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Next-Generation Photodynamic Therapy: Combining Light and Nanotechnology for Targeted Cancer Treatment

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Abstract:

Photodynamic therapy (PDT) has received significant interest as one of the least invasive and spatially selective cancer treatments. It uses photosensitizers excited by light of a certain wavelength to produce cytotoxic reactive oxygen species (ROS) to discriminately destroy cancerous cells, leaving normal tissue intact. PDT is effective in the treatment of superficial malignancies; however, the applicability is limited by poor light penetration, poor selectivity of photosensitizers about tumor specificity, and systemic side effects, among others. Nanotechnology has offered radical solutions to overcome these challenges by enabling the possibility of designing nanoparticle (NP)-based systems to increase the aqueous solubility of the photosensitizer, as well as targeting the tumors and effective production of reactive oxygen species. This review sums up the recent advances of nanoparticle-mediated PDT over the last decade, including approaches and designs of nanoplatforms, targeted PDT, photo-physical activation approaches, generation of ROS, therapeutic safety, and translation. We highlight the challenges we cannot overcome so far, such as nanoparticle synthesis reproducibility, light dosimetry, hypoxia in tumors, and regulatory barriers, and the new technologies that are only going to gain more significance, such as nanomedicine controlled by artificial intelligence (AI) and combination therapy. Collectively, they represent a paradigm shift towards a next-generation PDT as a safe, precise and personalized cancer treatment.

Keywords: Photodynamic therapy, Targeted cancer therapy, Reactive oxygen species, Nanomedicine, Light-activated therapy.

Introduction

Cancer has been one of the most recalcitrant health issues, and globally it triggers up to 10 million deaths annually. Despite the immense advances in the field of conventional oncological treatments, like surgery, chemotherapy, and radiotherapy, remain highly constrained (1, 2). Even though these therapies may be effective in reducing tumor load, they are also typically associated with systemic toxicities, destruction of normal cells not targeted, and countermeasures by the tumor cells. Not only do these limitations decrease the overall effectiveness

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of treatments, but they also influence the quality of life of patients, and, therefore, innovative and more selective and less invasive treatment methods are required urgently (3).

Photodynamic therapy (PDT) has garnered quite a significant amount of attention as a possible competitive or complementary therapeutic modality among cancer patients. PDT relies on a combination of three key components: a photosensitizing agent (photosensitizer, PS), light of a certain wavelength that fits within the absorption spectrum of the PS and molecular oxygen that is present in tissues (4). Upon exposure to the activating light, the PS is substoichiometrically excited to long-lived triplet multiplicity by a photochemically induced ground-state to excited-singlet transfer followed by intersystem crossing to the long-lived triplet. That excited PS can then convert its energy to surrounding molecular oxygen, producing highly reactive oxygen species (ROS), mainly singlet oxygen (1 O 2), and other radicals. These ROS cause local oxidative damage to valuable cellular molecules such as lipids, proteins, and nucleic acids, causing cancerous cells to die. Additionally, PDT can cause tumor vessels and tumor microenvironment damage and enhance antitumor immunity and contribute to the prolonged therapeutic response (5).

Absence of Targeting Specificity: The traditional PSs lack tumor selectivity and are prone to the occurrence in non-targeted tissues, which has been noted as one of the factors leading to the need for developers of enhanced targeting controls (6).

Over the past couple of years, nanotechnology has been redefining the operations of the drug delivery field and biomedical imaging, offering new answers to problems that are bound to emerge in PDT. The photosensitizers can also be encapsulated by NPs (10-200 nm) to enhance solubility, provide protection against early degradation, and minimize the circulation time (7). Besides these, nanoparticles can improve the selective delivery of PSs to the tumor through passive accumulation based on the enhanced permeability and retention (EPR) effect and active targeting based on the recognition of tumor-specific receptors by surface-functionalized ligands. Further nanoplatforms possess inherent stimuli-responsive features that enable the release of the PS at tumor microenvironment to desirable locations and under controlled conditions in response to particular stimuli such as acidic pH, redox gradients or enzyme activity (8).

New nanomaterials may also carry agents to overcome tumor hypoxia, such as loading the material with oxygen-impermeable materials, or catalysts to create supplemental oxygen (urgently required by the cells) internally. The other pivotal development is the upconversion nanoparticles (UCNPs) that turn deep red/near-infrared (NIR) light into visible light to actuate a conventional PS in vivo, which can be seen as simply penetrating tissue (9).

Taken together, these developments could considerably increase the efficacy of PDT, its safety rate, and its use in the clinic, where its efficacy may be extended to a wider range of tumors, including deep-seated tumors (10).

This review will explain in detail the use of nanotechnology in the treatment of cancer through photodynamic therapy. We review methodically the recent advances in nanoparticle platforms design, molecular and cellular tumor targeting, photophysics of ROS-generating, preclinical, clinical and safety issues. We also discuss critically the problem of translation to nanoparticles-facilitated PDT and promising prospects and opportunities. We hope to leave a methodological roadmap that can guide the research and professional contribution of the future towards the creation of the next generation of PDT protocols that will transform the arena of targeted cancer therapy.

Nanoparticle Platforms in PDT: Design and Functionalization

Nanoparticles (NPs) have emerged to be multi-functional and versatile delivery vehicles that can enhance the sensitivity and specificity of photodynamic therapy (PDT). Encapsulation or conjugation of NPs to photosensitizers (PSs) offers the potential to improve solubility, stability, pharmacokinetics and tumor targeting of PSs with reduced systemic toxicity (11). Moreover, the nanoparticle may be modified to respond to some stimuli in the tumor or in the external environment, causing the therapeutic drug payload to be released and activated. During this session, a list of the most researched nanoplatforms employed in PDT is provided with a detailed description of structural characteristics and how they can be functionalized, in addition to the advantages of using such structures (12).

Liposomes and Micelles

An example of a vesicle that is bilayered and rounded and which is mainly made of phospholipids is called a liposome and has the same structure as the cell membranes. This similarity to the structure offers extremely high biocompatibility and enables the encapsulation of a broad therapeutic repertoire of drugs. Liposomes mimic the cancer core-shell system that allows to entrap of water-soluble photosensitizers in the hydrophilic core and lipophobic compounds in the hydrophobic bilayer (13). They have high PS solubility when stored in liposomes and are not easily digested by enzymes or degraded. It is also notable that certain liposomal PDT systems (including

verteporfin liposomes) had already gained regulatory and clinical approval, and that they represented their potential translation (14).

The significance of surface modification of liposomes is, it must proceed in a manner that it prolongs the circulation period and increases the specificity of targeting. PEGylation of nanoscopic carriers to achieve hydrophilicity inhibits opsonin socialization and uptake in the RES and prolongs systemic circulation. Active targeting, in which the PS binds to overexpressed receptors on tumor cells or tumor-associated vasculature, may be incorporated once again into functionalized PS delivery (15). Also, immunomodulatory molecules may be added to regulate the tumor microenvironment.

Nanosized objects formed by self-assembling amphiphilic block copolymers, in their turn, are called micelles and contain hydrophilic and hydrophobic parts. Photosensitizers with lipophilic properties (that most PS molecules are limited to only by a few constraints of water solubility) are readily dissolved in their hydrophobic interstitium (16). The micelles are smaller (10-100 nm) than liposomes, and this can be translated into greater penetration depth and cellular uptake efficiency in the tumor cell. Improved micellar systems utilize stimuli-sensitive polymers that may be liberated by PSs in response to low-basic environments, elevated enzyme concentrations or redox environments commonly found in the tumor microenvironment. This would minimize the off-target effects and maximize the therapeutic index (17).

Gold Nanoparticles

Special physicochemical properties of gold nanoparticles have been achieved due to the scattering of light by collective oscillation of conductive electrons (surface plasmon resonance, or SPOR) (18). This makes AuNPs highly absorbent and optically scattering at the visible wavelengths and the NIR wavelengths that are used twice in the PDT. In addition to the ability to deliver PSs, the AuNPs can also adopt light energy and subsequently transform it into heat, referred to as the photothermal effect, and can induce synergistic effects but not combinatoric effects when combined with PDT-mediated generation of ROS (19).

AuNPs with objectively determinable optical properties (size dependence) as well as biodistribution and surface chemistry can be prepared in varying sizes and shapes (spheres, rods, shells, cages). These surfaces can easily accept thiolated ligands and consequently can be conjugated to PS molecules, target group antibodies or peptide or stealth coating such as PEG (20). It enables the surveillance and targeting of tumors with the assistance of multi-functionalization. Additionally, to reach integrated theranostic applications, photoacoustic imaging, computed tomography (CT), and surface-enhanced Raman scattering (SERS) imaging technologies may use AuNPs as contrast agents (21).

Mesoporous Silica Nanoparticles (MSNs)

Mesoporous silica nanoparticles possess highly ordered pore structures and adjustable pore sizes ranging between 2-10 nm with very large surface areas and pore volumes, resulting in high loading capacities compared to conventional silica nanoparticles. The range of photosensitizers into which one can introduce the SNs is typically broad, encompassing synergistic therapeutics that can include chemotherapeutics, gene therapies or oxygen-generating catalysts (1, 2).

Any biomedical application of the material is attributed to inherent biocompatibility and chemical stability, and is associated with MSNs. It is worth noting that MSNs are readily modified on their surface with multiple functional groups, and surface-bound functional groups can be conjugated to both targeting ligands (e.g., folate, transferrin) and stimuli-sensitive formulations, called gatekeepers, that prevent lock-up of potential PS-leakage before its occurrence (3). These gatekeepers can be designed to react to tumor targeting cues such as acidic pH, glutathione or proteolytic enzymes such that cargo release is specific to the tumor (4).

Alongside this, the co-delivery of agents to achieve tumor hypoxia, e.g. catalase or perfluorocarbon compounds, could be used in MSNs to increase oxygen in the local area to enhance the production of ROS and PDT efficacy. It is this multi-functional nature that makes MSNs a highly useful platform in combination therapy and precision oncology (5).

Carbon Nanomaterials

A significant subset of nanoparticles is represented by carbon-based nanomaterials, including graphene oxide (GO), carbon dots (CDs), and carbon nanotubes (CNTs) with unique optical, electronic, and chemical properties in PDT. Oxidized PS on two-dimensional graphene (GO) has a high surface area, allowing conjugation and photothermal and photodynamic properties. Targeting ligands have been incorporated into the functionalization, resulting in high uptake in tumor cells and high biocompatibility via high dispersibility in water (6).

Carbon dots are nanometric fluorescent carbon nanoparticles that are photostable and can be tuned. Their intrinsic fluorescence may enable concomitant imaging and therapy (theranostics). CdS nanoporous objects may be functionalised with PS molecules to form functioning ROS makers in the presence of light (7).

CNTs are hollow cylinders composed of graphene

that have good thermal conductivity and absorption of [NIR]. The multifunctional systems with carbon nanomaterials can be combined with diagnostic imaging, drug delivery and phototherapy to kill tumor cells synergistically (8).

Polymeric Nanoparticles

Polymeric nanoparticles made out of biodegradable and biocompatible polymers such as poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), chitosan and poly(ethylene glycol) (PEG) have been used extensively as controlled drug delivery vehicles in PDT. These polymers can be customized selectively concerning their particle size, surface charge, degradation profile, and drug release profile by altering its molecular weight, ratio of copolymer, and surface functionalization (9).

Polymeric nps provide defense against encapsulated PSs that eliminate premature degradation by improving pharmacokinetics and biodistribution (10). The use of stimuli-sensitive bonds or coatings would enable release of PS under tumor-specific conditions (low pH, high glutathione, active enzymes, etc.). These smart polymeric systems enhance the target drug delivery and minimize the side effects of the drug on the system (11). Also, polymeric nanoparticles can support concurrent delivery of therapeutic, chemotherapeutic and immunomodulatory payloads (e.g., PSs), and provide synergistic effects in anticancer therapy. The modularity of polymer chemistry also allows incorporation of imaging agents and offers the opportunity to image-guide PDT, and in real time, track drug distribution (12).

Upconversion Nanoparticles (UCNPs)

The new type of nano-material is called upconversion nanoparticles, which can transform low-energy near-infrared (NIR) photons into higher-energy visible or ultraviolet light through an anti-Stokes luminescence reaction. Lanthanide ions (e.g. Yb3+, Er3+, Tm3+) are usually doped in UCNPs and possess the advantage of absorbing tissue-penetrating NIR light (c. 980 nm) and emitting shorter wavelengths that can, in turn, trigger conventional photosensitizers that would otherwise need visible light excitation (13).

This characteristic feature effectively overcomes one of the main weaknesses of PDT, namely, low tissue penetration of activating light, to permit non-invasive therapy of deep-set tumors. UCNP-PDT systems have been demonstrated to possess ideal photostability and low autofluorescence backdrop in addition to creating minimal tissue damage, owing to the intrinsic utilization of NIR (14).

Moreover, UCNP surfaces might be designed to be effectual delivery- and conjugation-oriented to PS molecules, resulting in tumor specificity and enhanced treatment efficacy. UCNPs are the nanotechnology of the future of PDT as they target and penetrate tissues ultra-deeply (15).

Targeting Strategies in Nanoparticle-Enhanced PDT

Photosensitizers (PSs) selective distribution and activation in the tumor tissues, but not in healthy cells, is a highly reliable indicator of the therapeutic efficacy of photodynamic therapy (16). Nanoparticle-based delivery platforms significantly enhance a tumor-specific delivery through multiple mechanisms of tumor targeting that capitalize on tumor-specific physiological and molecular features. These include passive targeting based on physiological abnormalities to localise to the tumor, active targeting based on ligand receptor interactions, and stimuli-responsive modalities that aim to exploit the unique tumor microenvironment. Nanopurified-enhanced PDT has a superior efficacy, fewer side effects, and a greater therapeutic index (17).

Passive Targeting via the Enhanced Permeability and Retention (EPR) Effect

One of the earliest mechanisms to have been exploited, and by far the most common in the present day, is passive tumor targeting under the Enhanced Permeability and Retention Effect (EPR) effect. The aberrant, disorganized vasculature of solid tumors is usually non-uniform with distances of 100 nm to 2 micrometers between endothelial cells (18). The resulting injury to vessel integrity enables the extravasation of circulating nanoparticles (usually 10 100 nm in diameter) into the vascular system out of the tumor interstitial space. The fact that tumors also have defective lymphatic drainage and, therefore, retention of the nanoparticles in the tumor microenvironment over time is also normal (19).

The EPR effect consequently allows the accumulation of PSs in tumor tissue over normal organs to a favorable degree, increasing PS local concentration and consequently local efficacy in selectivity of PDT. The other opportunistic effects of the improved retention include increased duration of therapeutic exposure and subsequent expanded exposure to become light-activated (20).

Being the most fundamental of the foundations, the EPR effect demonstrates a significant heterogeneity among the types of tumor, their stage, and even among patients with the same stage. Tumor blood flow, rate of perfusion, interstitial pressure, and matrix have all been found to be highly significant in EPR efficacy (21). In the case of highly vascularized tumors such as glioblastomas, the EPR can be high compared to poorly vascularized tumors, such as pancreatic adenocarcinomas, with a dense stroma that can experience low nanoparticle penetration.

Moreover, the age of the patient, sites of his/her tumor and past treatment procedures are among such systemic components that affect the delivery of nanoparticles via EPR (22).

Single administration of EPR is hence likely to yield inadequate and heterogeneous therapeutic results emphasizing the role of further targeting methodologies to improve therapeutic performance and precision within clinical PDT (23).

Active Targeting Through Ligand-Receptor Interactions

Nanoparticles can also be engineered to address the inherent negative attributes of passive accumulation, including active targeting with ligands that can bind receptors or other biomarkers that appear in excess on cancer cells or other stromal elements. This endocytosis has two advantages: massive uptake and intracellular delivery of PSs and an added specificity due to a reduced off-target effect (24).

More generally engaged ligands, and their targets are:

Folate and Folate Receptors: Folate receptors have been over-expressed in numerous malignant cells, including ovarian, breast and lung cancer. Folate-conjugated nanoparticles exploit this interaction between the receptor and ligand to enable higher tumor cell targeting and uptake. To allow the successful tumor targeting without the production of immunological responses, folate is a small molecule ligand (25).

Transferrin and Transferrin Receptors: The Transferrin receptors in the cancer cells are augmented during rapid cell growth to cope with the augmented demand for iron. Nanoparticles conjugated with transferrin are the only nanoparticles that endocytose through receptor-mediated endocytosis and therefore exhibit high uptake and intracellular delivery of PSs (26).

Peptides (e.g. RGD Motif): RGD peptides (RGD) bind integrin receptors, of which 8 is highly expressed on tumour endothelium and cancer cells, resulting in a higher tumour targeting and penetration. GD-functionalized nanoparticles are also capable of producing anti-angiogenic effects (27).

Targeting Agents: Monoclonal antibodies may serve to target the nanoparticles to particular attractive sites on the tumor, including epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and other tumor-associated antigens. This extreme specificity of targeting improves selective binding to malignant cells and endocytosis, leading to a high PS delivery (28).

Aptamers and Other Ligands: DNA- or RNA-based aptamers represent another, and possibly low-immunogenicity, alternative to antibodies to address a wide spectrum of tumor-associated targets (29).

Parallel to tumor cell specificity, active targeting could be employed to maximize other PDT effects, such as control of the tumor microenvironment, such as vascular disruption, immune cell recruitment and stroma remodelling (30).

Stimuli-Responsive and Environment-Sensitive Targeting

Compared to normal tissue, tumor microenvironments are radically distinct and are characterized by acidic levels of extracellular pH, hypoxia, increased concentrations of reactive oxygen species (ROS), and excess enzymes. A new approach to add more precision and site-specificity to therapeutic potential and minimize systemic effects is the nanoparticles that can recognize such stimuli and release or activate PS (31).

Key types of stimuli-responsive targeting systems include:

pH-Responsive Systems: Extracellular pH of solid tumors tends to be low (pH 6.5-6.8) relative to the normal pH (~7.4) due to disrupted metabolism and low perfusion (32). Acid-functionalized nanoparticles (e.g., hydrazone, cis-aconityl) or acid-sensitive polymer switch and degrade in acidic conditions, leading to the release of PSs in the acidic environment, more commonly in the tumor microenvironment or even within the cells (endosomes/ lyosomes). The pH-sensitivity offers low early drug release in the bloodstream and prefers drug bioavailability in tumor bone location (33).

Redox-Responsive Linkers: The reducing agent, glutathione (GSH), defines the intracellular environment of cancer cells, as the concentrations of reducing agents are usually more than 100 and 1000 times higher than in extracellular body fluids. A disulfide bond or other redox-labile bond is a nanoparticle that uses this gradient to specifically release PSs in tumor cells. This method provides intracellular PDT activation of certain agents (34).

Enzyme-Responsive Nanoparticles: Certain enzymes, like matrix metalloproteinases (MMPs), cathepsins, and phospholipases, are in excess or exuded in tumor cells. In NP-based systems, protective coating layers or gatekeepers that are conjugated to the NP via enzyme-cleavable peptides or bonds are also inert in circulation but interact with target enzymes in the tumor to allow the NP to unzip and release the PS load (35). This is a more specific enzyme-activated release, and physiological constraints to drug delivery are avoided (36). Hypoxia-Activated Prodrugs and Systems: Since hypoxic areas of tumors inhibit the formation of ROS, and thus effective treatment, there exists the issue of hypoxia and tumor areas that must be treated by a prodrug process. Other novel methods involve hypoxia-responsive element, which either activates prodrugs or liberates oxygen-producing

molecules in the low oxygen regions. In another example, nanoparticles can be used to introduce catalase to break down overexpressed hydrogen peroxide in tumors into oxygen, decreasing hypoxia. Alternatively, the PSs may be hypoxia-activated to induce little or no activity when there is oxygen and only in the hypoxic areas of tumor cells (37).

Externally Triggered Systems: In addition, nanoparticles can be programmed to respond to externally induced stimuli (e.g. temperature (thermo-responsive) or magnetic field (magneto-responsive) or ultrasound (sonodynamic activation) or light of a specific wavelength), and spatiotemporal regulation of PS activation may be employed (38).

Molecular Mechanisms of ROS Generation and Photophysical Principles

Nanoparticle platforms can enhance these photophysical and photochemical processes in many ways, often by several different mechanisms (40):

In protruding the lifetime PS Triplet State: PS lifetime may be enhanced by encapsulating or conjugating PS molecule in nanoparticles, which entraps the PS in a kind of nano protection coating. This trapping increases the lifetime of the excited state triplet, which increases the probability of energy transfer to the molecular oxygen to stimulate the formation of ROS (41).

Metallic NanoPlasmonic Enhancement: Metallic nanoparticles, particularly gold and silver, have localized surface plasmon resonance (LSPR) whereby conduction electrons vibrate as a mass upon the illumination of light. This effect enhances the electromagnetic field around the nanoparticle, so PS molecules are more easily excited and the energy transfer processes are improved to generate more ROS (42).

Co-delivery of Catalytic or Enzyme-Mimetic Agents: Nanocarriers can be designed such that they deliver PSs in combination with catalytic or enzyme-mimetic agents that can be used to generate a catalytic amount of the synthesis of oxygen, peroxides or other oxidized products (43). These catalysts regulate the tumor microenvironmental condition by degrading disease-endogenous hydrogen peroxide to produce molecular oxygen, which relieves hypoxia, and supplies enough molecular oxygen to facilitate vigorous ROS production. Such a co-delivery approach will overcome the major limitation of PDT in the hypoxic tumors (44). Enhanced Light Absorption due to Nanoparticle Photonic Upconversion: The nanoparticles would enhance the light absorption cross-section of the PSs. Upconversion nanoparticles (UCNPs) are one such example; they convert deep penetrating near-infrared (NIR) light to visible light that can then power PSs to generate ROS efficiently in deep-seated tumors where direct light excitation is challenging to attain (45).

Though optimum action of ROS is vital as far as elimination of tumors is concerned, the balance in this sensitive action must be monitored so as to prevent collateral damage. Excessive levels of ROS can overwhelm antioxidant systems in the surrounding normal tissues and lead to unintended cytotoxicity and inflammation (46). In contrast, production of ROS may be suboptimal, resulting in failure to kill a tumor and therapeutic failure. In this way, PDT nanoparticle characteristics, including ROS generation dynamics and targeting, have to be optimized to simplify its use to the maximum benefit and mitigate its side effects (47).

Preclinical and Clinical Advances in Nanoparticle-Enabled PDT

Preclinical Efficacy in Diverse Cancer Models

These are validated in an expanding literature of in vitro and in vivo experiments that have shown the increased effectiveness of nanoparticle-enhanced PDT in a broad range of cancer models (48).

Breast cancer: EGFR-targeted, gold nanorods conjugated to chlorin e6 (Ce6) are demonstrated to reduce tumor volume by 80 percent in a mouse with a combination of photothermal and photodynamic effects (49).

Lung cancer: PDT of mesoporous silica nanoparticles in lung carcinoma cells in the presence of mitochondrial-targeting IR-780 led to the development of a necrotic cell death resulting from the production of ROS and mitochondrial dysfunction (50).

Glioblastoma: Conjugation of porphyrin derivatives with graphene oxide and activation by NIR light increased the survival of mice with intracranial glioma by increasing BBB crossing and prolonged generation of ROS (51).

Colon cancer: PH-sensitive upconversion nanoparticles that are loaded with a near-infrared dye called indocyanine green (ICG) have shown 70 percent suppression of tumor growth in xenograft models (52).

Clinical Trials and Translation

This was shown to be safe and moderately efficacious in a phase II trial of liposomal benzoporphyrin derivative (BPD) activated by laser in head and neck cancer. In pancreatic cancer, a Phase I trial of porphyrin-nanoparticle showed synergistic targeting at low toxicity. The barriers to clinical use include scalability of the nanoparticles, reproducibility of the nanoparticles, regulatory concerns, and complexity of customized lighting configurations on the patient (53).

Safety and Biocompatibility Considerations

Safety, biocompatibility is one of the most critical

issues related to the development of a nanoparticle-based PDT system. The adsorptive interaction of nanoparticles with the biological milieu is also determined by various significant factors, including the size, surface charge, chemical composition and degradation characteristics of the nanoparticles. All these parameters interact to affect the biodistribution, immune recognition, their clearance, and potential toxicity which all need to be optimized to provide the most desirable therapeutic effect whilst reducing the adverse effects (54).

The size range of nanoparticles can be extensive (10 to 200 nanometers), and through the so-called enhanced permeability and retention (EPR) effect, they can be concentrated in a tumor tissue by passive targeting. Within this size range, nanoparticles are also prone to sequestration through the mononuclear phagocyte system (MPS), including in the liver, the spleen, and the kidney cells. This extrasystemic deposition or accumulation causes the risk of multiple organ toxicities or organ-selective toxicities when given repeatedly as a result of the long-term retention, which may cause inflammation or dysfunction of the organs (55).

The question of the surface charge of a nanoparticle is also a major consideration in how it communicates with the plasma or with the immune cells. Nanoparticles that are positively charged will be more likely to have an affinity with the cells; they will also cause higher degrees of cellular toxicity and complement activation, resulting in an immune response (56). Conversely, neutral or negatively charged particles have a lower probability of binding nonspecifically to proteins, and immune clearance and immune recognition do not depend on the surface chemistry or reactive functional groups on them (57).

Further effects on the biocompatibility and degradation depend on the composition of the materials. Inorganic nanoparticles (e.g., gold or silica), which are non-biodegradable or slowly bio-persistent in vivo, are desirable due to attractive optical or structural characteristics, but there is concern over their long-term persistence and possible chronic toxicity. The benefits of biodegradable polymers are that they can be degraded in a controlled manner with non-toxic by-products, thereby being less prone to accumulation and aiding in safer clearance in the body (58).

The other notable observation is that nanoparticle preparations can also be immunogenic. Unintentional activation of innate immune responses, particularly through the complement cascade, can lead to unwanted effects up to mild inflammation and acute cardiovascular or respiratory adverse events in the manifestation of reaction to complement activation related pseudoallergy (CARPA). Not only do these immune responses harm patient safety, they may accelerate the clearance of nanoparticles to diminish the effects of therapy (59).

A series of design solutions is added to reduce such risks. The steric repulsive force formed by covalent conjugation of nanoparticles with hydrophilic polymers such as polyethylene glycol (PEG) prevents protein adsorption (opsonization), and immune recognition and causes a marked prolongation of the circulatory life of the nanoparticle in the body (60). PEGylation is widely practised and is effective in reducing immunogenicity; however, in certain patient groups, anti-PEG antibodies are appearing, due to which other stealth coatings using zwitterionic polymers, polysaccharides, or biomimetic cell membrane-derived polymers are being explored with assertion of superior biocompatibility and immune evasion (61).

Targeted surface functionalization with tumor-specific binders (e.g. antibodies, peptides and small molecules) has the benefits of improving tumor specificity, reducing off-target binding and inducing immunotoxicity. To this effect, systemic exposures and consequent toxicities by nanoparticles can be minimized through close dosage tuning and targeting of nanoparticles at sites of local delivery (preferable to systemic delivery by nanoparticles wherever possible) (62).

In the evaluation of the safety of nanoparticle-PDT systems, preclinical toxicological testing is required. In vitro cytotoxicity tests, hematology, biochemical, organ histopathology, immunotoxicology and pharmacokinetic studies are primarily subject to extensive testing to identify biodistribution and excretion. Physicochemical characterization, including particle size distribution, surface charge, concentration of endotoxin, and state of aggregation, should be standardized to ensure reproducibility as well as be regulation-compliant (63).

Their safety and quality must be adequately guaranteed by regulatory bodies, e.g., the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), before clinical approval. Early safety in nanoparticles development facilitates more convenient transfer to the clinic and avoids unexpected toxicities, and accelerates regulatory approval (64).

Challenges and Opportunities for Next-Generation PDT

Technical and Biological Barriers

Effective delivery of an adequate light dose of the photosensitizers (PSs) in the deep tumor tissues is one of the most significant constraints of photodynamic therapy (PDT). The fact that visible light will not penetrate the biological tissue more than a few millimeters, often restricts the usefulness of PS to the topical lesions, or the invasive techniques will be

necessary. Improvements in fiber-optic technology, light-emitting implantable systems, and upconversion nanoparticles that enable the conversion of near-infrared (NIR) light to visible wavelengths are significant to overcome these challenges and enable uniformity and control of light delivery in tumors to clinically relevant depths (65).

The biologic barriers to PDT activity are significant tumor hypoxia. The availability of molecular oxygen is closely linked to the formation of reactive oxygen species (ROS), yet hypoxia has been reported to occur in a number of solid tumors due to the presence of a hydrophobic circulatory system and elevated cellular proliferation rate (66). This removes much of the ROS production that is threatening cytotoxicity. Multiple approaches to overcome this hypoxic microclimate include concomitant administration of oxygen carriers, e.g. hemoglobin-based nanoparticles, perfluorocarbon emulsions or catalase-mimicking enzymes that produce O2 locally. Furthermore, the development of hypoxia-activated photosensitizers capable of producing cytotoxic species at a hypoxic setting offers a possible alternative to the traditional PDT (67).

Heterogeneity refers to the problem of nanoparticle manufacturing. Reproducibility, efficacy of therapeutics and safety factors may be adversely affected by potential variability of size distribution, surface chemistry, payload loading, and batch-to-batch reproducibility conditions (68). This inconsistency is dangerous when it comes to quality regulation and regulatory approval processes that demand rigid standardization of synthesis procedures and solid dependence of characterization methods. Effective clinical translation and the probability of nanoparticle-enhanced PDT becoming a widely utilized technology depend critically on the ability to prepare nanoparticles in a stable form, especially concerning their homogeneity (69).

Emerging Innovations

Theranostics: Nanoparticle platform allows the co-delivery of imaging agents to allow simultaneous diagnosis, real-time monitoring of treatments and directed delivery of photodynamic therapy (70). To determine the biodistribution of nanoparticles, evaluate therapeutic response and remodel parameters of treatment continuously, to optimize treatment response and minimize side effects, this two-prong system is possible (71).

Multifunctional Nanoplatforms: Multi-functional nanocarriers may be employed to deliver photosensitizers concomitantly with chemotherapeutic agents or immunomodulatory therapeutic molecules and/or gene editing technologies such as CRISPR-Cas9. The advantage of the combinatorial approach is the promotion of synergistic therapeutic effects, to overcome cancer through multiple, which will overcome drug resistance and escalate total therapy expenses (72).

Machine Learning and Artificial Intelligence: ML-based algorithms are applied to extremely large datasets to refine nanoparticle design parameters to optimize features, including size and surface chemistry and cargo loading; ML can also be used to optimize an individualized approach to treatment based on patient-specific tumor features. These data-oriented plans facilitate quick building, improve target exactness, and streamline PDT plans that are of utmost treatment worthiness (73).

External Stimuli -Triggered Release: This enables the application of external stimuli remotely to release photosensitizer like ultrasound waves, magnetic and electric pulses. With stimuli-responsive systems, a spatiotemporal control of therapy is possible, and thereby, off-target effects are minimized, or the therapy is made more specific (74).

DISCUSSION

Oncolytic viruses (75) represent a rapidly maturing class of cancer therapeutics that combine direct tumor lysis with stimulation of systemic antitumor immunity. Unlike conventional treatments that primarily target malignant cells or pathways, OVs exploit tumor-specific vulnerabilities such as impaired antiviral signaling and abnormal surface receptor expression to selectively replicate in cancer cells (76). This unique mechanism enables OVs to serve as both cytotoxic agents and immune modulators, positioning them at the interface of virotherapy and immunotherapy (77).

A central advantage of OVs is their dual mechanism of action. Direct oncolysis leads to rapid tumor cell destruction, while the release of tumor-associated antigens, damage-associated molecular patterns, and viral pathogen-associated signals activates innate and adaptive immunity (78). In this sense, OVs act as an in situ cancer vaccine, promoting recruitment of dendritic cells, priming of cytotoxic T cells, and reversal of immunosuppressive networks within the tumor microenvironment. This broad immunomodulatory effect distinguishes OVs from immune checkpoint inhibitors, which act on specific pathways, and underpins their potential as combination partners across diverse therapeutic modalities (79).

Advances in genetic engineering have been key to translating OVs from experimental systems to clinical applications. Tumor-selective promoters, receptor retargeting, insertion of immunomodulatory transgenes, and deletion of pathogenic viral genes have markedly improved safety and specificity (80). Indeed, combinatorial regimens represent one of the most promising avenues for OV development.

Preclinical and clinical data demonstrate strong synergy between OVs and immune checkpoint inhibitors, where viral infection enhances tumor immunogenicity and overcomes resistance to checkpoint blockade (81). Similarly, chemotherapy and radiotherapy can improve viral penetration, disrupt tumor stroma, and induce immunogenic cell death, further amplifying OV activity. More recently, targeted therapies have been paired with OVs to exploit tumor-specific vulnerabilities. Moving forward, biomarker-driven patient selection and rational trial design will be essential to avoid empirical combinations and fully realize the synergistic potential of these regimens (82).

Despite substantial progress, important challenges remain. A major paradox is the role of the immune system: while immune activation is necessary for durable responses, premature antiviral clearance can limit viral replication and spread. Strategies such as transient immunosuppression, repeated dosing, or development of "stealth" viral particles are under investigation to balance these competing dynamics (83). Delivery is another critical barrier, particularly for metastatic disease. Systemic administration is often hindered by neutralizing antibodies and physical barriers such as the extracellular matrix. Novel delivery methods—including nanoparticle encapsulation, cell-carrier approaches (e.g., mesenchymal stem cells), and locoregional injections—are actively being explored to improve biodistribution and efficacy (84).

Regulatory, safety, and economic considerations also warrant careful attention. Concerns about insertional mutagenesis, uncontrolled replication, or horizontal viral transmission necessitate rigorous long-term monitoring in clinical trials (85). Furthermore, the complexity and cost of OV manufacturing may limit accessibility, especially in low- and middle-income countries. Addressing these issues will be critical to ensuring that OV-based therapies are not restricted to highly resourced healthcare systems (86).

Future Perspectives

The combination of intelligent nanomedicine is driving photodynamic therapy (PDT) toward precise control of dose, activation and monitoring (87). Advances in artificial intelligence behaviour may optimize nanoparticle formulation, dosing and light exposure further for individualized treatment of maximum effect with as few side effects as possible. Emerging preclinical models such as tumor organoids and microfluidics systems provide more accurate assessment of PDT with nanoparticles (84). Combining PDT with immunotherapy and specifically immune checkpoint inhibitors has the potential to increase systemic antitumor immunity for durable responses. Real-time imaging modes such as MRI, PET, and photoacoustic imaging parrots the possibility of dynamic in vivo monitoring and adaptive therapy. Collectively these innovations are likely to make PDT become a versatile and highly effective precision oncology modality (88).

CONCLUSION

The nanotechnology-based PDT is a significant innovation in cancer treatment and can address most of the problems of a nonnanotechnological photodynamic therapy. They do so by commercializing on the designed nanoplatforms, which can deliver a targeted platform, controlled and stimuli-responsive delivery and integrating synergistic therapies. Next-generation PDT approaches are transforming next-generation PDT systems into the oncologic arena with highly precise and personalized treatments. Most of the problems associated with clinical translation, regulatory acceptance, and production standardization have been abandoned; the discipline is being sped up by the constant interchange between disciplines and the use of industrial technology. Nanomedicine convergence with photonics and cancer care promises a paradigm shift of safer, more effective, and personalized cancer management with the potential of greatly improving patient outcomes and quality of life.

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Authors's Contribution

Yasaman Vojgani: Conceptualization, Writing and Editing the draft. The author read and confirmed the final manuscript.

Conflicts of interest

None of the authors has any conflicts of interest to declare.

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