latest developments and challenges encountered in their clinical application. In conclusion, this review highlights the potential of Nanoparticle-based phototherapy as a capable platform for precision medicine applications in oncology and beyond.

Keywords: Nanoparticle-based phototherapy; Precision medicine; Theranostics

1. Introduction

Phototherapy is a rapidly advancing therapeutic strategy that utilizes the combination of nanoparticles and light. Near-infrared (NIR) phototherapy is a rapidly gaining therapeutic strategy that leverages the combination of nanoparticles and light [1-3]. Phototherapy is a rapidly emerging therapeutic approach that brings together nanoparticles and light [4-7]. Despite tremendous progress in diagnosis and treatment, cancer and other chronic diseases continue to be major causes of morbidity and mortality globally and a huge burden on health care systems [8-10]. Surgery, chemotherapy, radiotherapy, and immunotherapy have significantly improved patients' prognosis. Still, the current therapies are not selective, have systemic side effects, multidrug resistance, and a poor therapeutic index. These limitations have prompted the investigation of alternative therapeutic approaches that are more precise in targeting disease whilst causing the least harm to normal tissues [11-14]. Precision medicine, in this context, represents a paradigm shift aimed at developing therapies that account for the variability of the disease, its molecular profile, and each patient's specific characteristics [15-17]. Because of its high level of control and its ability to elicit a therapeutic response through external light exposure, phototherapy has attracted significant interest. The two major types of phototherapies are photodynamic therapy (PDT) and photothermal therapy (PTT). The mechanism of PDT is the light-activation of a photosensitizing agent, which produces reactive oxygen species (ROS), such as singlet oxygen, that can cause oxidative damage to cells and cell death [1, 18]. However, PTT uses photothermal agents that convert light energy into heat, inducing hyperthermia in diseased tissue, which can lead to its destruction [19]. However, it should be noted that PDT and PTT have several advantages over traditional therapeutic options: spatiotemporal control, low systemic toxicity, minimal invasiveness, and minimal damage to normal tissues surrounding the tumor [18, 20]. These benefits are significant, but there are some limitations to the conventional phototherapeutic drugs [18, 20]. The most common problems with the traditional photosensitizers are a lack of water solubility, inability to target tumors, and rapid systemic clearance. Similarly, numerous photo-thermal agents exhibit suboptimal PDT conversion efficiency and low tissue specificity. Furthermore, the efficacy of phototherapy is often constrained by limited light penetration into tissues, hypoxic tumor microenvironments, and the heterogeneous distribution of drugs in diseased tissues. To tackle these challenges, the development of platforms based on nanoparticles to achieve greater selectivity, stability and therapeutic efficiency in phototherapy has been encouraged [6, 21-23].

Nanoparticles possess unusual physicochemical properties that make their use highly promising for biomedical applications. They are small, with a large surface area-to-volume ratio, can be tuned for optical properties, and can be modified with ligands to achieve efficient loading of therapeutic agents, long circulation times, enhanced permeability and retention (EPR) effects, and active targeting [14, 24]. Combining photosensitizers with photothermal agents, imaging probes, and therapeutic cargoes into a single nanoplatform can significantly improve the efficacy, specificity, and safety of phototherapy. Thus, the use of nanoparticles in phototherapy has become a promising approach to enhance the therapeutic efficacy in various diseases [1, 23, 25].

Over the past decade, significant efforts have been devoted to the design and engineering of sophisticated nanomaterials for phototherapies [2, 26]. Gold nanoparticles, carbon-based nanomaterials, semiconductor nanoparticles, polymeric nanoparticles, lipid-based nanocarriers, upconversion nanoparticles, metal-organic frameworks (MOFs), and two-dimensional materials such as MXenes have shown tremendous promise for improving the efficacy of phototherapy. These nanomaterials have exceptional optical properties and can be engineered to release drugs under physiological conditions, directing them to the desired target and improving therapy accuracy. In addition, multifunctional stimuli-responsive nanoplatforms have enabled the integration of therapy and diagnosis into a single platform, advancing theranostics [1, 25-27].

Emerging NIR light has also enhanced the potential of nanoparticle-based phototherapy [3, 28, 29]. NIR irradiation has several advantages over visible light: deeper tissue penetration, less scattering, and less photodamage to healthy tissues. In particular, the second near-infrared window (NIR-II: 1000–1700 nm) has attracted significant interest for its superior tissue penetration and improved imaging performance. Rapid progress in the development of nanomaterials that respond to NIR radiation has enabled more efficient approaches for treating deep-seated tumors and other hard-to-reach pathological conditions that were difficult to reach with traditional phototherapeutic methods [1, 30-33]. In addition to direct cytotoxic effects, there is increasing evidence that the local tumor environment can be modified by the application of nanoparticles for phototherapy and that systemic immune responses can be triggered. Due to cellular damage, phototherapy can trigger immunogenic cell death (ICD), leading to the release of tumor-associated antigens, damage-associated molecular patterns (DAMPs), and pro-inflammatory cytokines. These events lead to dendritic cell maturation, T-cell activation, and long-term anti-tumor immunity. With these considerations in mind, phototherapy is being considered in combination with other treatments, such as immunotherapy, chemotherapy, and gene therapy, to achieve a synergistic therapeutic effect and combat resistance mechanisms [2, 34, 35].

Nanotechnology, phototherapy, molecular imaging, AI-assisted diagnostics, and precision medicine have converged to drive the creation of next-generation therapeutic platforms for personalized disease management [14, 25, 36]. However, several obstacles remain that prevent clinical translation: deep tissues, nanoparticle toxicity issues, complex biological interactions, tumor heterogeneity, manufacturing scale-up, regulatory issues, and long-term biosafety evaluation. To make nanoparticle-based phototherapy clinically useful, these challenges must be overcome [37-43]. While a few reviews have covered individual aspects of PDT, PTT, and nanomedicine, few comprehensively address molecular mechanisms, advanced nanomaterial engineering, immune modulation, theranostic applications, and precision medicine. Thus, this review aims to summarize the molecular and cellular mechanisms of nanoparticle-based phototherapy, recent developments in the design of nanoparticles and systems activated by NIR, novel theranostic and personalized treatments, and the challenges and future perspectives for clinical translation. Altogether, this review seeks to convey an understanding of how nanotechnology-based phototherapy is becoming a next-generation precision medicine platform for oncology and other disease applications, Figure 1.

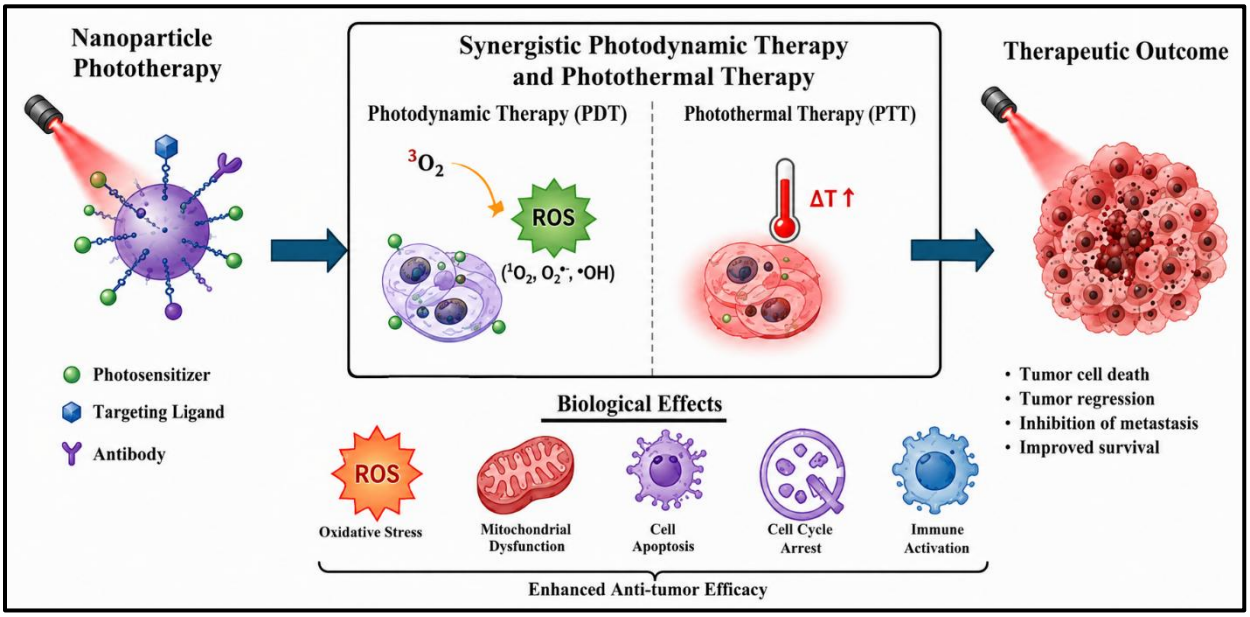

Figure 1. A schematic illustration of nanoparticle-mediated phototherapy that involves reactive oxygen species generation and photothermal effects for tumor ablation.

2. **Precision-Medicine Framework**

Nanoparticle-based phototherapy is a very promising approach in precision medicine, combining the benefits of external control of light activation, targeted delivery of nanoparticles to the tumor, responsiveness of the tumor microenvironment, and the adaptive therapeutic function of nanoparticles [1, 36, 44]. In contrast, while traditional therapeutic methods result in systemic toxicity and lack of selectivity, nanoparticle-based phototherapy allows selective therapeutic activation with an external light source [43, 45, 46]. Light is a noninvasive, spatiotemporally controllable stimulus that allows for precise temporal and spatial control of therapy, and treatment effects are primarily limited to diseased tissues with minimal collateral damage to surrounding healthy tissues. This on/off switch is particularly important in precision medicine, where the patient's characteristics, tumor location, and tumor biological heterogeneity are key considerations in determining treatment [47-50].

Therapeutic precision is also enhanced at the nanoscale with passive and active targeting mechanisms. Passive targeting involves the EPR effect, in which nanoparticles accumulate in tumors due to leaky blood vessels and reduced lymphatic drainage [51-54]. The process of binding a ligand to nanoparticles is known as active targeting and allows nanoparticles to bind to receptors that are specifically overexpressed on diseased cells. This comprises folate receptor-targeted nanoparticles, hyaluronic acid-targeted nanoparticles conjugated to CD44, and peptide-modified nanoplatforms targeting tumor integrins to enhance the effectiveness of phototherapy [55-58]. Recently, Yang et al. (2023) designed Au44 nanoclusters with superior tumor

accumulation, high precision, and efficient PTA tumor ablation, as well as multifunctional tumor-targeting and tumor-treatment-process monitoring [59]. Zhang et al. (2023) reported DNA-templated Ag@Pd nanoclusters that combined NIR-II imaging, PTT, and nanocatalytic functions, enabling precise tumor targeting and treatment monitoring while enhancing therapeutic efficacy [60]. The construction of stimuli-responsive nanoplatforms that respond to the tumor microenvironment (TME) is a key aspect of precision-oriented phototherapy. Tumors exhibit acidic pH, hypoxia, elevated glutathione levels, elevated ROS levels, and increased expression of enzymes such as MMPs [61-65]. These conditions can be used to selectively trigger the delivery of therapeutic agents, activate photosensitizers, or increase photothermal conversion in diseased tissues using nanoparticles [61, 64-66]. Examples of this include pH-responsive polymeric nanoparticles that deliver photosensitizers in tumor-acidic environments, hypoxia-responsive nanomaterials that enhance the efficiency of PDT under low-oxygen conditions, and enzyme- or redox-responsive nanoplatforms that trigger drug release at tumor sites [67-71]. Hypoxia-responsive systems can further overcome tumor oxygen deficiency by generating or supplying O_2, thereby improving therapeutic efficiency under low-oxygen conditions. For example, self-oxygenating nanoplatforms have been shown to enhance ROS production during sonodynamic therapy while simultaneously activating synergistic pathways, such as cuproptosis, thereby improving antitumor efficacy. Such strategies highlight the potential of TME-reconstruction approaches to overcome key limitations of conventional phototherapy and related modalities [71]. HPB@MET further demonstrates a ROS-amplifying strategy, where nanozyme-mediated peroxidase-like activity enhances intracellular ROS levels in tumor cells. In the acidic tumor microenvironment, its degradation releases metformin, which induces mitochondrial dysfunction and promotes additional ROS accumulation through electron leakage. This synergistic ROS overproduction effectively inhibits tumor proliferation, highlighting the potential of nanozyme-based drug delivery systems for TME-targeted cancer therapy [70]. ZnPP@FQOS demonstrates a pH/redox dual-responsive strategy that enhances ROS-mediated PDT by remodeling cancer-associated fibroblasts and suppressing antioxidant defenses in tumor cells. This results in amplified intracellular ROS generation and improved therapeutic efficacy under the tumor microenvironment. Additionally, it promotes strong immune activation, highlighting its potential for synergistic photodynamic–immunotherapy, Figure 2 [69]. Stimuli-responsive polymeric nanoparticles have emerged as intelligent nanoplatforms for cancer theranostics, enabling controlled drug delivery, enhanced tumor targeting, and real-time therapeutic monitoring. TME-responsive systems triggered by acidity, hypoxia, ROS, GSH, or tumor-associated enzymes significantly improve tumor accumulation, penetration, and on-demand drug release. These strategies, especially when combined with chemo-phototherapy, offer synergistic therapeutic effects while minimizing systemic toxicity [64]. Song et al. (2023) engineered a semiconducting polymer nanoplatform that binds to fibrin and exhibits strong NIR-II absorption for photoacoustic (PA) imaging-guided PTT, enabling selective targeting, in vivo imaging, and precise thermal ablation, Figure 3A [72]. Likewise, Dong et al. (2024) described the development of NIR-II nanotheranostics based on

croconaine that successfully ablated tumors under NIR-II irradiation and demonstrated long-lasting systemic antitumor immune responses, Figure 3B [73].

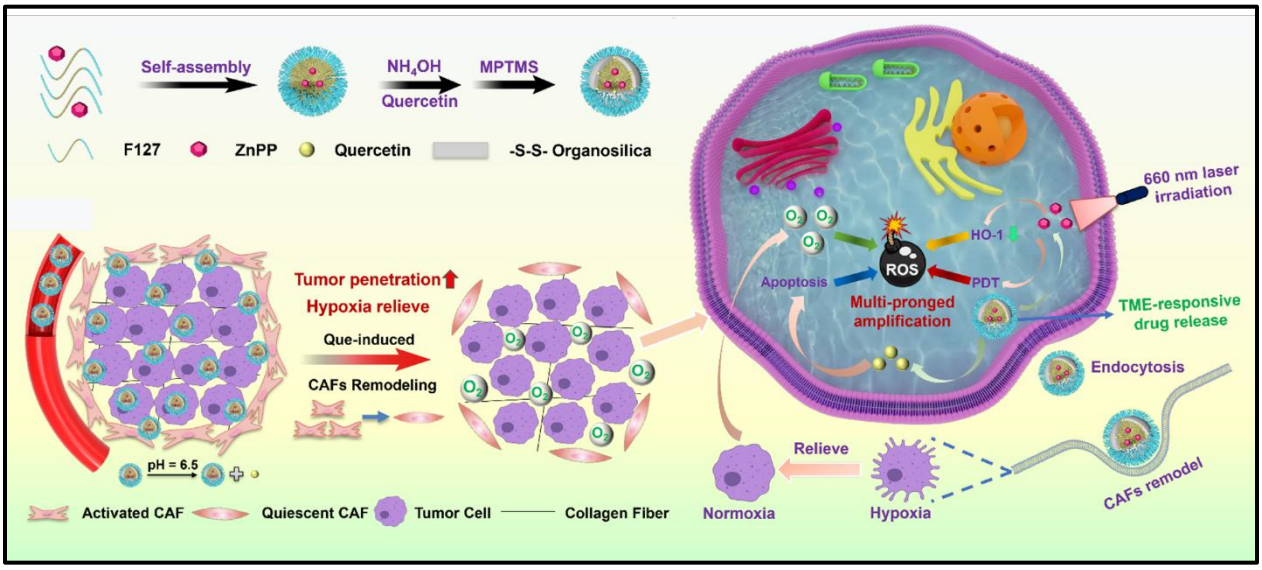

Figure 2. Schematic illustration of ZnPP@FQOS-mediated multi-pronged ROS amplification for the treatment of fibroblast-rich tumors. Reproduced with permission from [69].

Su et al. (2025) developed a brain-targeting NIR-II polymeric phototheranostic nanoplatform for orthotopic glioblastoma, enabling image-guided adaptive therapy with improved targeting efficiency and reduced off-target toxicity [74]. Single-component phototherapeutic agents, such as the cyanine-based NanoIR805-PEG, have been developed to enable combined PDT and PTT under a single excitation wavelength, demonstrating efficient tumor ablation in vitro and in vivo [75]. An all-in-one phototheranostic system (OTAB@cRGD NPs) has been developed by integrating aza-BODIPY with a donor–acceptor structure to enable NIR-II imaging-guided Type-I PDT and PTT under a single 808 nm laser excitation. The engineered intramolecular charge-transfer enhances intersystem crossing, promoting efficient ROS ($O_2^{\bullet-}$) generation and strong photothermal conversion for synergistic tumor ablation. This platform demonstrates precise tumor targeting, real-time imaging, and effective in vivo antitumor efficacy, highlighting its potential for integrated NIR-II diagnosis and therapy [76]. Aggregation control of D–π–A photosensitizers has emerged as an important strategy to optimize photothermal and photodynamic performance. By extending the conjugation length, penta-ene–based PE-CLD nanoparticles were engineered to suppress H-aggregation and promote favorable J-aggregation, enabling strong NIR absorption extending into the NIR-II region. These nanoparticles exhibit efficient photothermal conversion, ROS generation, and dual NIR-II fluorescence/photoacoustic imaging capabilities, resulting in effective, image-guided, synergistic PDT/PTT tumor therapy in vivo [77]. A low O_2-dependent type-I photosensitizer (LTPA) has been developed for NIR-II fluorescence imaging-guided photodynamic/PTT of glioblastoma (GBM), addressing both tumor hypoxia and blood–brain barrier (BBB) limitations. The angiopep-2–modified self-assembled nanoparticles enable BBB penetration,

tumor targeting, and efficient generation of $O_2^{\bullet-}$ along with strong photothermal conversion under 808 nm irradiation, ensuring effective therapy under both normoxic and hypoxic conditions. This strategy demonstrates significant in vivo GBM suppression and highlights a promising approach for designing hypoxia-tolerant phototheranostic systems [78]. A smart switchable phototheranostic platform (BOD-D) has been developed to enable sequential imaging-guided cancer therapy by transforming NIR-I–guided PDT into NIR-II–guided PTT. Under light activation, the system releases nitric oxide (NO), enhancing the therapeutic efficacy of gas therapy while simultaneously overcoming tumor hypoxia-associated limitations. This cascade design enables real-time imaging-guided, programmable multimodal tumor ablation, offering a strategy for intelligent, adaptive phototherapy [79].

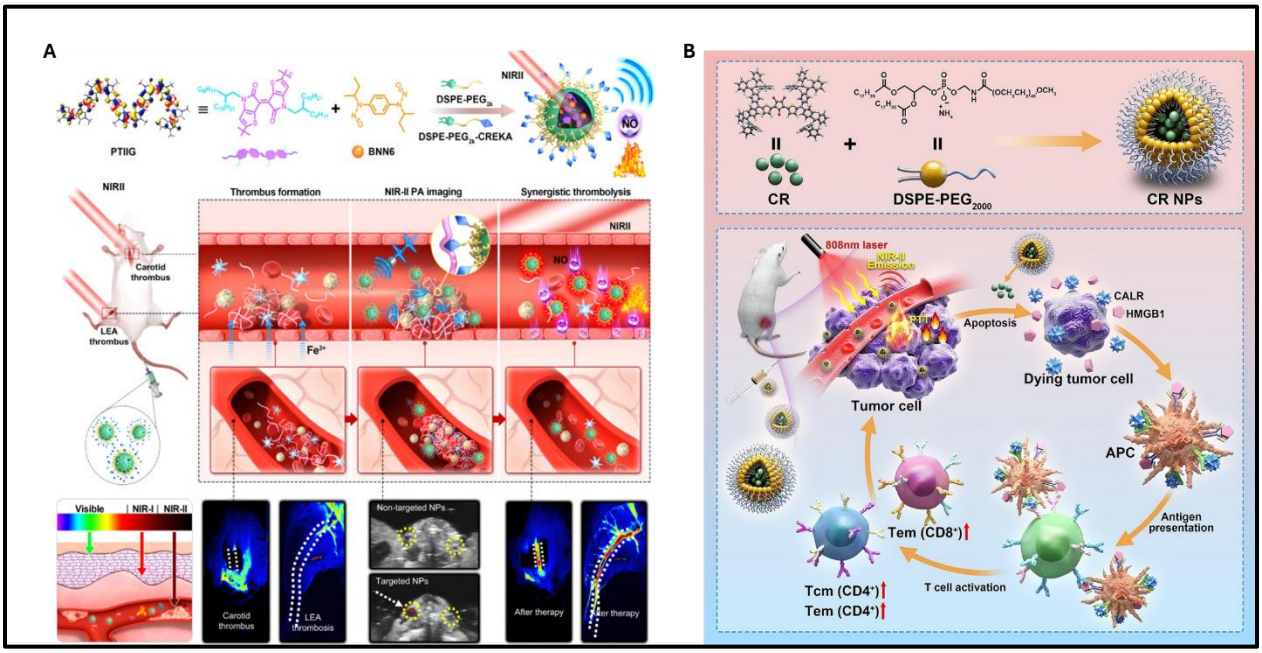

Figure 3. A). Schematic illustration of targeted nanoprobes towards fibrin for NIR-II PA imaging and synergistic treatment of thrombosis through both photodynamic and photothermal therapy. Reproduced with permission from [72]. B). The illustration shows croconaine-dye nanoparticles targeted to a tumor, with fluorescence-guided delivery for photothermal therapy. Reproduced with permission from [73]

3. **Role of Nanoparticles**

The delivery and application of nanoparticles as therapeutic agents are important for improving the efficacy and usefulness of phototherapy [1, 43, 80]. They have special physicochemical characteristics: tunable optical absorption, high surface/volume ratio, and controlled drug release, enabling precise modulation of therapeutic outcomes and multifunctional modalities [81-84]. The high photothermal conversion efficiency and strong light absorption of inorganic nanomaterials, such as gold nanoparticles, MXenes, and MOFs, are promising for PTT applications [85-87]. For instance, melanoma cells have been targeted with anti-MIA–functionalized gold nanoparticles, thereby selectively

increasing zinc phthalocyanine uptake. This results in increased ROS production and enhanced phototoxic antitumor activity [88]. This PDT is enhanced in lung cancer cells by green-synthesized gold nanoparticles (AuNPs) coupled to pheophorbide-a (AuNPs–Pheo-a), likely because the clusters increase the stability of the photosensitizer and its cytotoxicity under light. The nanoconjugate shows low dark toxicity and high laser-activated ROS-mediated cell death in A549 cells. Overall, it can be concluded that it is a biocompatible and efficient nanoplatform for targeted PDT applications [89]. To synthesize gold nanoparticles (AuNPs), green tea extract was used as a green reducing and stabilizing agent, and the reaction parameters were found to significantly affect AuNP size, plasmonic properties, and colloidal solution stability. The optimized AuNPs exhibited stable surface charge (−35.3 mV), high uniformity in morphology, and tunable SPR behavior, indicating high physicochemical stability. The in vitro study demonstrated concentration- and time-dependent cytotoxicity in MCF-7 cells, involving damage to the cell nucleus, suggesting that they could be used for reproducible, functional biomedical applications [90].

However, ligands used in the synthesis of MOFs are often unstable under harsh conditions, which has hindered the development of Zr-based MOFs. Chen and co-workers solved this problem by using a single-crystal-to-single-crystal post-synthetic exchange strategy to synthesize Zr-based MOFs based on BODIPY-derived ligands for the first time. Surface modification with fluorinated phosphate-functionalized PEG resulted in 69-L2@F, which can act as an oxygen carrier and photosensitizer to boost ROS generation under hypoxia. This platform demonstrated high PDT efficacy against TNBC cells and rapid tumor suppression in vivo when delivered via a hydrogel, indicating its potential for hypoxic tumor treatment, Figure 4 [91]. Zhuang and co-workers developed an electron-transfer strategy to convert conventional Type II MOFs into hypoxia-tolerant Type I systems by encapsulating thymoquinone (TQ) as an electron-transfer mediator. This approach promotes a dominant Type I ROS generation pathway by facilitating electron transfer from photoexcited MOFs to oxygen, thereby enhancing photodynamic efficacy under hypoxic conditions. The strategy was validated in porphyrin-based MOFs, where TQ-loaded systems showed significantly improved in vivo PDT efficacy in a 4T1 tumor model [92]. Cai and co-workers prepared nano Fe-soc-MOF via a liquid–solid–solution method and constructed a multifunctional theranostic platform by integrating polypyrrole (Fe-soc-MOF@PPy). The resulting nanocomposite exhibited efficient photothermal conversion under 808 nm irradiation, enabling effective tumor ablation in a 4T1 breast cancer model. This study demonstrates the potential of MOF–polymer hybrid core-shell systems for synergistic cancer imaging and PTT [93]. Liposomes, polymeric micelles, and dendrimers are examples of organic nanocarriers that are highly biocompatible and biodegradable and can carry high drug loads. They could inhibit the degradation of photosensitizers or photothermal agents before injection, thereby increasing circulation time [84, 94-96]. Exosome liposome hybrid vehicles (ELVs) are nanocarriers that are more biocompatible and stable, and can target cancer with high efficiency, making them promising nanocarriers for cancer theranostics. To enable deep-tissue fluorescence imaging and highly efficient PTT with 1064 nm irradiation, a lipophilic NIR-II cyanine dye-labeled ELV (NIR-C12-EL) has been developed. This platform exhibits

strong tumor targeting, excellent photothermal conversion efficiency, and high ablation efficiency against glioblastoma, indicating its potential as an NIR-II image-guided cancer therapy platform [97]. A lysosome-targeted, pH-responsive NIR-II phototheranostic platform (IRFEM@DHP) has been developed for nasopharyngeal carcinoma, integrating imaging-guided photodynamic and PTT. The system enables acid-triggered intracellular release and synergistic ROS/photothermal damage under NIR irradiation, resulting in precise tumor ablation with minimal off-target toxicity [98]. The incorporation of inorganic and organic components into hybrid nanoplatforms further broadens multifunctionality, enabling simultaneous imaging, targeting, and therapy in a single system. To achieve this, Yang et al. (2023) designed Au44 hybrid nanoclusters modified with ligands that showed greater tumor accumulation and could be used for more precise ablation via NIR-II photoacoustic imaging-guided PTT [59]. Zhang et al. (2023) designed DNA-templated Ag@Pd hybrid nanoclusters with imaging, catalytic, and photothermal properties for real-time monitoring. The combination of these two classes of materials leverages their best attributes into a single nanoplatform, enabling synergistic therapy, stimuli-responsive drug release, and theranostic applications [60]. Nanoparticles can also be delivered to a specific site, passively or actively, thereby increasing delivery to the diseased location and decreasing systemic toxicity. Passive targeting relies on the enhanced permeability and retention effect, while active targeting uses surface ligands that bind receptors overexpressed on tumor cells [1, 99-101]. Moreover, nanoparticles can overcome biological barriers such as tumor hypoxia, dense extracellular matrices, and limited tissue penetration. The use of oxygen-generating nanoparticles, catalase-mimicking nanozymes, and perfluorocarbon-based carriers has proven effective in reducing hypoxia, thereby improving the efficiency of PDT and therapeutic efficacy [1, 102-105]. Importantly, nanoparticles can facilitate the release of stimuli-activated therapeutic agents, releasing them only in pathological environments. Additionally, spatial and temporal control of drug release is provided by pH-sensitive polymers, redox-responsive linkers, and enzyme-activated systems, thereby improving safety and precision. The theranostic properties enable real-time imaging and adaptive treatment adjustments, making nanoparticle-mediated phototherapy suitable for precision medicine.

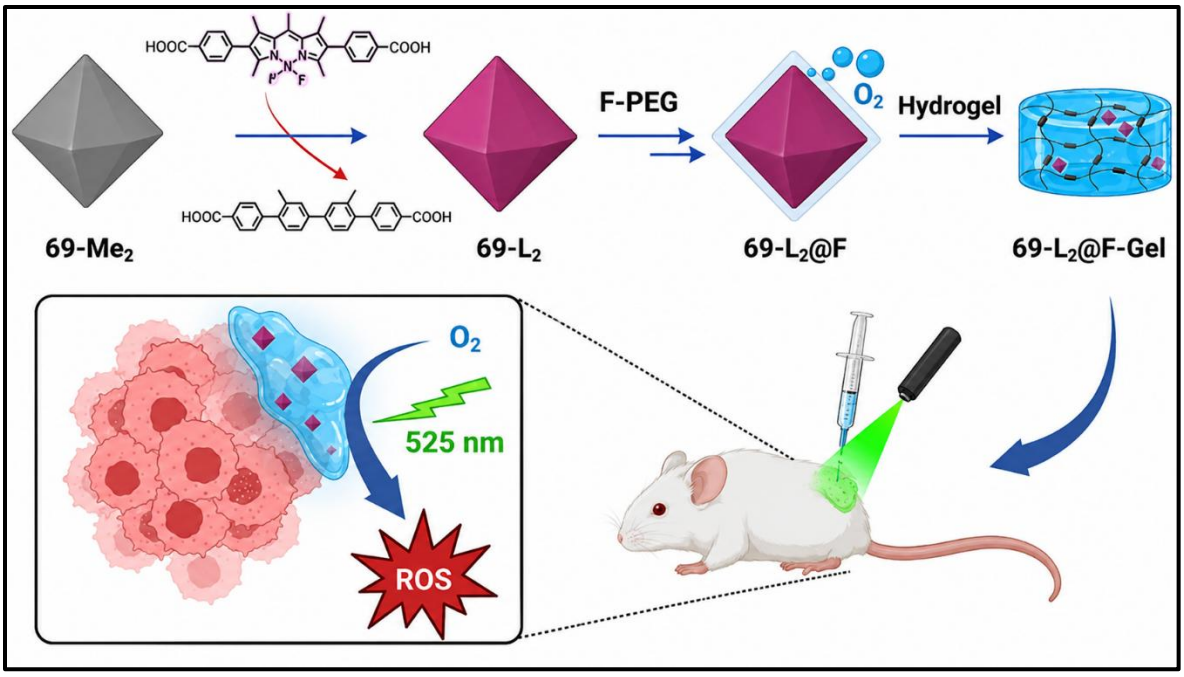

Figure 4. Schematic of MOF-based hydrogel (69-L_2@F-Gel) for oxygen-enhanced photodynamic therapy. Reproduced with permission from [91].

4. **Recent Research Trends**

The development of new phototherapy using nanoparticles has been mainly motivated by the need for greater treatment depth, selectivity, and therapeutic efficiency. The extension of the second near-infrared (NIR-II) window (1000nm-1700nm) is one of the most remarkable advancements in phototherapy [106-108]. NIR-II light provides deeper tissue penetration, reduced scattering, and improved imaging resolution, enabling imaging of deep-seated tumors [107-109]. NB/CuS@PCM nanoparticles were designed as a thermo-responsive platform combining NIR-II PTT and chemodynamic therapy. Upon 1060 nm laser irradiation, CuS generates heat for tumor ablation and triggers drug release, while in the acidic tumor microenvironment, Cu ions released deplete glutathione and produce toxic ROS via Fenton-like reactions. Meanwhile, borneol increases intracellular ROS levels, thereby amplifying oxidative stress and enhancing antitumor efficacy in vivo [110]. A biomimetic TNBC cell membrane–coated nanoplatform was developed for combined NIR-II PTT, chemotherapy, and immune checkpoint blockade. Ag_2S quantum dots enabled imaging-guided PTT and promoted immunogenic cell death, while PD-L1 inhibitors enhanced immune activation. The system showed strong tumor targeting, improved immune response via DAMP release, and significantly reduced lung metastasis, demonstrating effective synergistic immunotherapy against TNBC [111]. A D–A type thiopyrylium-based NIR-II fluorophore (H4-PEG-PT) was developed with frequency upconversion luminescence and strong mitochondrial targeting ability. It enabled high-resolution imaging of mitochondria at very low concentrations and efficiently converted NIR-II light into heat for ROS-independent PTT. In vivo, it showed strong tumor accumulation and excellent NIR-II image-guided photothermal ablation,

demonstrating effective mitochondria-targeted theranostics for cancer treatment [112]. A self-reporting NIR-II photosensitizer system (HOEt-PI, Me-PI, Et-PI) was designed to enable real-time monitoring of PDT outcomes. Among them, Et-PI showed optimized aggregation behavior, enhancing ROS generation and triggering sequential subcellular targeting from the membrane to mitochondria and, finally, to the nucleoli, indicating programmed cell death. Under 1250 nm excitation, it enabled three-photon fluorescence imaging for high-contrast live/dead cell discrimination, providing a strategy for NIR-II–guided deep-tissue PDT with real-time therapeutic feedback [113]. A NIR-II fluorescence nanotheranostic platform (RSSDCHI) was developed for real-time monitoring of drug release and combined chemo-PDT. The system showed dual responsiveness to hyaluronidase and glutathione, enabling targeted tumor activation and high tumor-to-normal tissue imaging contrast. Importantly, NIR-II fluorescence intensity correlated with drug release, allowing visualization of delivery dynamics and prediction of therapeutic outcomes, thereby enhancing precision cancer treatment [114]. Song et al. (2023) successfully ablated deep tumors using a semiconducting polymer nanoparticle (SPN) that targets fibrin, which was activated by photoacoustic imaging [72]. Likewise, Dong et al. (2024) used croconaine-based NIR-II nanoparticles that could enable fluorescence-guided PTT while simultaneously eliciting systemic antitumor immunity [73].

Stimuli-responsive and logic-gated nano platforms have also been developed, further improving treatment specificity. These “smart” nanoparticles can respond to various signals associated with the tumor, such as acidity, hypoxia, high glutathione levels, or specific enzymes, thereby triggering phototherapy only within the pathological microenvironment [115-118]. For instance, A pH-responsive UiO-66-based nMOF (DI@UiO-TPF3) was developed for combined chemo-photothermal-PDT. The system co-loaded doxorubicin and indocyanine green, while a TK-PEG-F3 modification enabled tumor targeting via nucleolin recognition and improved stability. It exhibited efficient drug loading, stimuli-responsive release, and strong synergistic anticancer effects in vitro through combined chemotherapy and PTT/PDT, while reducing toxicity to normal cells [119]. A pH-sensitive cRGD-functionalized polymeric nanoparticle was developed to combine chemotherapy and PDT, with real-time FRET-based drug release monitoring. The system co-assembled epirubicin and a porphyrin-based photosensitizer within an amphiphilic polymer carrier, enabling tumor-targeted delivery and imaging-guided tracking of cellular uptake. It exhibited strong synergistic anticancer activity in vitro and significantly improved therapeutic efficacy in vivo compared to free drug, demonstrating a versatile platform for chemo-PDT with real-time monitoring capability [120]. A pH-sensitive TCAD@Ce6 nanoparticle system was developed for NIR fluorescence-guided chemo-PDT of lung cancer. The platform co-delivered doxorubicin and chlorin e6, enabling acid-triggered drug release in the tumor microenvironment. It showed enhanced tumor accumulation via the EPR effect, strong cellular uptake, and significantly improved anticancer efficacy through synergistic chemotherapy and photodynamic-induced apoptosis both in vitro and in vivo [121]. A hypoxia-tolerant Type-I semiconducting polymer photosensitizer prodrug (HTPSNiclo) was developed for enhanced

photodynamic immunotherapy. The system enabled efficient ROS generation under hypoxic tumor conditions while simultaneously releasing a STAT3 inhibitor (niclosamide) in response to tumor biomarkers. This dual action inhibited immunosuppressive signaling (STAT3/HIF-1α), boosted activation of dendritic cells and cytotoxic T cells, and greatly enhanced in vivo antitumor efficacy and survival in 4T1 tumor models relative to conventional PDT, Figure 5 [122].

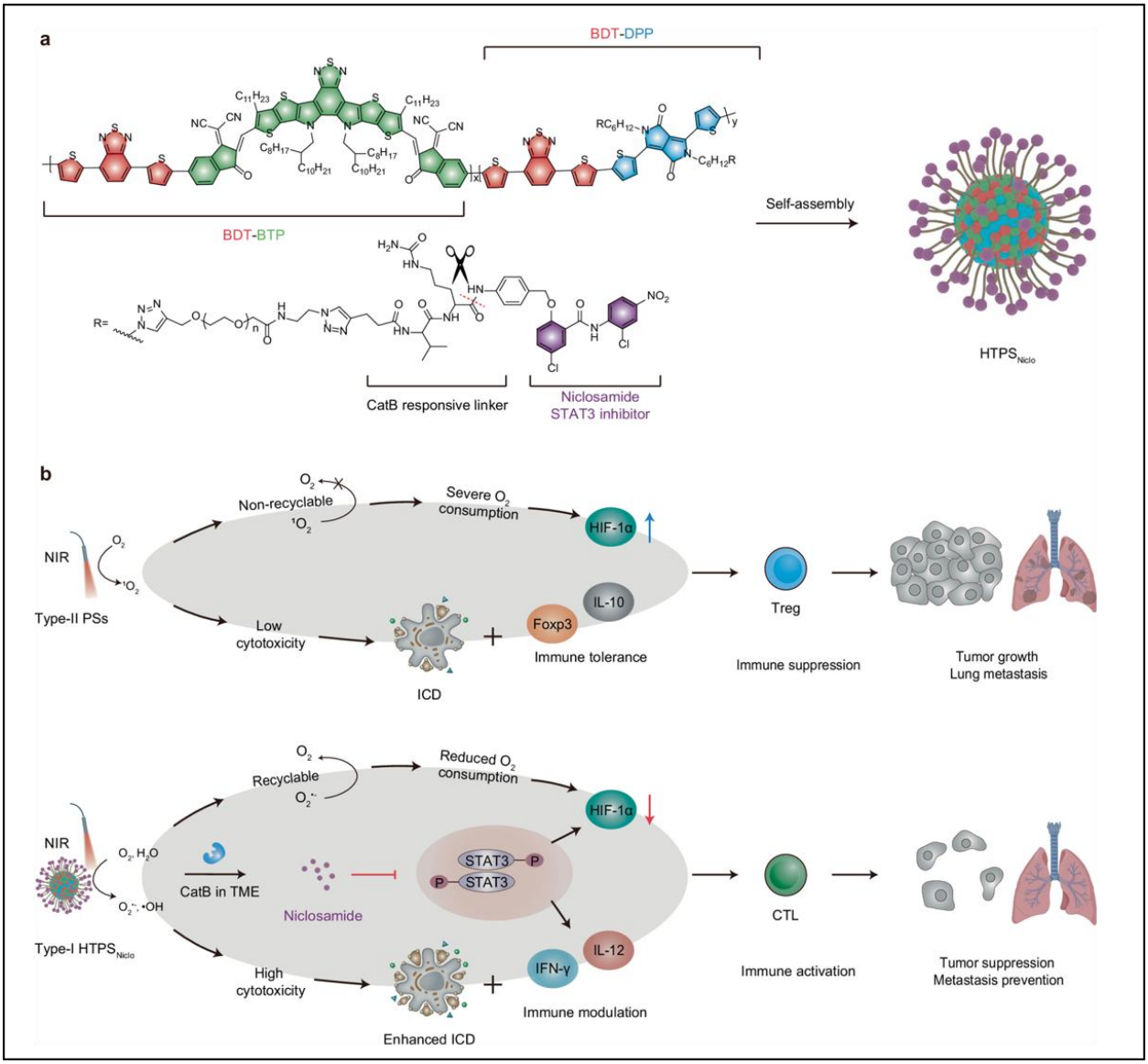

Figure 5. Schematic illustration of a polymeric photosensitizer prodrug that can tolerate hypoxia for use in photo-immunotherapy. Reproduced with permission from [122].

At the same time, photoimmunotherapy, a treatment that combines phototherapy and immunotherapy, is receiving increased attention. The immunogenic cell death triggered by nanoparticles used for phototherapy can lead to the release of tumor-associated antigens and DAMPs, thereby activating

dendritic cells and T lymphocytes. This treatment has been shown to cure local tumors and to induce systemic antitumor immunity. This mechanism would also be beneficial for treating metastatic or recurrent disease when combined with other immunotherapies, such as immune checkpoint blockade or vaccines [2, 123, 124]. Mesoporous hexagonal zinc porphyrin-silica nanoparticles (MPSNs) were developed for combining PTT, PDT, and immunotherapy. After loading with the immune adjuvant R837, the system induced strong immunogenic cell death and promoted dendritic cell maturation through pH-responsive release. In combination with PD-L1 checkpoint blockade, it generated robust systemic antitumor immunity, effectively suppressing both primary and metastatic tumors with minimal toxicity [123]. Chen et al. developed GSH/NIR sequentially activated gas nanoadjuvants by co-assembling aggregation-induced emission (AIE) photosensitizers with MnCO-based components into mesoporous silica nanocarriers. The biomimetic system was used for the first time to achieve tumor microenvironment-responsive activation, which boosted the efficacy of PDT and immune stimulation to combat tumors [125]. Membranes of dendritic cells (DCs) were used to coat AIE nanoparticles loaded with photosensitizers, creating a biomimetic AIE nanoparticle system. This design maintained high ROS generation and enhanced immune interactions by “hitchhiking” T-cells across membranes. Lipid droplets were selectively taken up by the system, leading to T cell activation and proliferation and a strong anti-tumor immune response, representing a novel PDI approach targeting lipid droplets [126]. The cancer cell membrane, Type-I AIE photosensitizers, and glutamine antagonists were co-encapsulated into a biomimetic, homogeneous, and targeted nanoplatform (CTTPA-G).

This system reprogrammed tumor metabolism, induced immunogenic cell death, alleviated tumor hypoxia, and promoted dendritic cell maturation while supporting T-cell metabolic demands. When combined with anti-PD-1 therapy, it generated strong abscopal effects, effectively suppressing metastasis and establishing long-term antitumor immune memory [127]. Tang et al. designed NIR-absorbing AIE photosensitizers bearing methoxy substituents to enhance fluorescence, photoacoustic signals, and ROS generation via improved intersystem crossing, enabling efficient Type-I/II PDT under hypoxic conditions. These AIEgens were formulated into nanoparticles with an oxygen-responsive paclitaxel prodrug and M1 macrophage membrane coating to achieve tumor targeting and deep imaging. The system enabled imaging-guided, self-accelerating PDT chemotherapy immunotherapy, inducing immunogenic cell death and strong systemic antitumor immune responses against both primary and distant tumors [128]. Liu et al. developed a metabolic engineering strategy by conjugating an AIE photosensitizer (TPApy) with D-alanine to form a modified substrate for bacterial cell wall synthesis. This enabled the generation of TPApy-labeled lysozyme with imaging and photodynamic properties. Upon light activation, the system produced ROS and effectively eliminated malignant melanoma through combined photodynamic and immune-mediated effects, demonstrating a potential minimally invasive strategy for tumor treatment and recurrence prevention [129]. Lou et al. developed a caged peptide AIEgen nanoplatform (GCP) that self-assembled with miR-140 to form GCP/miR-140 nanoparticles for enhanced immunotherapy. After

cellular uptake, enzymatic and redox-responsive cleavage released GO203, miR-140, and the AIE photosensitizer PyTPA, enabling multi-level PD-L1 downregulation via both mRNA degradation and MUC1-related signaling suppression. Simultaneously, PyTPA-mediated PDT induced immunogenic cell death and tumor antigen release, thereby amplifying immune cell activation and significantly improving antitumor immune responses [130]. Lou et al. developed a cascade-amplified nanocomplex (PMRA/poly (I: C)) based on a peptide-modified AIE photosensitizer (PyTPA) for synergistic photodynamic and immune therapy. The system enhanced chemokine production and immune cell infiltration in the tumor microenvironment while promoting T-cell activation via poly (I: C)-mediated immune stimulation. Additionally, peptide-mediated PD-1/PD-L1 blockade further enhanced antitumor immunity, resulting in robust tumor antigen release and near-complete tumor responses in murine models [131]. Xiao et al. engineered an optically programmable NIR-responsive nanoparticle system based on D–A–D type AIE polymers for precise tumor and organelle targeting. The system underwent NIR-triggered transformation in the tumor microenvironment, enabling deep penetration, mitochondrial targeting, and strong ROS generation for PDT. This cascade activation induced immunogenic cell death and enhanced synergistic photodynamic immunotherapy in an orthotopic TNBC model, demonstrating effective fluorescence-guided NIR-II cancer treatment [132]. Xiao et al. designed a tri-block polymeric nanoplatform (NPsT) integrating an oxaliplatin (Pt (IV)) prodrug, an NIR-responsive AIE photosensitizer, and a nuclear-targeting peptide. The self-assembled nanoparticles efficiently translocated to the nucleus and, upon 808 nm irradiation, released active oxaliplatin while simultaneously generating ROS for PDT. This dual action enhanced DNA damage and induced strong immunogenic cell death, demonstrating an effective chemo–photodynamic strategy for nucleus-targeted cancer immunotherapy [133]. Tang et al. designed a NIR-II AIE-based molecule (TPA-BT-DPTQ) with a donor–acceptor structure and steric shielding groups to reduce aggregation-caused quenching and enhance optical performance. Encapsulated into DSPE-PEG2000-MAL nanoparticles, it exhibited high biocompatibility, strong photothermal conversion, and excellent imaging capability. The resulting nanoplatform enabled multimodal imaging (fluorescence, photothermal, and photoacoustic) and efficient photothermal-induced tumor cell apoptosis in vivo, demonstrating strong potential for image-guided personalized cancer theranostics [134]. Yin et al. developed a NIR-II AIEgen (C12T-BBT) with high photothermal conversion efficiency, which was formulated into tumor-targeted cRGD@C12T-BBT nanoparticles. The system enabled mild PTT with strong tumor selectivity and biocompatibility, inducing immunogenic cell death via CRT exposure and HMGB1 release. Importantly, it enhanced antitumor immunity by promoting NK cell infiltration and increasing pro-inflammatory cytokines (IL-6, TNF-α) and granzyme B expression, demonstrating effective photothermal immune synergy [135]. Yu et al. synthesized a NIR-II AIEgen (TST) with reversible fluorescence and photothermal properties and assembled it with CPT-PEG and the A2AR antagonist AZD4635 to construct a multifunctional nanoplatform (CAT-NP). The system enabled strong NIR-II imaging and H_2O_2-responsive drug release, where intracellular degradation enhanced camptothecin release and photothermal

conversion. CAT-NP induced immunogenic cell death and strengthened antitumor immunity by blocking the CD39–CD73–A2AR immunosuppressive pathway via AZD4635, achieving combined chemo/photothermal/immune therapy [136].

With the continuous development of nanomaterials technology, new functional materials with excellent phototherapeutic properties are being developed. High photothermal conversion efficiency, tunable ROS generation, and stimuli-responsiveness for structural versatility can be achieved with MXenes and MOFs. Upconversion nanoparticles (UCNPs) convert NIR light to higher-energy emissions, enabling deep-tissue activation of photosensitizers and simultaneous imaging. Furthermore, hybrid organic-inorganic systems integrate imaging, targeting, and various therapeutic modalities into a single nanoplatform, enabling multifunctional precision therapy. Furthermore, the use of artificial intelligence (AI) and machine learning (ML) in nanoparticle design is revolutionizing phototherapy. AI models can identify optimal nanoplatform designs and radiation doses for a specific patient by analyzing high-dimensional data on nanoparticle physicochemical characteristics, body distribution, and disease-specific efficacy. This will enable personalized phototherapy, making it more effective and safer. Preliminary research indicates that ML-driven optimization of nanoparticles can yield improved tumor targeting, controlled drug delivery, and adaptive therapy, paving the way for a new era of precision nanomedicine.

5. **Clinical Translation Challenges**

While there has been significant progress to date in using nanoparticles for phototherapy, some hurdles remain before they reach the clinic. The trouble with using phototherapy to treat tumors is that the light doesn't easily penetrate the tissue. NIR-II light is known to have superior tissue penetration and has been used to achieve excellent deep-tissue detection. Other methods (interstitial illumination, fiber-optic delivery) may be required, making the procedure more complex and more time-consuming in the clinic and possibly restricting their use in clinical practice. The stability and pharmacokinetics of nanoparticles are major challenges. Nanoparticles can also aggregate in vivo in biological fluids, be rapidly cleared by the mononuclear phagocyte system, or become extra- or off-target in organs such as the liver and spleen, thereby reducing therapeutic efficacy and systemic toxicity. Another challenge for clinical use has been toxicity, especially chronic toxicity, and biocompatibility, where the long-term effects of nanomaterials, especially inorganic ones, have been a concern and must be thoroughly assessed for biodegradability, clearance, and immunogenicity.

In addition, there is variability in the tumor and the microenvironment. These differences in vascular architecture, density of the extracellular matrix, infiltration by immune cells, and the hypoxic environment of the accumulation site can be problematic in that the accumulation of the nanoparticles, as well as their therapeutic activation and response to therapy, may vary from one patient to another and even vary at the accumulation site within a single patient. Manufacturing nanoparticles is a complex process from a production perspective, where factors such as batch-to-batch variation, reproducibility, and cost are important for large-scale production. The lack of standardized characterization protocols and regulatory guidelines for nanomedicines further complicates current technical

challenges in quality control, clinical trials, and potential approval. The solutions to these problems will involve multiple strategies, including the development of stable, biocompatible, and biodegradable nanoparticles, optimization of light delivery to the tumor, standardization of manufacturing and evaluation protocols, and careful consideration of the various aspects of tumor-specific heterogeneity. The challenges involved in translating from the laboratory to the clinic are essential to ensure the safe, effective, and patient-specific use of nanoparticles in phototherapy.

6. **Conclusion**

The revolution in the treatment of modern diseases lies in phototherapy using nanoparticles, a multifunctional, highly targeted, and non-invasive approach. The strategy involves light activation and nanotechnology to target and provide an effective therapeutic intervention with minimal systemic toxicity. The synergistic effect of both the PDT and PTT mechanisms, along with the development of nanostructures and theranostic systems, has significantly enhanced therapeutic effectiveness. Over the last few years, the research and development of NIR-II phototherapy, stimuli-responsive nanodevices, and immune modulation have further expanded its applications, and nanoparticle-based phototherapy is an indispensable part of next-generation precision medicine. Despite this, several challenges remain before clinical translation of such a system is possible, including low-light penetration, nanoparticle safety, and clinical scalability. The therapeutic potential of this phototherapy and its wide application in medicine will depend on future interdisciplinary studies, technological advances, and the development of a standardized evaluation procedure.

Declaration of Competing Interest

The author declares no competing financial interests.

Authorship contribution statement

Mushtaq Ahmad: Investigation, writing original draft, writing a review & editing. Saadullah Khattak: Supervision, Conceptualization, Writing, review & editing.

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References

[1] D.S. Chauhan, R. Prasad, M. Dhanka, N. Kaur, H. Vithalani, K. Liyanapathirana, R. Hebbandi Nanjundappa, H. Gao, C.S. Umeshappa, Signal Transduction and Targeted Therapy, 11 (2026) 95.
[2] Y. Cai, T. Chai, W. Nguyen, J. Liu, E. Xiao, X. Ran, Y. Ran, D. Du, W. Chen, X. Chen, Signal Transduction and Targeted Therapy, 10 (2025) 115.
[3] Z. Xie, T. Fan, J. An, W. Choi, Y. Duo, Y. Ge, B. Zhang, G. Nie, N. Xie, T. Zheng, Chemical Society Reviews, 49 (2020) 8065-8087.
[4] D.K. Chatterjee, L.S. Fong, Y. Zhang, Advanced drug delivery reviews, 60 (2008) 1627-1637.
[5] A. Banstola, Z.-T. Lin, Y. Li, M.X. Wu, Advanced Drug Delivery Reviews, 219 (2025) 115549.
[6] X. Zhang, S. Wang, G. Cheng, P. Yu, J. Chang, Engineering, 13 (2022) 18-30.
[7] A. Hak, V.R. Shinde, A.K. Rengan, Photodiagnosis and Photodynamic Therapy, 33 (2021) 102205.

[8] F. Bray, M. Laversanne, H. Sung, J. Ferlay, R.L. Siegel, I. Soerjomataram, A. Jemal, CA: a cancer journal for clinicians, 74 (2024) 229-263.
[9] K. Hacker, Mayo Clinic Proceedings: Innovations, Quality & Outcomes, 8 (2024) 112-119.
[10] C. Hajat, E. Stein, Preventive medicine reports, 12 (2018) 284-293.
[11] A.C. Begg, F.A. Stewart, C. Vens, Nature Reviews Cancer, 11 (2011) 239-253.
[12] V.P. Torchilin, Nature reviews Drug discovery, 13 (2014) 813-827.
[13] D. Fan, Y. Cao, M. Cao, Y. Wang, Y. Cao, T. Gong, Signal Transduction and Targeted Therapy, 8 (2023) 293.
[14] M.J. Mitchell, M.M. Billingsley, R.M. Haley, M.E. Wechsler, N.A. Peppas, R. Langer, Nature reviews drug discovery, 20 (2021) 101-124.
[15] S.M. Sisodiya, Epilepsia, 62 (2021) S90-S105.
[16] N. Akhoon, International journal of preventive medicine, 12 (2021) 12.
[17] I.R. König, O. Fuchs, G. Hansen, E. von Mutius, M.V. Kopp, European respiratory journal, 50 (2017).
[18] X. Li, J.F. Lovell, J. Yoon, X. Chen, Nature reviews Clinical oncology, 17 (2020) 657-674.
[19] S. Yuan, J. Zhou, J. Wang, X. Ma, F. Liu, S. Chen, J.-X. Fan, G.-P. Yan, Molecular Pharmaceutics, 21 (2024) 467-480.
[20] J. Chen, H. Yu, T. Zheng, X. Zhang, C. Chen, P. Sun, RSC advances, 15 (2025) 15450-15475.
[21] B. Wang, S. Hu, Y. Teng, J. Chen, H. Wang, Y. Xu, K. Wang, J. Xu, Y. Cheng, X. Gao, Signal Transduction and Targeted Therapy, 9 (2024) 200.
[22] G. Li, C. Wang, B. Jin, T. Sun, K. Sun, S. Wang, Z. Fan, Cell Death Discovery, 10 (2024) 466.
[23] S.S. Lucky, K.C. Soo, Y. Zhang, Chemical reviews, 115 (2015) 1990-2042.
[24] Y. Zheng, Z. Li, H. Chen, Y. Gao, European Journal of Pharmaceutical Sciences, 144 (2020) 105213.
[25] B. Nasseri, E. Alizadeh, F. Bani, S. Davaran, A. Akbarzadeh, N. Rabiee, A. Bahadori, M. Ziaei, M. Bagherzadeh, M.R. Saeb, Applied Physics Reviews, 9 (2022).
[26] J. Shi, P.W. Kantoff, R. Wooster, O.C. Farokhzad, Nature reviews cancer, 17 (2017) 20-37.
[27] K. Lu, C. He, W. Lin, Journal of the American Chemical Society, 136 (2014) 16712-16715.
[28] K. Deng, C. Li, S. Huang, B. Xing, D. Jin, Q. Zeng, Z. Hou, J. Lin, Small, 13 (2017) 1702299.
[29] R. Vankayala, K.C. Hwang, Advanced Materials, 30 (2018) 1706320.
[30] G. Hong, A.L. Antaris, H. Dai, Nature biomedical engineering, 1 (2017) 0010.
[31] D. An, J. Fu, B. Zhang, N. Xie, G. Nie, H. Ågren, M. Qiu, H. Zhang, Advanced Functional Materials, 31 (2021) 2101625.
[32] Y.H. Chien, K.K. Chan, T. Anderson, K.V. Kong, B.K. Ng, K.T. Yong, Advanced Therapeutics, 2 (2019) 1800090.
[33] S. Wang, C. Zhang, F. Fang, Y. Fan, J. Yang, J. Zhang, Journal of Materials Chemistry B, 11 (2023) 8315-8326.
[34] J. Zou, L. Li, Z. Yang, X. Chen, Nanophotonics, 10 (2021) 3229-3245.
[35] C. Ma, Z. Cheng, H. Tan, Y. Wang, S. Sun, M. Zhang, J. Wang, Frontiers in Immunology, 15 (2024) 1447817.
[36] U. Chitgupi, Y. Qin, J.F. Lovell, Nanotheranostics, 1 (2017) 38.
[37] D. Lee, S. Kwon, S.-y. Jang, E. Park, Y. Lee, H. Koo, Bioactive Materials, 8 (2022) 20-34.
[38] M.Z. El-Sadek, M.K.A. El-Aziz, A.H. Shaaban, S.A. Mostafa, A.-H.S. Wadan, Photochemical & Photobiological Sciences, 24 (2025) 1489-1511.
[39] C.Y. Tsang, Y. Zhang, Chemical Society Reviews, 53 (2024) 2898-2931.
[40] M. Overchuk, R.A. Weersink, B.C. Wilson, G. Zheng, ACS nano, 17 (2023) 7979-8003.
[41] C. Kong, X. Chen, International journal of nanomedicine, (2022) 6427-6446.
[42] J. Hwang, N. Oh, M.S. Kang, C.-Y. Yoo, J.-H. Park, D.-W. Han, M. Kwak, International Journal of Nanomedicine, (2026) 1-19.
[43] D. Dinakaran, B.C. Wilson, Frontiers in Bioengineering and Biotechnology, 11 (2023) 1250804.
[44] V. Krishnaswami, B. Loushambam, S. Subramanian, J. Raja, S. Vijayaraghavalu, Current Pharmaceutical Design, (2025).

[45] J. Buiel, J. Robert, D. Mekhjian, D.S. Chauhan, X. Banquy, Advanced Therapeutics, 8 (2025) 2400347.
[46] I.F. Almadani, M.F. Almadani, N. AlSawaftah, W.H. Abuwatfa, G.A. Husseini, in: Micro, MDPI, 2024, pp. 827-844.
[47] P. Hashim, A.T. Shaji, A.S. Amrutha, S. Ahmad, RSC Medicinal Chemistry, 16 (2025) 2360-2372.
[48] Z. Huang, P. Limsakul, Y. Wu, T. Guo, Y. Wang, Z. Wu, L. Zhu, M.E. Allen, L. Liu, Y. Wang, Nature Communications, (2026).
[49] L. Huang, Y. Wang, M. Yu, X. Nie, Y. Yuan, B. He, Z. Sun, J. Xu, L. Shi, H. Yao, European Journal of Medicinal Chemistry, (2025) 118537.
[50] K. Wang, X. Mao, W. Xie, X. Liu, Q. Zhou, D. Wu, Q. Zhu, B. Liu, Chemical Science, (2026).
[51] X. Jia, H.-N. Ye, H. Weng, N. Huang, Y. Yu, J.-P. Xue, Materials Science and Engineering: C, 104 (2019) 109849.
[52] V. Mundra, Y. Peng, S. Rana, A. Natarajan, R.I. Mahato, Journal of Controlled Release, 220 (2015) 130-140.
[53] E.J. Chung, L. Leon, C. Rinaldi, Nanoparticles for biomedical applications: fundamental concepts, biological interactions and clinical applications, Elsevier, 2019.
[54] J. Fang, H. Nakamura, H. Maeda, Advanced drug delivery reviews, 63 (2011) 136-151.
[55] X. Zhao, H. Li, R.J. Lee, Expert opinion on drug delivery, 5 (2008) 309-319.
[56] S. Narayanan, N. Binulal, U. Mony, K. Manzoor, S. Nair, D. Menon, Nanotechnology, 21 (2010) 285107.
[57] F.S. Anarjan, Nano-Structures & Nano-Objects, 19 (2019) 100370.
[58] A. Prajapati, S. Rangra, R. Patil, N. Desai, V.G.S. Jyothi, S. Salave, P. Amate, D. Benival, N. Kommineni, Receptors, 3 (2024) 323-361.
[59] G. Yang, X. Mu, X. Pan, Y. Tang, Q. Yao, Y. Wang, F. Jiang, F. Du, J. Xie, X. Zhou, Chemical Science, 14 (2023) 4308-4318.
[60] Y. Zhang, Y. Li, J. Li, F. Mu, J. Wang, C. Shen, H. Wang, F. Huang, B. Chen, Z. Luo, Advanced Healthcare Materials, 12 (2023) 2300267.
[61] Q. Pang, Z. Xu, T. Sun, S. Yue, Y. Yu, H. Lu, M. He, X. Chen, Y. Lu, J. Li, Nano Today, 58 (2024) 102421.
[62] M.J. Saadh, M.A. Mustafa, L.Y. Qassem, G.K. Ghadir, M. Alaraj, M.H.S. Alubiady, S.H.Z. Al-Abdeen, H.G. Shakier, M.Y. Alshahrani, A.H. Zwamel, Journal of Drug Delivery Science and Technology, 96 (2024) 105660.
[63] D. Wei, Y. Sun, H. Zhu, Q. Fu, ACS nano, 17 (2023) 23223-23261.
[64] T. Hu, C. Shen, X. Wang, F. Wu, Z. He, Chinese Chemical Letters, 35 (2024) 109562.
[65] K. Avgoustakis, A. Angelopoulou, Pharmaceutics, 16 (2024) 179.
[66] X. Meng, Y. Shen, H. Zhao, X. Lu, Z. Wang, Y. Zhao, Journal of nanobiotechnology, 22 (2024) 587.
[67] Y. Shi, Q. Yu, L. Tan, Q. Wang, W.H. Zhu, Angewandte Chemie, 137 (2025) e202503776.
[68] Q. Huang, F. Tong, J. Chen, M. Kayumov, Y. Lv, Y. Shi, B. Ye, H. Gao, Advanced Science, 12 (2025) e13567.
[69] J. Zou, C. Jiang, Q. Hu, X. Jia, S. Wang, S. Wan, Y. Mao, D. Zhang, P. Zhang, B. Dai, Nature Communications, 16 (2025) 424.
[70] K. Li, Y. Huang, C. Xiu, BMC biotechnology, 25 (2025) 121.
[71] Y. Tang, L. Ge, D. Zhu, R. Hu, W. Chen, X. Zhen, X. Jiang, ACS nano, 19 (2025) 39228-39240.
[72] J. Song, X. Kang, L. Wang, D. Ding, D. Kong, W. Li, J. Qi, Nature Communications, 14 (2023) 6881.
[73] Y. Dong, H. Wang, X. Zhang, Y. Ding, Y. Zou, J. Wang, S.-C. Zhao, Z. Li, Journal of Nanobiotechnology, 22 (2024) 481.
[74] X. Su, Y. Liu, Y. Zhong, P. Shangguan, J. Liu, Z. Luo, C. Qi, J. Guo, X. Li, D. Lin, Nano Letters, 25 (2025) 3445-3454.
[75] J. Yuan, Y. Wang, M. Liu, D. Cheng, L. Yuan, Journal of Medicinal Chemistry, (2026).
[76] Y. Ren, X. Zhang, L. Li, Q. Yuan, B. Bao, M. Li, Y. Tang, Chemical Science, 16 (2025) 5089-5098.
[77] L. Li, J. Li, X. Huang, F. Yang, J. Wang, L. Zhao, J. Liu, G. Deng, Sensors and Actuators B: Chemical, 443 (2025) 138295.
[78] Y. Zhang, M. Zhao, D. Cheng, J. Zhu, B. Cheng, M. Miao, Q. Li, Q. Miao, ACS Applied Nano Materials, 7 (2024) 22117-22129.

[79] L. Sun, H. Wu, Z. Zhang, K. Wu, J. Sun, X. Dong, C. Dong, C. Zhao, X. Gu, D.H. Qu, Aggregate, 6 (2025) e70007.
[80] J. Li, S. Wang, F. Fontana, C. Tapeinos, M.-A. Shahbazi, H. Han, H.A. Santos, Bioactive Materials, 23 (2023) 471-507.
[81] F. Kurul, H. Turkmen, A.E. Cetin, S.N. Topkaya, Next Nanotechnology, 7 (2025) 100129.
[82] R. Tenchov, K.J. Hughes, M. Ganesan, K.A. Iyer, K. Ralhan, L.M. Lotti Diaz, R.E. Bird, J.M. Ivanov, Q.A. Zhou, ACS nano, 19 (2025) 4011-4038.
[83] N. Parvin, M. Aslam, M.N. Alam, T.K. Mandal, Nanomaterials, 15 (2025) 1733.
[84] S. Islam, M.M.S. Ahmed, M.A. Islam, N. Hossain, M.A. Chowdhury, Results in Surfaces and Interfaces, 19 (2025) 100529.
[85] N. Mohseni, D. Farahmand, S.A. Hosseinzadeh, K. Khosravipour, V. Valizadeh, Nano Select, 7 (2026) e70098.
[86] S. Huang, Y. Ye, C. Jiang, R. Wang, W. Hu, S. Raza, J. Ouyang, Y. Pan, J. Liu, Reactive and Functional Polymers, 193 (2023) 105743.
[87] S. Li, Z. Xu, R. Meng, E. Wen, Q. Peng, Precision Medicine and Engineering, 2 (2025) 100029.
[88] N.W. Nkune, H. Abrahamse, RSC advances, 14 (2024) 19490-19504.
[89] M. Zahra, H. Abrahamse, B.P. George, Scientific Reports, (2026).
[90] M.B. Mahmood, W. Bdaiwi, M.A. Dheyab, Inorganic Chemistry Communications, (2026) 116601.
[91] X. Chen, B.B. Mendes, Y. Zhuang, J. Conniot, S. Mercado Argandona, F. Melle, D.P. Sousa, D. Perl, A. Chivu, H.K. Patra, Journal of the American Chemical Society, 146 (2024) 1644-1656.
[92] J. Zhuang, S. Liu, B. Li, Z. Li, C. Wu, D. Xu, W. Pan, Z. Li, X. Liu, B. Liu, Angewandte Chemie, 137 (2025) e202420643.
[93] X. Cai, X. Deng, Z. Xie, Y. Shi, M. Pang, J. Lin, Chemical Engineering Journal, 358 (2019) 369-378.
[94] P. Liu, G. Chen, J. Zhang, Molecules, 27 (2022) 1372.
[95] B. Aldhubiab, R.M. Almuqbil, A.B. Nair, Pharmaceuticals, 18 (2025) 746.
[96] G. Jamirad, M. Seif, A. Montazeri, Journal of Molecular Liquids, 436 (2025) 128239.
[97] Y. Liu, M. Li, J. Gu, H. Huang, H. Xie, C. Yu, S. Roy, X. Chen, T. Kuang, Y. Zhang, S. Jiang, B. Guo, Colloids and Surfaces B: Biointerfaces, 245 (2025) 114258.
[98] Z. Li, S. Yang, H. Xiao, Q. Kang, N. Li, G.-l. Wu, S. Tan, W. Wang, Q. Fu, X. Tang, J. Zhou, Y. Huang, G. Chen, X. Tan, Q. Yang, Bioconjugate Chemistry, 35 (2024) 1015-1023.
[99] M.F. Attia, N. Anton, J. Wallyn, Z. Omran, T.F. Vandamme, Journal of Pharmacy and Pharmacology, 71 (2019) 1185-1198.
[100] J. Li, Q. Wang, G. Xia, N. Adilijiang, Y. Li, Z. Hou, Z. Fan, J. Li, Pharmaceutics, 15 (2023) 2233.
[101] F. Ciftci, A.C. Özarslan, I.C. Kantarci, A. Yelkenci, O. Tavukcuoglu, M. Ghorbanpour, Pharmaceutics, 17 (2025) 121.
[102] X. Li, Y. Wu, R. Zhang, W. Bai, T. Ye, S. Wang, Frontiers in Molecular Biosciences, 8 (2021) 683519.
[103] C. Ruan, K. Su, D. Zhao, A. Lu, C. Zhong, Frontiers in chemistry, 9 (2021) 649158.
[104] V. Ghassemifar, A. Zahedi, M.S.S. Meigoli, T. Mokhtari, S.S.M. Zadeh, M. Parsafar, M.K. Zenjanab, R.J. Esfahlan, Biomedicine & Pharmacotherapy, 191 (2025) 118543.
[105] M.P. Krafft, Current Opinion in Pharmacology, 53 (2020) 117-125.
[106] X. Chen, Z. Lin, N. Cheng, Y. Mo, L. Lu, J. Hou, Z. Li, X. Nie, S. Gao, Q. Hua, Materials Today Bio, 32 (2025) 101871.
[107] D. Ma, H. Bian, M. Gu, L. Wang, X. Chen, X. Peng, Coordination Chemistry Reviews, 505 (2024) 215677.
[108] B. Xu, K. Xu, S. Li, H. Sheng, H. Li, X. Zhang, Y. Wang, S. Feng, J. Chen, Advanced Interventional Materials, 1 (2026) 100016.
[109] J. Li, J. Ling, C. Yao, Frontiers in Chemistry, 10 (2022) 1054913.
[110] B. Huang, Y. Huang, H. Han, Q. Ge, D. Yang, Y. Hu, M. Ding, Y. Su, Y. He, J. Shao, Frontiers in Bioengineering and Biotechnology, 9 (2021) 751757.
[111] W. Xiong, Z. Cheng, H. Chen, H. Liang, M. Wang, Y. Chen, J. Ying, Y. Cai, J. Chai, K. Dou,

Advanced Functional Materials, 34 (2024) 2410841.
[112] H. Zhou, X. Zeng, A. Li, W. Zhou, L. Tang, W. Hu, Q. Fan, X. Meng, H. Deng, L. Duan, Nature communications, 11 (2020) 6183.
[113] J. Wang, X. Zhao, X. Zhu, S. Wang, X. Sun, Q. Zhang, X. Chen, A. Wang, M. Yang, H. Zhou, Analytical Chemistry, 96 (2024) 19404-19413.
[114] Q. Xie, J. Liu, B. Chen, X. Ge, X. Zhang, S. Gao, Q. Ma, J. Song, ACS Applied Bio Materials, 5 (2022) 711-722.
[115] Q. Ahmad, S. Mehdi, B. Shaukat, R. Siqqique, M.T. Asif, A. Malik, S. Khan, R. Siddiqui, N.A. Khan, M.H. Mehmood, OpenNano, (2026) 100296.
[116] D. Bi, X. Yang, Y. Wang, J. Yong, F. Yang, X. Tan, Y. Li, D. Zheng, P. Li, Frontiers in Immunology, 17 (2026) 1714249.
[117] R. Zhu, X. Yu, Y. Zhang, J. Zhang, S. Li, D. Li, Y.J. Ma, Chemical Engineering Journal, (2026) 175025.
[118] H. Sun, Y. Li, M. Xue, D. Feng, International Journal of Nanomedicine, (2025) 7987-8001.
[119] Y. Luo, Y. Cong, J. Liu, L. Huang, W. Cheng, P. Xu, Y. Yin, H. Hong, W. Xu, New Journal of Chemistry, 47 (2023) 3395-3405.
[120] C. Du, Y. Liang, Q. Ma, Q. Sun, J. Qi, J. Cao, S. Han, M. Liang, B. Song, Y. Sun, Journal of nanobiotechnology, 17 (2019) 113.
[121] W. Hou, X. Zhao, X. Qian, F. Pan, C. Zhang, Y. Yang, J.M. de La Fuente, D. Cui, Nanoscale, 8 (2016) 104-116.
[122] J. Yu, J. Wu, J. Huang, C. Xu, M. Xu, C.Z.H. Koh, K. Pu, Y. Zhang, Nature Communications, 16 (2025) 153.
[123] J. Yue, Q. Mei, P. Wang, P. Miao, W.-F. Dong, L. Li, Journal of nanobiotechnology, 20 (2022) 181.
[124] Z. Lin, T. He, M. Kang, W. Xie, D. Wang, B.Z. Tang, Aggregate, 6 (2025) e70189.
[125] K. Wang, Y. Li, X. Wang, Z. Zhang, L. Cao, X. Fan, B. Wan, F. Liu, X. Zhang, Z. He, Nature communications, 14 (2023) 2950.
[126] X. Xu, G. Deng, Z. Sun, Y. Luo, J. Liu, X. Yu, Y. Zhao, P. Gong, G. Liu, P. Zhang, Advanced Materials, 33 (2021) 2102322.
[127] W. Xie, B. Chen, H. Wen, P. Xiao, L. Wang, W. Liu, D. Wang, B.Z. Tang, ACS nano, 16 (2022) 10742-10753.
[128] X. Kang, Y. Zhang, J. Song, L. Wang, W. Li, J. Qi, B.Z. Tang, Nature Communications, 14 (2023) 5216.
[129] L. Shi, X. Liu, Y. Li, S. Li, W. Wu, X. Gao, B. Liu, Advanced Science, 9 (2022) 2105807.
[130] J. Dai, J.J. Hu, X. Dong, B. Chen, X. Dong, R. Liu, F. Xia, X. Lou, Angewandte Chemie International Edition, 61 (2022) e202117798.
[131] J. Dai, X. Dong, R. Liu, B. Chen, X. Dong, Q. Wang, J.-J. Hu, F. Xia, X. Lou, Biomaterials, 285 (2022) 121528.
[132] D. Wei, Y. Chen, Y. Huang, P. Li, Y. Zhao, X. Zhang, J. Wan, X. Yin, T. Liu, J. Yin, Nano Today, 41 (2021) 101288.
[133] D. Wei, Y. Huang, B. Wang, L. Ma, J. Karges, H. Xiao, Angewandte Chemie International Edition, 61 (2022) e202201486.
[134] D. Yan, M. Wang, Q. Wu, N. Niu, M. Li, R. Song, J. Rao, M. Kang, Z. Zhang, F. Zhou, Angewandte Chemie International Edition, 61 (2022) e202202614.
[135] Y. Feng, J. Ni, H. Xie, N. Zhu, W. Liu, L. Guo, J. Zhang, J. Di, S. He, H. Hu, Biomaterials, 321 (2025) 123340.
[136] Z. Wang, L. Yu, Y. Wang, C. Wang, Q. Mu, X. Liu, M. Yu, K.N. Wang, G. Yao, Z. Yu, Advanced Science, 9 (2022) 2104793.